The 510(k) Law and Regulations

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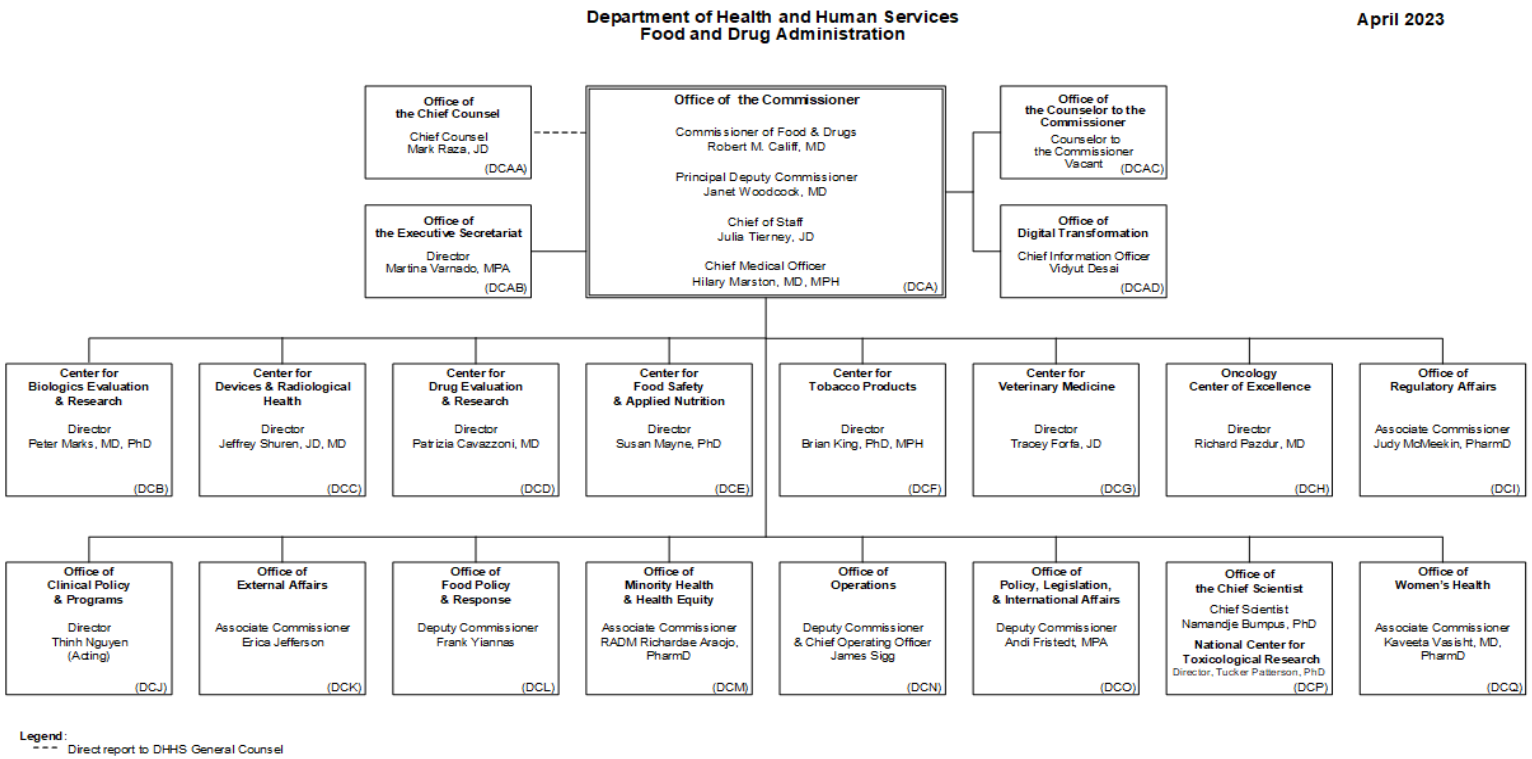
Medical Device Amendments 1976

First statute to place stringent controls on medical devices and diagnostics

- Devices were required to be classified (1, 2, or 3)

- Required Manufacturers to:
  - Register with FDA
  - Follow Quality Procedures (GMPs)
  - Obtain Marketing Clearance/Approval (510k, PMA, PDP)
  - Report **Adverse Events/malfunctions -Medical Device Reporting (MDRs)**

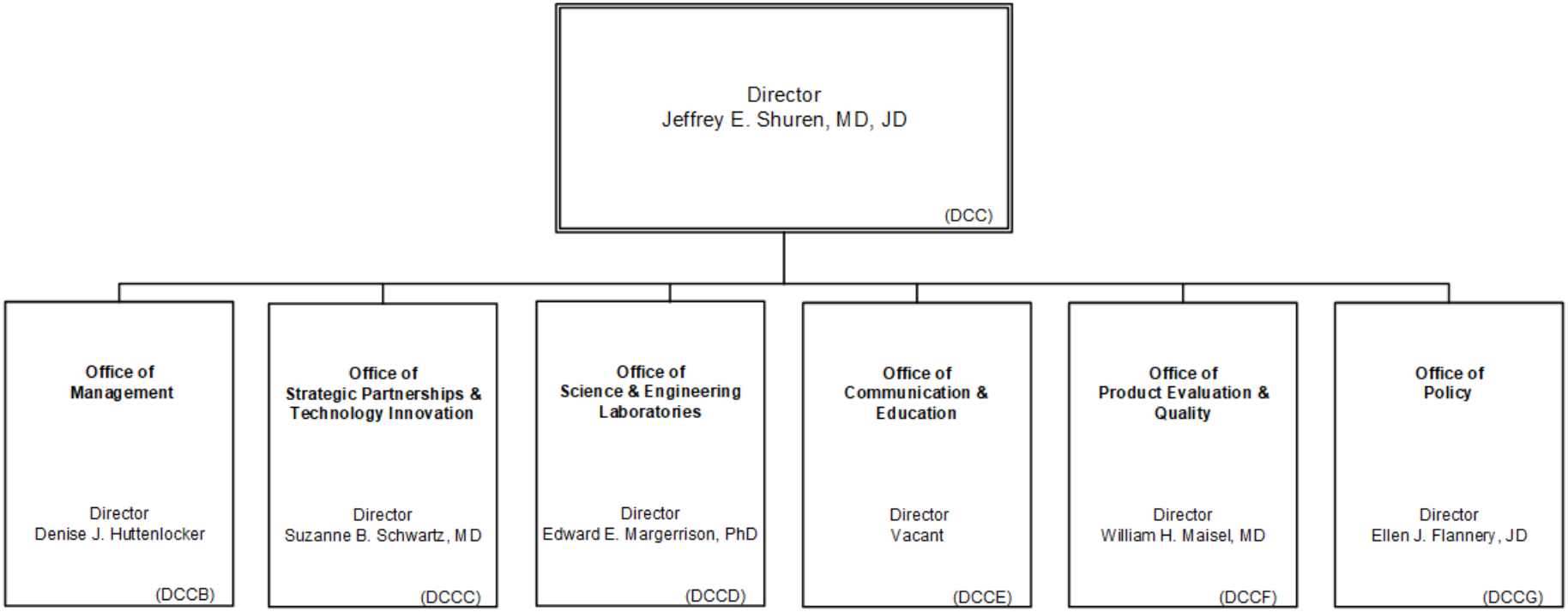
FDA Org Charts

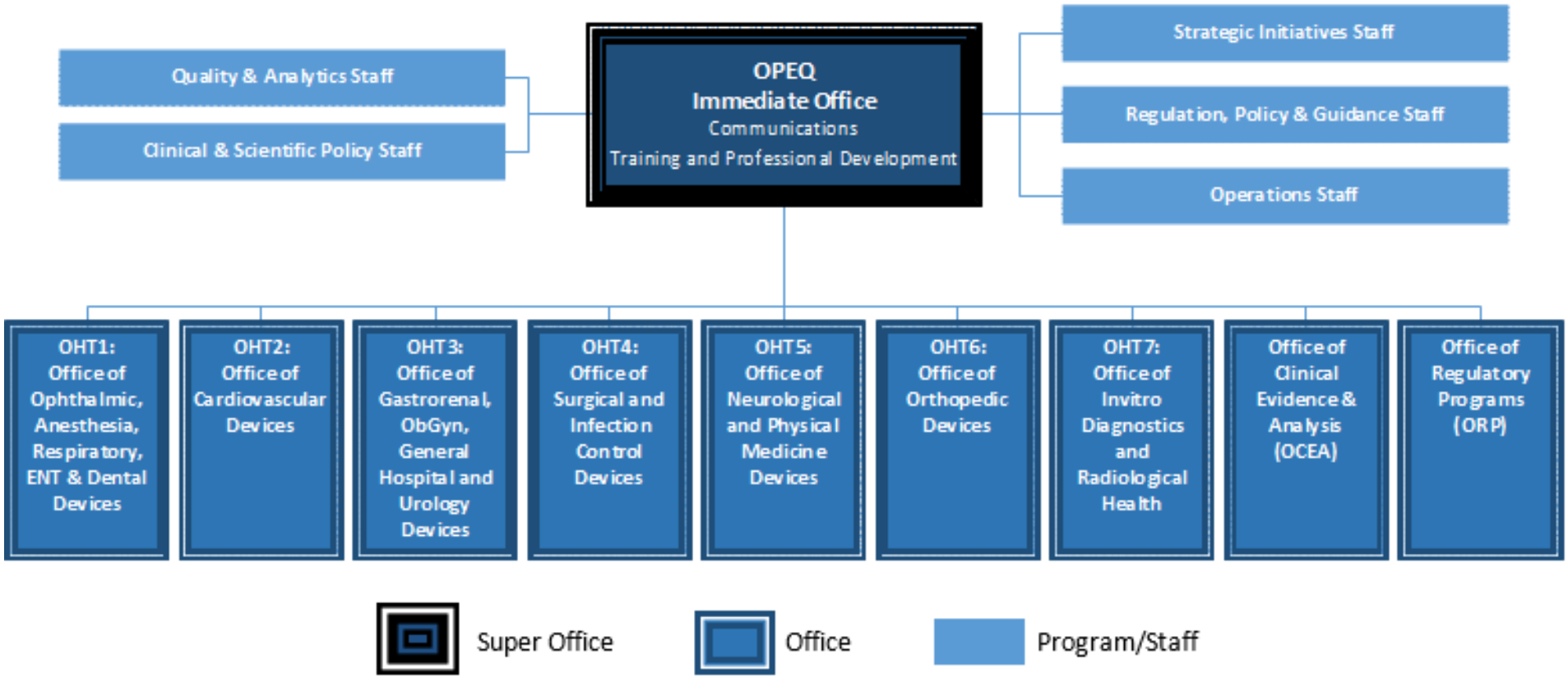


CDRH Organization

May 2023

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




Quality & Analytics Staff
Clinical & Scientific Policy Staff
OPEQ
Immediate Office
Communications
Training and Professional Development
Strategic Initiatives Staff
Regulation, Policy & Guidance Staff
Operations Staff
OHT1: Office of Ophthalmic, Anesthesia, Respiratory, ENT & Dental Devices
OHT2: Office of Cardiovascular Devices
OHT3: Office of Gastrorenal, ObGyn, General Hospital and Urology Devices
OHT4: Office of Surgical and Infection Control Devices
OHT5: Office of Neurological and Physical Medicine Devices
OHT6: Office of Orthopedic Devices
OHT7: Office of Invitro Diagnostics and Radiological Health
Office of Clinical Evidence & Analysis (OCEA)
Office of Regulatory Programs (ORP)
Super Office
Office
Program/Staff

Office of Product Evaluation and Quality

- OPEQ protects and promotes the public health by **evaluating**, enhancing and ensuring compliance with medical device laws through the Recall, Inspection and Audit, Registration & Listing, Allegations of Regulatory Misconduct, Import, Export, Premarket and Labeling, and Bioresearch Monitoring programs.

- CDRH Leadership

Definition of a Medical Device

- An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar article, including any component, part, or accessory which is:
  - Recognized in the official National Formulary, or the United States pharmacopeia, or any supplement to them
  - Intended for use in the **diagnosis of disease or conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals**
  - Intended to affect the structure or any function of the body of man or other animals
- Which does **NOT achieve its primary intended purposes through chemical action within or on the body** of man or other animals and which is **NOT dependent upon being metabolized for the achievement of its intended purposes.** The term "device" does not include software functions excluded pursuant to section 520(o).

Definition of Device
Food Drug and Cosmetic Act 201(h)

Sec 3060. Clarifying Medical Device Software Regulation

- Added section 520(o) of the FDCA which narrows FDA's jurisdiction over 5 categories of software functions.
- The term device in section 201(h) does not include a software function that is intended:
  A. For Administrative support of a healthcare facility
  B. For maintaining or encouraging a healthy lifestyle
  C. To serve as electronic patient records
  D. For transferring, storing, converting formats or displaying laboratory test or other device data and results.

Section 3060 (cont)

E. For the purpose of:

- displaying, analyzing or printing medical information about a patient or other medical info (such as peer reviewed clinical studies and clinical practice guidelines)
- Supporting or providing recommendations to a healthcare professional (including about prevention, diagnosis or treatment); and
- Enabling a healthcare professional to independently review the recommendations such that it is not the intent that the health professional rely primarily on such recommendations for clinical decisions

Even if a software function meets the criteria for (E), the exemption will not apply if the function ”is intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system

Classification of Devices

- Section 513 of the FDCA required that all devices in the US be classified into Class 1, 2, or 3.
- Most Class 2 devices require a 510(k) review and SE determination by FDA.
- New unclassified devices are automatically Class 3 and require a PMA or they need an initial *De Novo* to classify them as Class 1 or Class 2.
  - If Class 2 then subsequent devices of the same type would also be Class 2 and require the same premarket review (510(k))

Device Classification Process

Panels and devices subset by Medical specialties

(Panel given two-digit code and devices a 7-digit classification code)

Anesthesiology	21 CFR 868.####
Cardiovascular	21 CFR 870.####
Clinical Chemistry & Toxicology	21 CFR 862.####
Hematology & Pathology	21 CFR 864.####
Immunology and Microbiology	21 CFR 866.####
Dental	21 CFR 872.####
Ear, Nose, Throat	21 CFR 874.####
Gastroenterology-Urology	21 CFR 876.####
General and Plastic Surgery	21 CFR 878.####
General Hospital and Personnel Use	21 CFR 880.####
Microbiology	21 CFR 866.####
Neurological	21 CFR 882.####
Obstetrical and Gynecological	21 CFR 884.####
Ophthalmic	21 CFR 886.####
Orthopedic	21 CFR 888.####
Pathology	21 CFR 864.####
Physical Medicine	21 CFR 890.####
Radiology	21 CFR 892.####
Toxicology	21 CFR 862.####

513(g) Requests

- Mechanism to ask FDA how the device should be classified.
  - FDA will provide
    - Information on whether a PMA or a 510(k) is required
    - The appropriate Pro Code to use etc.
    - If there are relevant guidance documents to follow
  - FDA will not:
    - Agree that a device is SE to another device
    - Tell you the types of studies required for approval and marketing of the device

- This is a useful tool if you need information about a device
- FY 2023 User Fees:
  - $5,961 Standard
  - $2,980 Small Business

513g Guidance Document

De Novo Guidance Documents

- General Info on De Novo Requests
- Acceptance Review for De Novo Classification Requests
- User Fees & Refunds for De Novo Classification Requests
- FDA and Industry Actions on De Novo Classification Requests: Effect of FDA Review Clock & Goals

Now and Later…..The Path Forward

- Premarket Notifications-510(k)
  - Background
  - Content/Format-Traditional 510(k)
  - New 510(k) Paradigm
    - Abbreviated 510(k)
    - Special 510(k)
  - Safety & Performance Pathway

- Modified Devices
  - When do they need a new 510(k)

510(k)s-Background

- The original intent of the program was to classify devices based on levels of control needed to assure safety and effectiveness
- Devices brought to market after the Medical Device Amendments of 1976
- Devices that are Substantially Equivalent (SE) to Non-PMA products are placed in the same regulatory class as the predicate
- Devices that are Not Substantially Equivalent are Class III devices

510(k) Background (cont.)

- Three Classifications:
  - Class I – General Controls
  - Class II – General Controls and Special Controls
  - Class III – General Controls and Premarket Approval (PMA)

General Controls

Adulteration; misbranding; device registration and listing; premarket notification exemption; including repair, replacement, or refund; records and reports; restricted devices; and good manufacturing practices.

Special Controls

Class II devices for which general controls alone are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance. Special controls are **usually device-specific** and include: **Performance standards, Post-market surveillance, Patient registries** and **Special labeling requirements**

510(k) Clearance

- **FDA clearance** through the **510(k)** process **means** the agency is in agreement with the manufacturer that a medical device is similar to a previously approved product. ... This is described by the **FDA** as a risk- and evidence-based classification process.

510(k)s ARE required when…..

- A medical device is introduced into commercial distribution in the U.S. *AND*
  - PMA not required
  - No exemption
- A legally marketed [510(k)-able] device is significantly modified in design, components, method of manufacture or intended use

….and also NOT required when….

- You are selling *unfinished** devices to another firm for further processing
- Device is being distributed by your firm *AND* a U.S. manufacturer holds the 510(k)
- You are a re-packager/re-labeler *AND* existing labeling or condition of device is the “same”
- You are an importer of a foreign made device *AND* the 510(k) is held by a foreign manufacturer

*narrow interpretation of “unfinished”

510(k)s can be submitted by…

- U.S. manufacturers *introducing* a device
- Specification developers *introducing* a device
- Foreign manufacturers/exporters or U.S. representatives/importers or foreign manufacturers introducing a device
- Re-packers/re-labelers who make labeling changes or whose operations significantly change the device

510(k)s are NOT required when…

- Device is classed as PMA device or 510(k) exempted
- Device was legally distributed by the firm in the U.S. prior to May 28, 1976 (pre-amendment/grandfathered) *AND* the device is still the "same"
- Rights to market a pre-amendment/cleared device have been acquired *AND* device is still the "same"

510(k)s are…

- A marketing application submitted to the FDA to demonstrate that the device is **substantially equivalent** to one legally in commercial distribution in the United States: (1) before May 28, 1976; or (2) to a device that has been determined by FDA to be substantially equivalent *AND* does not require a PMA.

What is "Substantial Equivalence"?

Substantial Equivalence

- Premarketing submissions made to FDA to demonstrate substantial equivalence to a predicate
  - Same intended use and…
    - Same technological characteristics, OR
    - Different technological characteristics, but is as safe and effective as the predicate and does not raise new questions re: S&E

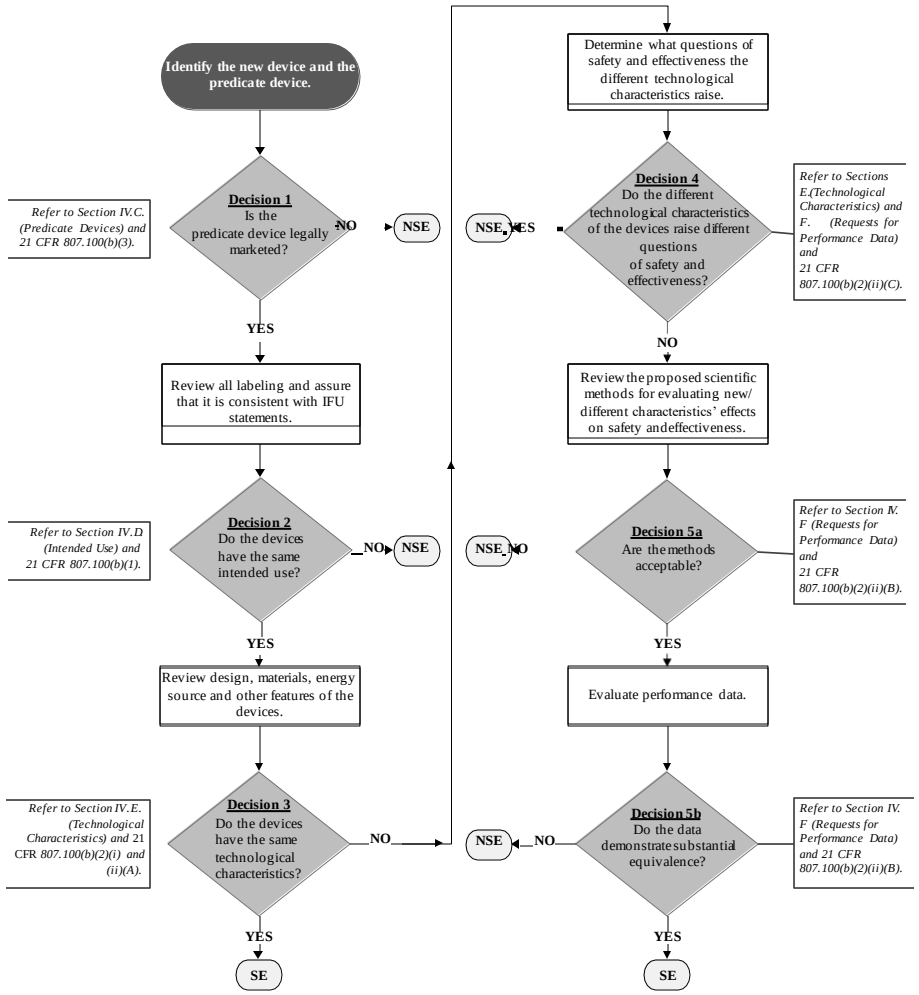
Types of Predicate Devices…

- Legally marketed prior to May 28, 1976
- Reclassified from Class III to Class II or Class I
  - Reclassified using the **De Novo** Process-applies to low and moderate risk devices that have been classified as class III because they were found not substantially equivalent (NSE) to existing devices
  - **De Novo**-risk-based evaluation for reclassification into class I or II within 30 days of receipt of an NSE determination
  - Reclassed by the FDA based on a petition from industry
- SE through 510(k) process
- Evaluation of Automatic Class III Designation
- *AND* not withdrawn from market due to a design safety issue

Relevant 510(k) Guidance documents

- The 510(k) Program(2014)
- Deciding When to submit a 510(k) for a change to Exisiting Device (2017)
- Special 510(k) Program
- Refuse to Accept Policy for 510(k)s
- General/Specific Intended Use

Appendix A. 510(k) Decision-Making Flowchart



SE = "Substantially Equivalent"
NSE = "Not Substantially Equivalent"
IFU = "Indications For Use"

This Flowchart is not intended to be used as a 'stand-alone' document and should only be considered in conjunction with the accompanying text in this guidance.

The 510(k) Program: Evaluating SE in Pre market Notifications
https://www.fda.gov/media/82395/download

Let's look at the FDA thinking……

"…the agency has received previous Congressional guidance which bears directly on the issue of substantial equivalence in the Report of the Committee on Interstate and Foreign Commerce on the Medical Device Amendments of 1976 (Senate Report):

The committee believes that the term, substantial equivalence, should be construed narrowly where necessary ***to assure the safety and effectiveness of a device*** *but not narrowly where differences between a new device and a marketed* ***device do not relate to safety and effectiveness.***"

Guidance for Industry-General/Specific Intended Use (11/4/98)

510(k)s-Background (cont.)

- FDA Actions (21 CFR 807.100)
  - Order Declaring a Device as SE
  - Order Declaring a Device NSE
    - ➡ ***Orders*** *"shut off"* the review clock
- Request Additional Information (AI)
  - ➡ Formal Requests include due date for response. Typically 30 days but can get 180 day extension

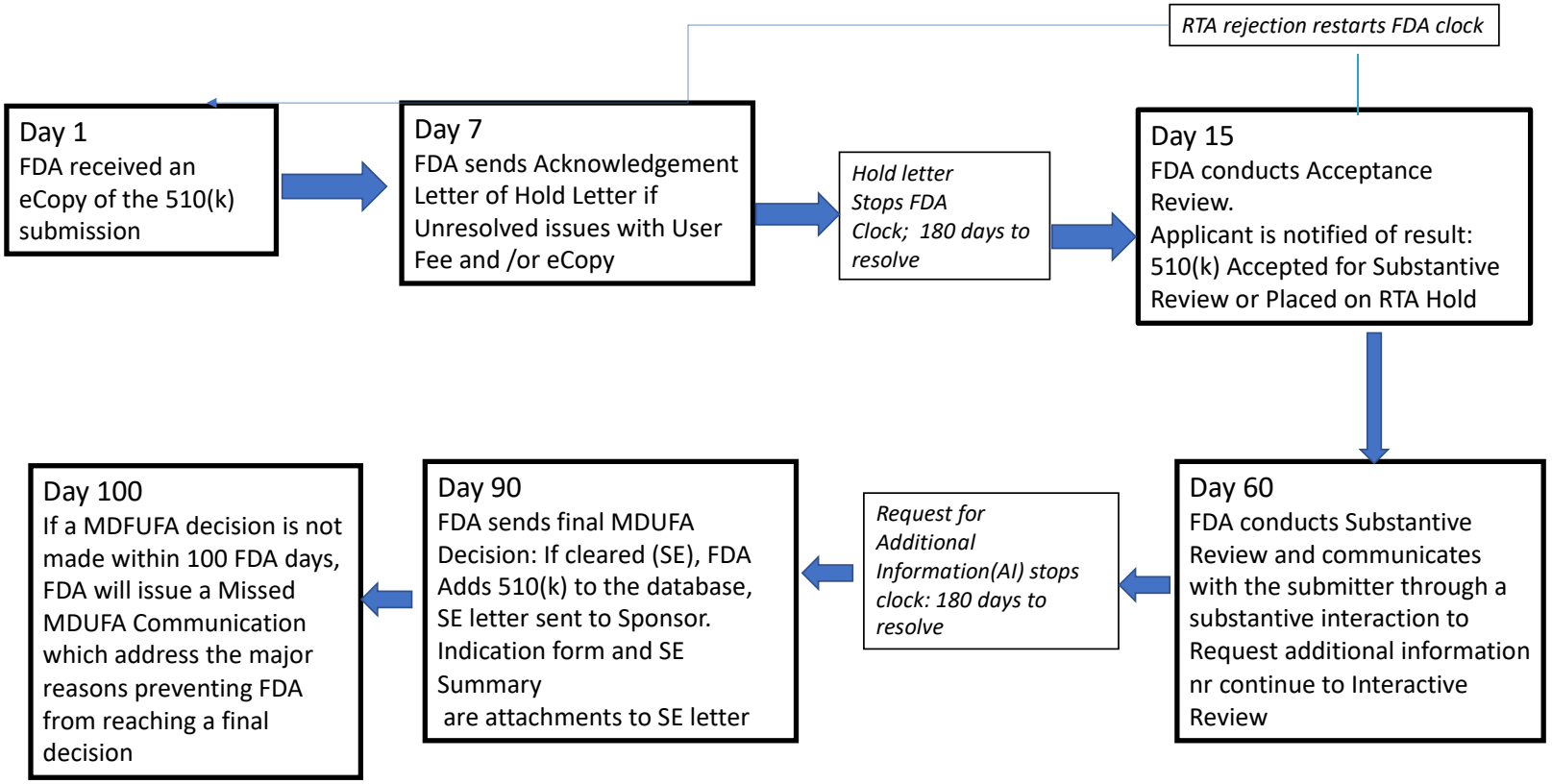
FDA Actions (cont.)

- Advise 510(k) Not Required
  - ➡ "Not a Device" or "Exempt from 510(k)" Decision
  - ➡ Decisions "shut off" the review clock
- Issue a Notice of Withdrawal

510(k)s –Background (cont.)

- Timing and Review Process
  - 4 types of 510(k) submissions:
    - Traditional
    - Abbreviated
    - Special-New Guidance Issued 09/2019
    - Safety & Performance Pathway
- 510(k) determinations within 90 days for Traditional and Abbreviated Submissions (Abbreviated=“expedited”)
- 510(k) determinations within 30 days for Special Submissions

510(k) Average Review Timelines



eSTAR Program

- The eSTAR Program is an interactive PDF form to develop a submission
  - https://www.fda.gov/medical-devices/how-study-and-market-your-device/voluntary-estar-program
- Includes templates for both DeNovo and 510(k) submission.
- CDRH does not intend to conduct an RTA review for submissions submitted as an eSTAR
- Required after Oct.1, 2023

eSTAR Program (cont.)

- Does not change the FDA review process and timelines
- Submission will be done via the FDA portal
- eSTAR submission does not need to comply with the eCopy Guidance Document
- eSubmissions Guidance link
- https://www.fda.gov/media/152429/download

  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-submission-template-medical-device-510k-submissions

Content/Format-Traditional 510(k)

- Getting started

1. Identify Predicate Device(s)
   - Focus on intended use, but don't neglect technology
     - FDA databases: 510(k), classification
     - Internet searches? Medical, Competitive literature

2. Locate Guidance Documents/Standards
   - CDRH search for Device-Specific Guidance
   - Listed under regulation as Special Control
   - FDA Recognized Standards
   - Review 510(k) Guidance/Manual
     - https://www.fda.gov/medical-devices/premarket-notification-510k/510k-submission-programs#resources

Contents:

- 510(k) Cover Letter and/or Coversheet and Supporting Documentation
- Cover Letter: FDA recommended in Guidance Documents
- Premarket Submissions Coversheet, FDA Form 3514
- User Fee Coversheet, Form FDA 3601 (N/A for Third Party Review): Note: Fee must be paid before submission of 510(k)

User Fee Amendments

FY 2023 Review Fee 510(k):	$ 19,870	Standard
	$4,967	Small Business
FY 2023 Review Fee (De Novo)	$132,464	Standard
	$33,116	Small Business

Contents: (cont.)

- Title Page and Table of Contents: List each required item with page numbers, including a list of attachments/appendices
- Device Name: Including both the trade, common, or proprietary name and the classification name
- Medical Device User Fee Cover Sheet

Contents: (cont.)

- Registration Number: Owner or Operator submitting the 510(k) (if don't have one, state this: Registration is NOT required to submit a 510(k) …..then Registration is required within 30 days of marketing the device)
- Class III Summary and Certification: Summary of the types of S&E problems associated with the type of device being compared and a citation to the information upon which the summary is based (21CFR 807.94)
- Financial Certification or Disclosure Statement
- Declaration of Conformity and Summary Reports
- Executive Summary

Contents: (cont.)

- Device Description
- Substantial Equivalence Discussion
- Proposed Labeling (IFU / Labels)
- Sterilization Shelf Life: Including sterilization method, validation method, SAL, packaging to maintain the device sterile, maximum levels of EtO residues (EO only), statement of non-pyrogenicity and determination method (blood or cerebrospinal fluid contacting devices), radiation dose/methodology
- Shelf Life: Including packaging and product shelf lift testing
- Biocompatibility
- Software: If device is computer controlled, software and/or hardware, validation and verification information must be included
- Electromagnetic Compatibility and Electrical Safety
- Performance Testing – Bench
- Performance Testing - Animal

Contents: (cont.)

- Performance Testing – Clinical
- 510(k) Summary or Statement: 510(k) Summary or Statement: Summary of Safety and Efficacy info. upon which a determination of SE can be based; statement that the S&E information will be made available to any person within 30 days of a written request (21 CFR 807.92 and 21 CFR 807.93)

FDA Review

- FDA Refuse to Accept Policy for 510(k)s

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM315014.pdf#page=17

- FDA will pre-review the 510(k) submission using the RTA checklist. This is intended to screen submission for acceptable content before they are provided to the review and the start of the review clock.
- If unacceptable, FDA will refuse the 510(k) and return to the submitter
- Important to ensure ALL questions in RTA Checklist are addressed in 510(k)

Contents: (cont.)

- Forms
  - Certification of Compliance with ClinicalTrials.gov Data Bank, Form FDA 3674
  - …..submit in a 510(k) that “refers to, relates to or includes in information on a clinical trial”
  - http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/ListFormsAlphabetically/
  - http://www.fda.gov/regulatoryinformation/guidances/ucm125335.htm

Format:

- Format and information required in a 510(k) are found in 21 CFR sections 807.87, 807.90, 807.92, 807.93, 807.94
- Guidance Documents for:
  - Traditional 510(k) Format
  - Abbreviated 510(k) Format
  - Special 510(k) Format
  - Safety & Performance Pathway
  - Guidance on Bundling Multiple Devices or Indications in a single Submission

510(k)s

- Abbreviated and Special 510(k)s

  http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm080187.htm
- Two optional approaches for obtaining marketing clearance
- Streamline the evaluation of 510(k)s for reserved Class I, Class II (non-exempt) and Pre-amendment Class III devices
- Abbreviated-Relies on the use of guidance documents, special controls and recognized standards
- Special-Utilizes QSR

Abbreviated 510(k)

- Reliance on a "Summary Report" outlining adherence (and deviations) to
  - relevant guidance documents,
  - special controls and/or
  - consensus standards
- Declaration of Conformity for Recognized Standard(s)
- Must include all required elements from the traditional submission
- Link to Guidance Document
  - Abbreviated 510(k) Format

Safety & Performance Pathway

- Expansion of Abbreviated 510(k)
- Voluntary Program for well understood device types
  - Only used for devices that identified in FDA S&P Guidance document
- Demonstrate that the device meets
  - FDA-recognized consensus standards
  - FDA guidance
  - Special Controls
  - Scientific literature
  - Historical 510(k) submission data

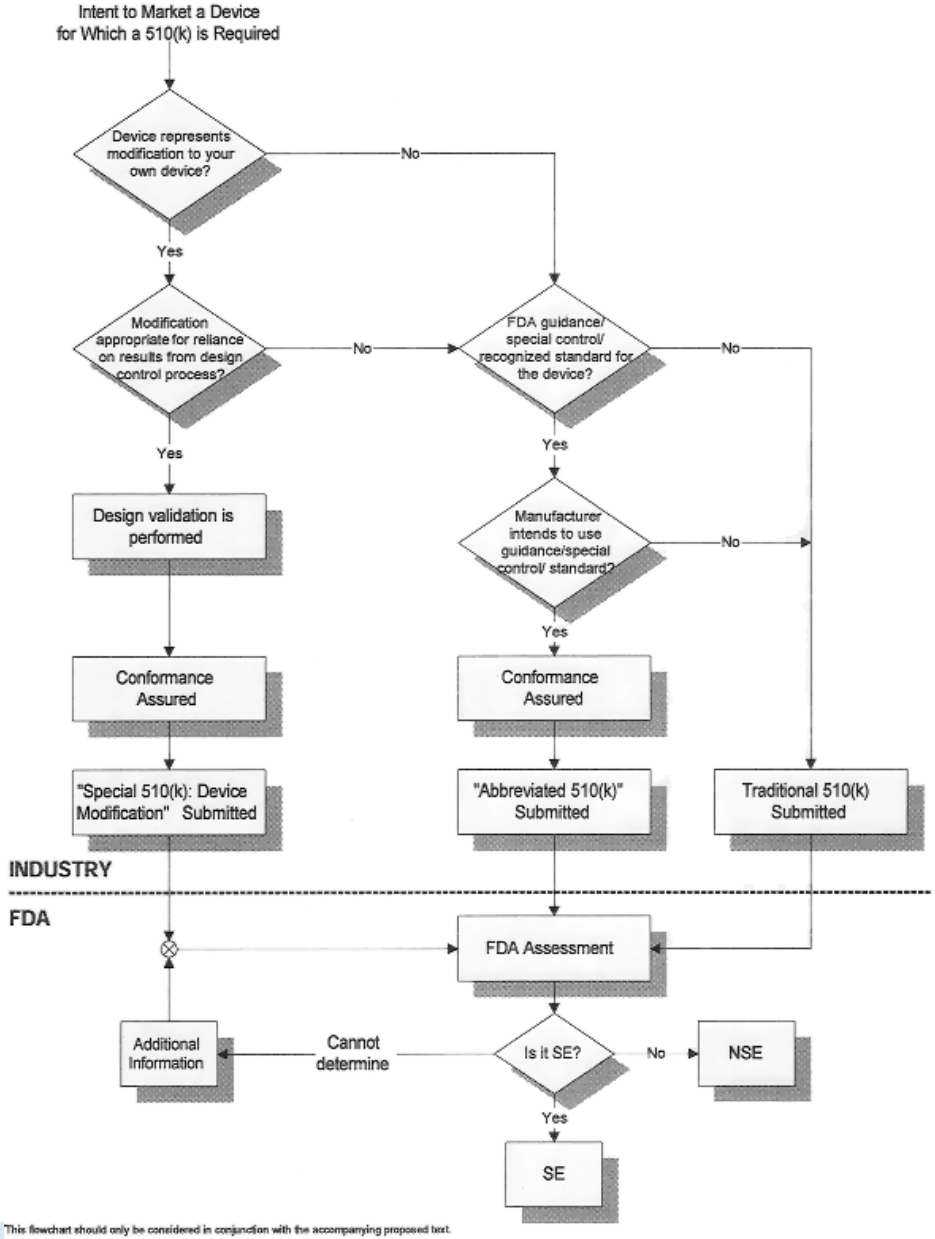
510(k)s –Special 510(k) Questions

- Guidance Document on Special 510(k) Program
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/special-510k-program
- Is it a change to the manufacturer's own device?
  - Special 510(k)s are for a change to the submitters own legally marketed predicate.
- Is performance data needed to evaluate the change?
  - If additional testing is required to support the change FDA will normally convert it to a traditional 510(k).
- Is there a well-established method to evaluate the change?
  - Special 510(k)s should not include complete test reports.

Special 510(k)

- Modification to legally marketed 510(k) device
- Change cannot affect the intended use or alter the fundamental scientific technology of the device
- Relies on design control requirements in 21CFR820.30- Summary information serves as the basis for clearance
- Conduct risk analysis, verification, validation activities to demonstrate that the design outputs of the modified device meet the design input requirements
- Submission can go in AFTER the manufacturing has ensured satisfactory completion of design control process
- Declaration of Conformity with design control requirements

The New 510(k) Paradigm



510(k)s –Modified Devices

- Deciding When to Submit for Changes….
  - New 510(k) must be filed for significant modifications to a legally marketed device
    - Guidance on when to Submit a new 510(k)
  - Modifications in design, components, method of manufacture or intended use
  - Significant=
    - Changes that could significantly affect safety or effectiveness
    - Major changes in the intended use of the device

Deciding When to Submit for Changes (cont.)

- FDA guidance provides “thought process” for 3 types of change:
  - Labeling
  - Technology, Engineering and Performance Changes
  - Material Changes (IVDs and Non-IVDs)

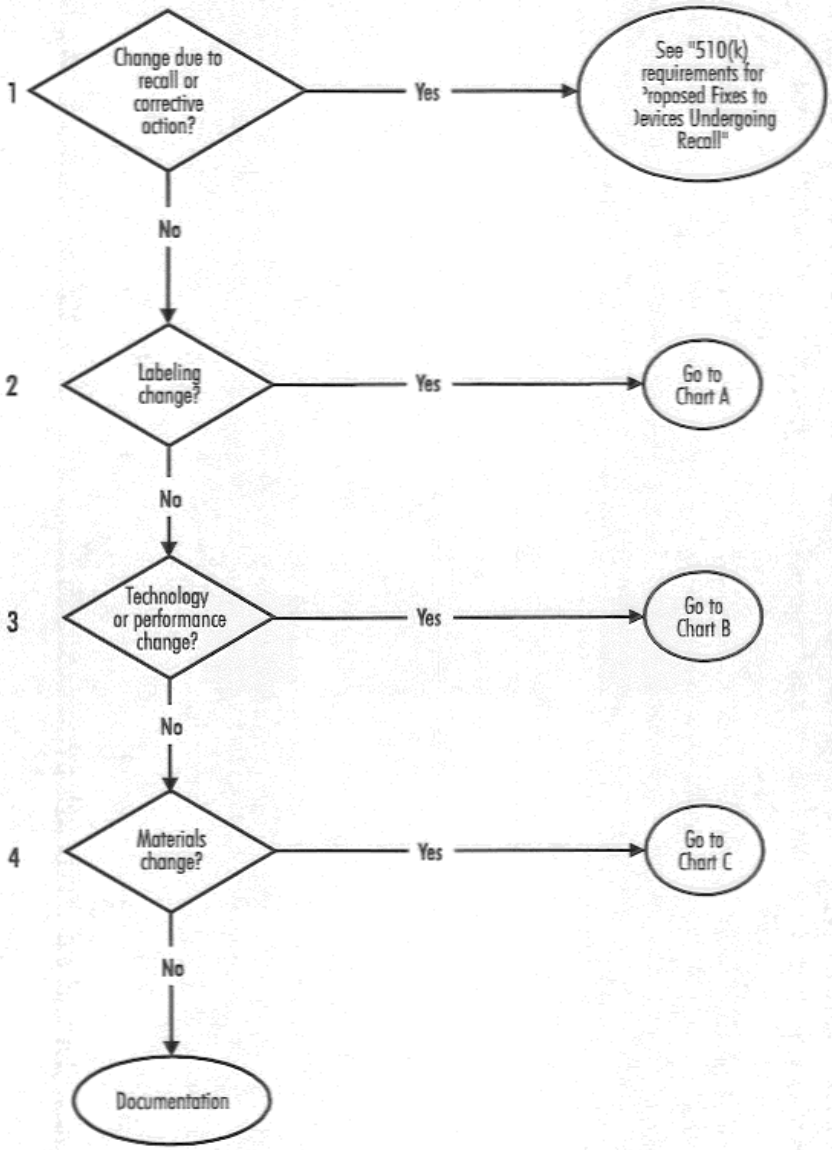
Deciding When to Submit for Changes (cont.)

- Guidance provides flowcharts and interpretive text (cookbook for internal Regulatory Affairs SOP)
  - Interpret “New 510(k) as “Strongly Consider Submitting a 510(k)”
  - Interpret “documentation” as “Document Your Analysis and File for Future Reference”

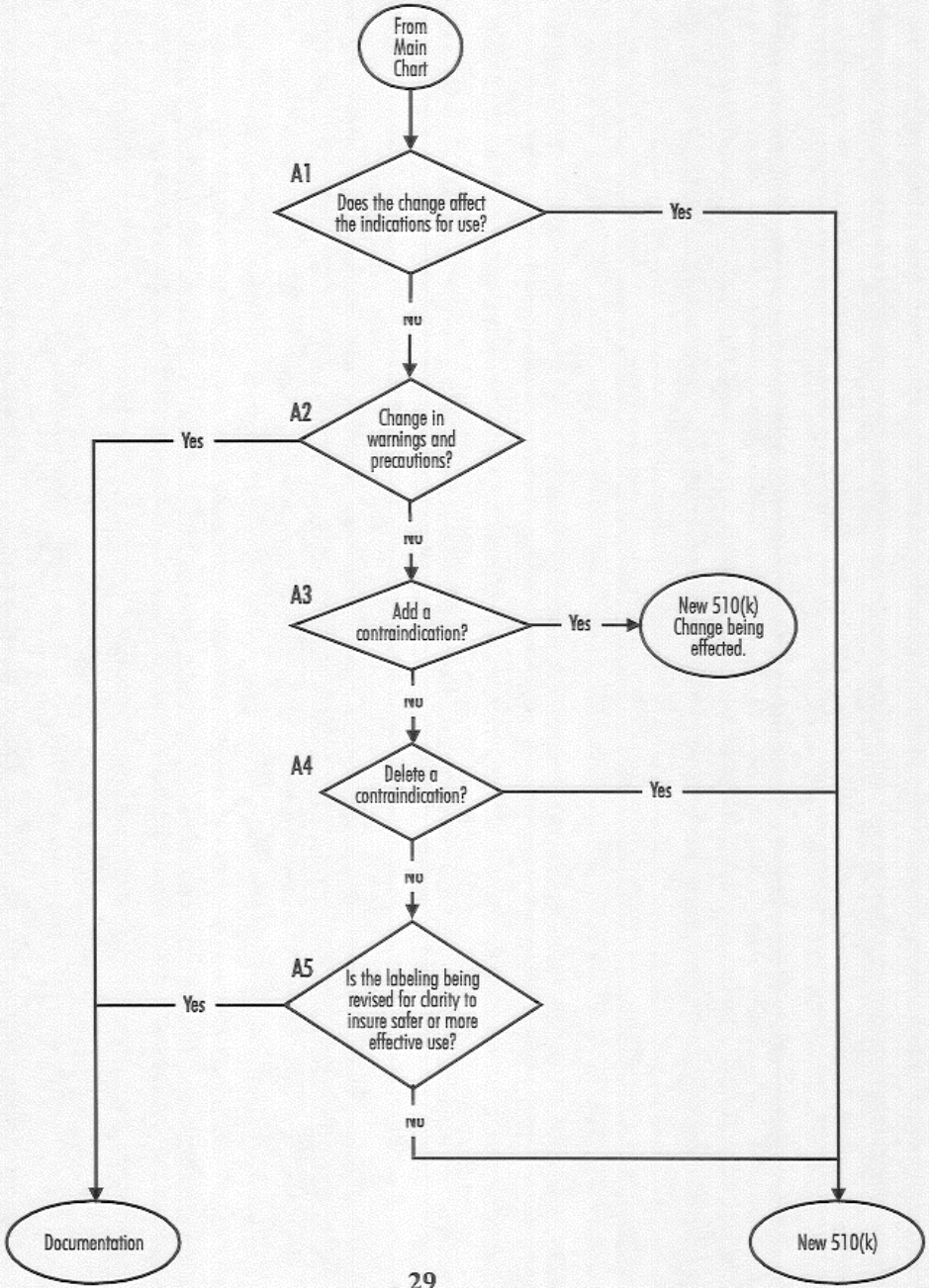
Deciding When to Submit for Changes (cont.)

- Key Assumptions:
  - Guidance applied using intended changes, not unforeseen results of implementing a change
  - Manufacturers should compare the change or changes to their device as previously found to be SE
  - Each change must be assessed individually and collectively with other changes made since the last 510(k) clearance
  - cGMP dependent!

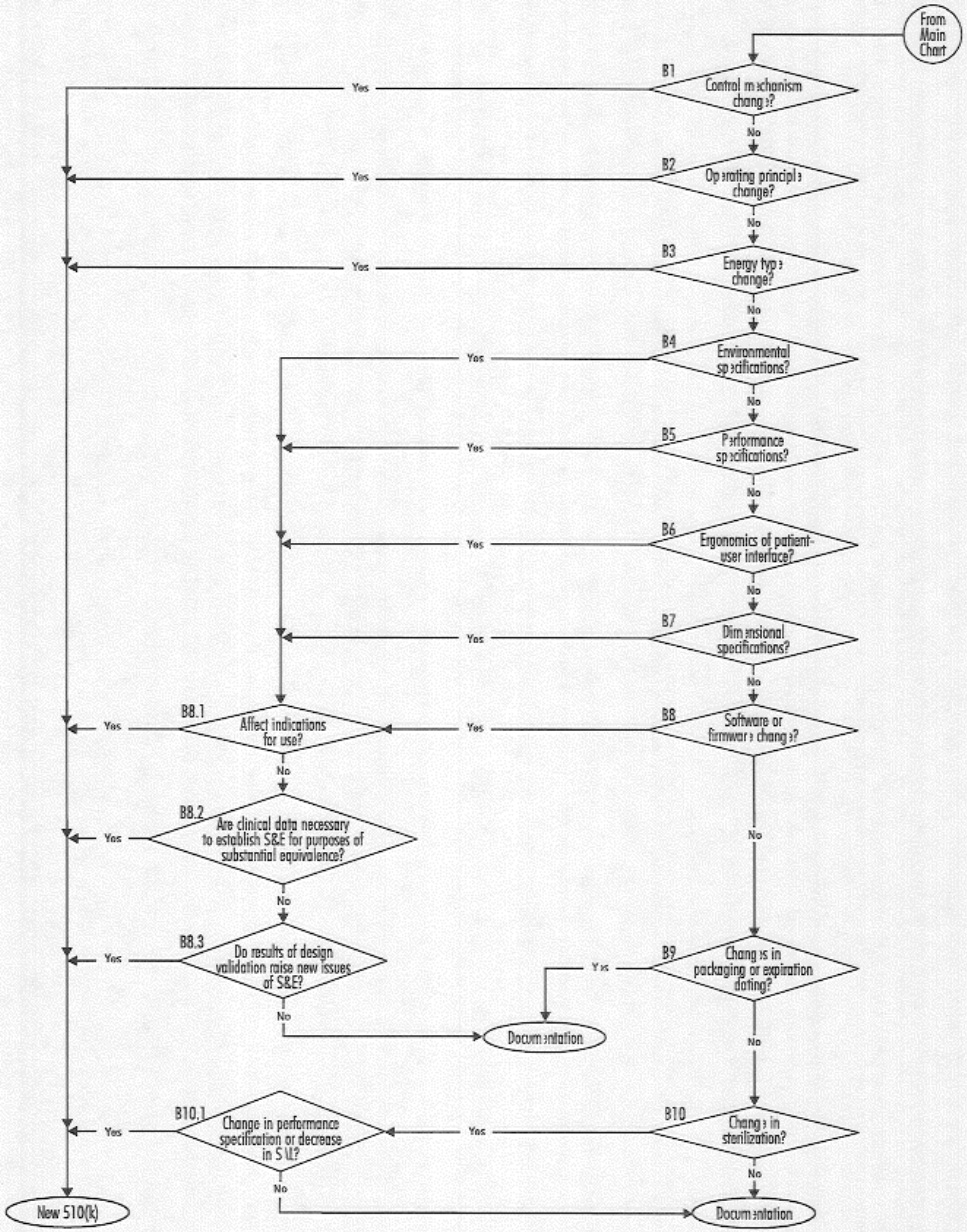
MAIN FLOWCHART
WHEN TO FILE A 510(k) AFTER CHANGE TO A LEGALLY MARKETED DEVICE



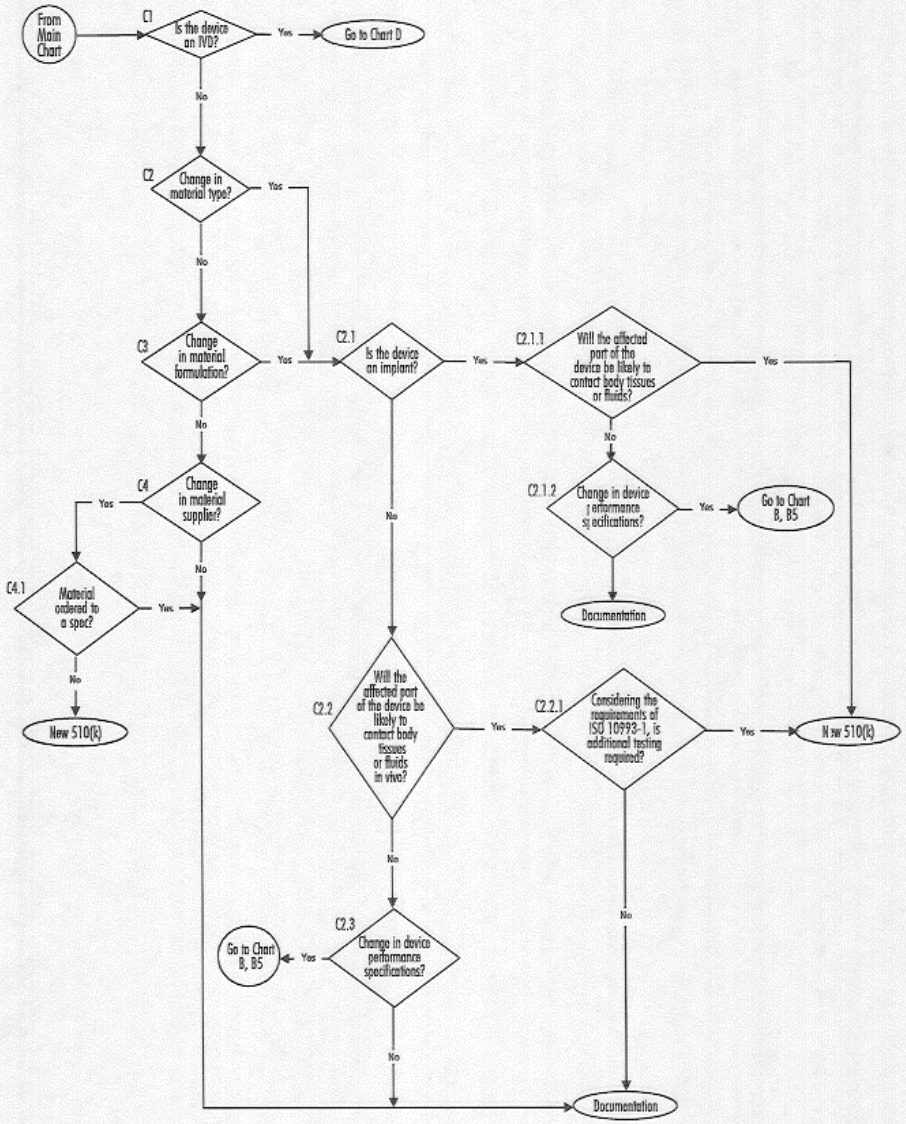
FLOWCHART A - IS IT A LABELING CHANGE?



FLOWCHART B - IS IT A TECHNOLOGY OR PERFORMANCE CHANGE?



FLOWCHART C - IS IT A MATERIALS CHANGE?



Bundling 510(k)s

- The process of incorporating multiple device types in a single 510(k) or incorporating multiple indications in a single 510(k).
  - Guidance on Bundling Multiple Devices or Indications in a single Submission
- Generally not encouraged
  - May slow down the review process if different groups within the agency need to review the submission
- May be very relevant for specific products
  - Changing a plastic component in a line of devices
  - Changing sterilization methods

Device Classification Number versus Product Code

Device also given product code (ABC)

Product codes continue to evolve

e.g. Limb Orthosis 21 CFR 890.3475 Class I

A limb orthosis (brace) is a device intended for medical purposes that is worn on the upper or lower extremities to support, to correct, or to prevent deformities or to align body structures for functional improvement.

Device Classification Number versus Product Code (cont.)

ITM Knee Cage

ITW Ankle joint- external brace

ITS Hip joint – external brace

ITQ Knee joint- external brace

KNP Corrective shoe orthosis

IQI Limb brace orthosis

ILE Arm sling, overhead support

ILH Hand splint & components

ILG Elastic stocking

IOY Arm support

Various Limb Orthoses
21 CFR 890.3475

Small Things that Make a Big Difference…

- Pre-Submission
  - Make sure your device isn't exempt (maybe petitioning for exemption is a better route)
  - Discuss 510(k) type, predicates, content with FDA
  - Determine if third-party review is viable
    - Third Party Review Program
  - Purchase/Review purged copies of predicate 510(k)s
  - Use Summary Tables and write clearly/succinctly
  - Keep indications for use identical throughout
  - Perform independent review for integrity and presentation
  - Paginate carefully and check that everything matches (TOC)

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Strategy and Planning

510(k) Submissions Workshop
May 15-17, 2023

Tony Blank
Tblank@AtriCure.com

Keys to Developing an effective Strategy and Plan

- Know the requirements and the processes
- Know the business objectives
  - Target patient population
  - Intended Claims
  - Planned design iterations
  - Interaction with other devices in portfolio
  - Timelines
  - Etc.
- Understand the resource needs
- Understand the environmental factors

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Building a Strategy: Begins with asking insightful questions

- Are there specific patient groups more likely than others to benefit from the product?
- Will this be a first of a kind product? Which products (if any) provide the same or similar patient benefits?
- Will this be a platform technology to be leveraged into iterations of the product?
- Does the organization have the technical and regulatory expertise to address any 'non-device' regulatory and manufacturing issues:
  - Incorporation of a drug or biologic into the product?
  - Wireless communication and programming?
  - Cybersecurity considerations?
- What (if any) business assumptions have been built into the approval of this project:
  - Time to market?
  - Claims?
  - Patient population?

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What drives these questions?

- Within the constraints defined by the business and functional strategies…
  - Minimize regulatory risk
  - Maximize regulatory predictability

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Some examples of constraints…

- Specific planned marketing claims
- Budget for testing
- Commitments to senior mgmt/investors
- Availability of components/finished devices
- Data requirements for reimbursement
- Etc.

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The Role of the Regulatory Professional

- Understand the project and the business requirements
- Develop regulatory strategies to minimize regulatory complexity and maximize regulatory predictability
- Know and communicate the regulatory process and likely expectations.
  - Submission type and content
  - Resources to determine regulator expectation
  - Timelines
  - Etc.
- Identify and communicate regulatory risks associated with project strategies (and opportunities to mitigate)
- Drive strategies for communicating with regulators
- Manage submission development and execution

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Other Functions

- R&D/Product Development
- Sterilization
- Operations
- Design Assurance
- Clinical/Medical
- Marketing
- Legal
- Sales

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Using FDA Guidance when planning and organizing the 510(k)

- FDA has produced a large number of Guidance documents
- They represent FDA's current thinking and recommendations on how to fulfill specific regulatory obligations
- Very broad range
- Available on the web and searchable…

https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

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Search All Guidance Documents:

510(k)

Showing 1 to 10 of 177 entries (filtered from 4,223 total entries)

Filter Results

Product

Subject

Date Issued

Draft or Final

FDA Organization

Open for Comment*

Document Type

Comment Closing Date on Draft*

Clear Filters

Show 10 entries

Export to Excel

Title	Date issued	FDA Organization	Subject	Draft or Final	Open for Comment	Comment Closing Date on Draft*	Docket Number
Refuse to Accept Policy for 510(k)s - Guidance for Industry and Food and Drug Administration Staff	01/30/2018	CDRH, CBER	Premarket, Administrative / Procedural	Final	No		FDA-2012-D-0523
Replacement Reagent and Instrument Family Policy for In Vitro Diagnostic Devices - Draft Guidance for Industry and Food and Drug Administration Staff	12/19/2017	CDRH	IDE, Premarket	Draft	Yes	03/18/2018	
Technical Considerations	12/05/2017	CDRH, CBER	Premarket, PMA,	Final	No	08/08/2016	FDA-

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Horizontal Guidance

- Examples:
  - Format for Traditional and Abbreviated 510(k)s - Guidance for Industry and FDA Staff https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm
  - Refuse to Accept Policy for 510(k)s https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm315014.pdf
  - Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm089593.pdf

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Vertical Guidance

- Examples:
  - Guidance for Industry: Guidance for the Content of Premarket Notifications for Intracorporeal Lithotripters https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073795.htm
  - Labeling for Permanent Hysteroscopically-Placed Tubal Implants Intended for Sterilization https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm488020.pdf
  - Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm380327.pdf

Using Guidance

- Determine which Guidance apply to your product/situation
- Assess ability to conform to recommendations in Guidance
- If plans require deviating from Guidance:
  - Develop rationale(s) for variance
  - Consider discussing with FDA before submission

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Considerations when Developing Testing Strategies

- Final Design vs. Prototypes
- Finished Devices vs. Components
- Unprocessed Devices vs. Finished Devices
- Leveraging results from similar or related products

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Leveraging results from similar or related products

- Valid, scientific rationale is a must
- Can you justify why the results of testing with the similar or related product is applicable to results from the finished medical device?
- Have you addressed the potential impact of differences in assembly, configuration, use and design has on the performance of the finished medical device?
- Realistically – Increasingly, leveraging of test results from similar or related products is being considered insufficient to support the new finished medical device.

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When are Clinical Data required?

- Guidance Document specified
  - In some cases, a product-specific guidance document will specify human clinical data are necessary
- When internal risk assessments identify risk mitigations which require clinical data
- FDA may conclude that clinical data are necessary to support claims of substantial equivalence as a result of new technology, patient care practices, etc.
- Results of previous clinical investigations not otherwise reported or referenced in the 510(k) (e.g., studies conducted outside of the United States) should be included,
- To support desired clinical outcome product claims
- To support clinical superiority claims

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Pre-Submission Interactions (Q-Subs)

- A formal written request from an applicant for feedback from FDA provided in the form of:
  - a formal written response or
  - a meeting or teleconference in which the feedback is documented in meeting minutes
- When FDA's feedback on specific questions is necessary to guide product development and/or application preparation (i.e., prior to intended submission of an IDE or marketing application)
- Request **must include specific questions** regarding review issues relevant to a planned IDE or marketing application (e.g., questions regarding pre-clinical and clinical testing protocols or data requirements).

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A Pre-Submission is NOT…

- A mechanism for FDA to design nonclinical test or clinical study protocols for the sponsor
- Phone calls or emails regarding questions that can readily be answered by the reviewer
- Interactive review of an active submission
- An RFD, 513(g), or appeal
- A determination or agreement meeting
- A meeting that is informational only (i.e., no FDA feedback requested) or to discuss a request for additional information as part of submission review

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Timelines

Day	Action
1	Sponsor provides three or more proposed meeting dates
15	FDA completes RTA and either accepts one of the Sponsor's dates or provides two alternatives prior to day 75
30	FDA and Sponsor should agree on a meeting date
40	FDA contacts Sponsor to resolve scheduling (if necessary)
70	Or FIVE days prior to scheduled meeting – FDA provides written feedback

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Reducing Risks Thru Pre-Subs

Topic	Risk to be Reduced
Acceptability of leveraging data from prior projects to support current project	Leveraging strategy not accepted when submitted
Animal testing – model and protocol	Testing protocol fails to provide necessary data to support submission
Bench testing – planned deviation from published Standard or Guidance	Test results not accepted
Clinical study design (e.g., patient population, endpoints, etc.)	Clinical study fails to generate data to support intended device claims and/or approval

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Timing Pre-Sub Interactions

- Impact to development schedule
- Availability of significant background information
- Balance of time and cost
- Impact to project risk

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Schedule Impact

- Pre-Sub Interactions take time:
  - Preparation of the request
  - Scheduling Meeting
  - Post-meeting clarification

- Keys to integrating into project schedule…
  - Identify Strategy Early
  - Staging Meetings by Priority and Impact

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Prioritization of Questions

- Greatest time and/or cost impact should be prioritized…
  - Animal study questions
  - Leveraging questions
  - Planned deviations from Standards and/or Guidances
  - Tests which take a long time and/or are very expensive
    - Carcinogenicity
    - Life testing
  - Tests which impact other tests or drive development direction

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Closing comments re: PreSubs

- Defining your objective …
  - Sufficient feedback to reduce a regulatory or program risk
  - Asking questions which can provide significant direction to the program to reduce time or expense
- Realistic Best Case:
  - FDA concurs with approach
  - FDA has significant concerns about proposal
- Refer to PreSub Guidance: https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf

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Selecting Predicate Devices

- Consider age of predicate (cleared 20 years ago vs. last year)
- Try to choose predicate with similar/same Indications for Use
- Try to choose predicate with similar technologies
- Avoid predicates with different use environments (e.g., home use vs. in-hospital)

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Breakthrough Devices Program

- The Breakthrough Devices Program is a voluntary program for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions.

- The goal is to provide patients and health care providers with timely access to these medical devices by speeding up their development, assessment, and review.

- Manufacturers have an opportunity to interact with the FDA's experts through several different program options to efficiently address topics as they arise during the premarket review phase, which can help manufacturers receive feedback from the FDA and identify areas of agreement in a timely way. Manufacturers can also expect prioritized review of their submission.

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Breakthrough Devices Program

- Eligibility
  - The device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions
  - The device also meets at least one of the following:
    - Represents Breakthrough Technology;
    - No Approved or Cleared Alternatives Exist;
    - Offers Significant Advantages or Existing Approved or Cleared Aternatives; or
    - Device Availability is in the Best Interest of Patients
- How to Request Designation
  - Request the Breakthrough Device designation by submitting a "Designation Request for Breakthrough Device" Q-Submission.
- More Information: Breakthrough Devices Program | FDA

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Safer Technologies Program (STeP)

- A voluntary program for certain medical devices and device-led combination products that are reasonably expected to significantly improve the safety of currently available treatments or diagnostics that target an underlying disease or condition associated with morbidities and mortalities less serious than those eligible for the Breakthrough Devices Program. Devices that are eligible for STeP, unlike those that are eligible for the Breakthrough Devices Program, may include devices that are intended to treat or diagnose diseases or conditions that are non-life-threatening or reasonably reversible.

- The goal is to provide patients and healthcare providers with timely access to these medical devices by expediting their development, assessment, and review.

- The Safer Technologies Program is a collaborative program intended to help reduce the time it takes to develop and obtain marketing authorization for eligible devices. It offers manufacturers an opportunity to interact with the FDA's experts through several different program options to efficiently address topics as they arise during the premarket review phase, which can help manufacturers receive feedback from the FDA in a timely way. Manufacturers can also expect interactive and timely communications, early engagement on Data Development Plans, sprint discussions, and senior management engagement to support the program, as resources permit.

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Safer Technologies Program (STeP)

- Eligibility
  - Not eligible for the Breakthrough Devices Program due to the less serious nature of the disease or condition treated, diagnosed, or prevented by the device
  - Should be reasonably expected to significantly improve the benefit-risk profile of a treatment or diagnostic through substantial safety innovations that provide for at least one of the following:
    - a reduction in the occurrence of a known serious adverse event;
    - a reduction in the occurrence of a known device failure mode;
    - a reduction in the occurrence of a known use-related hazard or use error; or
    - an improvement in the safety of another device or intervention
- How to Request Designation
  - Sponsors interested in participating in STeP as part of their device development should submit a Q-Submission requesting inclusion in STeP with this request highlighted in the cover letter. This request should be the only request in the Q-Submission.
- More Information: Safer Technologies Program (SteP) for Medical Devices | FDA

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THANK YOU!

Tblank@AtriCure.com

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Preparing the Submission

Monday, May 15, 2023

Speakers:
Michael Nilo, President and Principal Consultant, Nilo Medical Consulting
Dave McGurl, VP Regulatory Affairs, MCRA

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Bios and Background

Dave McGurl

Vice President, Orthopedic Regulatory Affairs, MCRA

14+ years of experience in orthopedics, medical devices, and regulatory affairs

Michael Nilo

President
Nilo Medical Consulting Group

14+ years of experience in medical device regulatory affairs and product development

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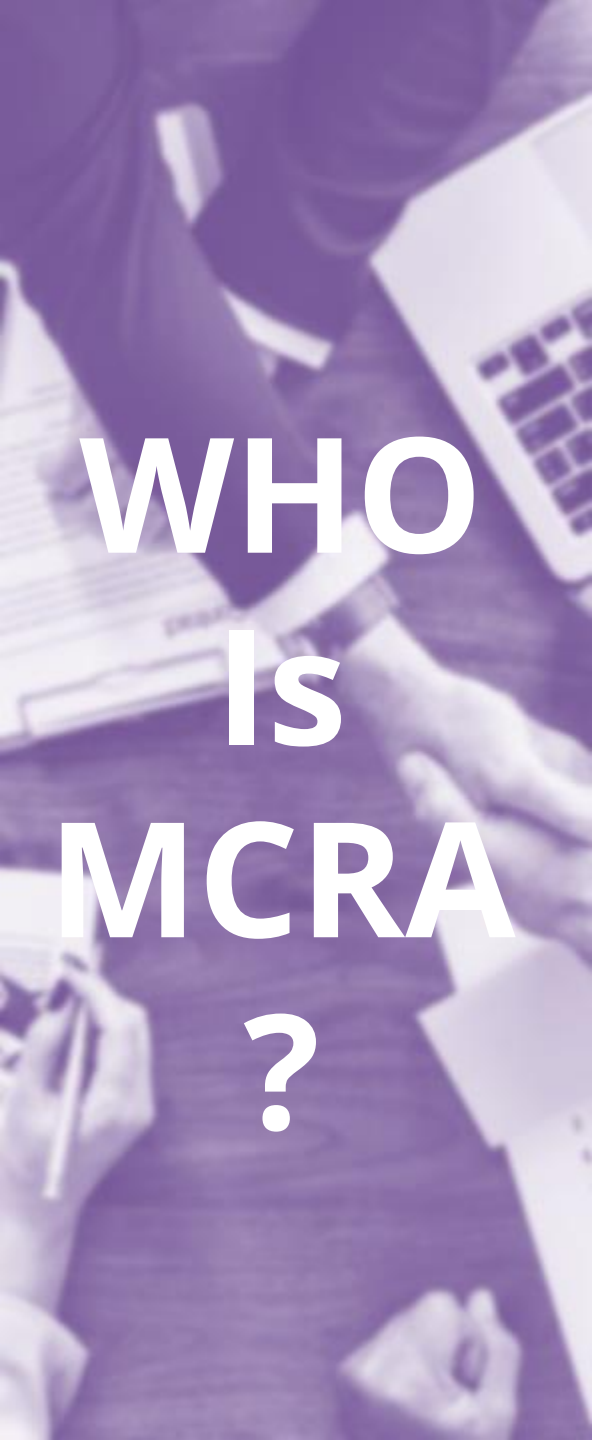

WHO Is MCRA ?

Global Clinical Research Organization

Clinical Study Full Service • Data Management • Biostatistics

Global Regulatory

Pre-market Regulatory • Post-market Regulatory • Breakthrough Designation • Biocompatibility • CE Mark • MDR/IVDR • Strategic Regulatory • UKCA Marks

Reimbursement, Health Economics, & Market Access

Strategic • Health Economics • Call Center for Pre-Authorization • Coding • Market Research • Evidence Generation • Reimbursement Leader Panels

Quality Assurance & Manufacturing

Gap Assessments • Audits & Inspection • Technical Documentation • Quality Management Systems • Design Support

Healthcare Compliance

Healthcare Compliance • Outsourced Chief Compliance Officer • Digital Health

Cybersecurity

Device Security Risk Assessment • Design Control Remediation • Security Gap Analysis • Threat Modeling • Internal & External Workshops

- Global Regulatory Support
  - Pre-market strategies and written deliverables
  - Post-market assessments
  - Available for advice or to act as your regulatory department
  - Flexible to accommodate companies of any size
- Quality Systems and Design Controls
  - Available to build QMS from scratch, support eQMS systems, mitigate 483s, perform internal audits, etc.

Agenda

- General Information
  - 510(k) flowchart
  - Identification of predicate device
  - Writing substantial equivalence
- Assembling the 510(k)
- eCopy requirements overview
- eSTAR transition Oct. 2023

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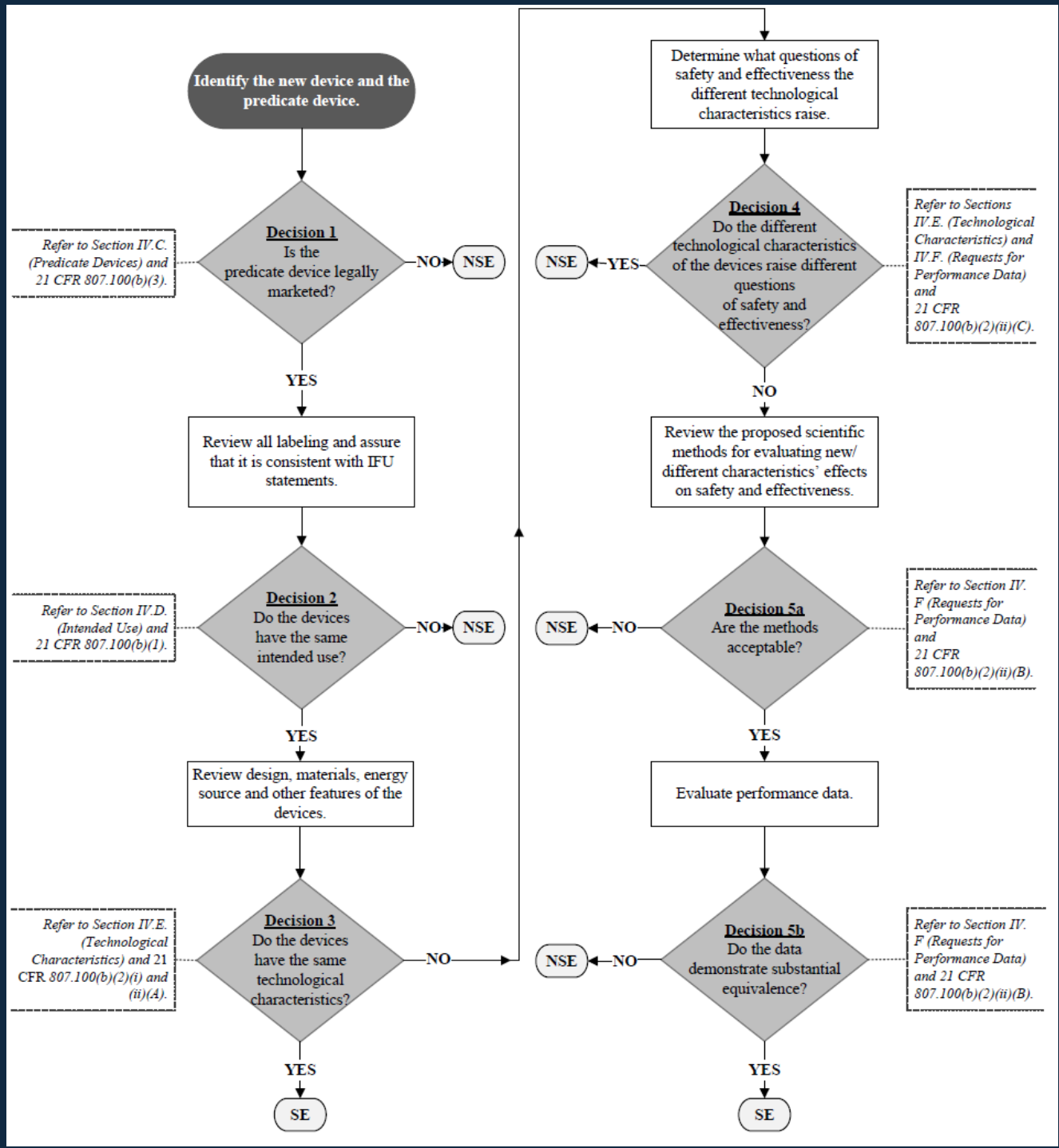
510(k) Flowchart

- FDA uses this flowchart to make their decisions regarding substantial equivalence
- Clients should use this flowchart to determine if they've chosen a good predicate device



Predicate Devices Definition

- **Predicate Device –** A legally marketed device (as defined in 21 CFR 807.92(a)(3)) to which a new device may be compared for a determination regarding substantial equivalence because the devices have the same intended use and the same technological characteristics or different technological characteristics that do not raise different questions of safety and effectiveness.
- **Primary Predicate Device –** A predicate device with indications for use and technological characteristics that are most similar to the new device. The primary predicate should be identified within a 510(k) submission.
- **Reference Device –** A legally marketed device that is intended to provide scientific and/or technical information (e.g., test methodology) to help address the safety and effectiveness of a new technological characteristic. Reference devices are not predicate devices and may only be used after Decision Point 4 on the 510(k) Decision-Making Flowchart.

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Predicate Identification

- Identify your indications
- Tools for Predicate searches
  - Google
  - 510(k) Database
  - Product Code Database
  - Regulation / Classification Database
  - AccessGUDID Database

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Google Search

- Use search terms
  - “510(k)”; Product Code; parts of indications statement
- Search surgical techniques, user manuals, package inserts, marketing materials
  - Product codes / UDI are helpful

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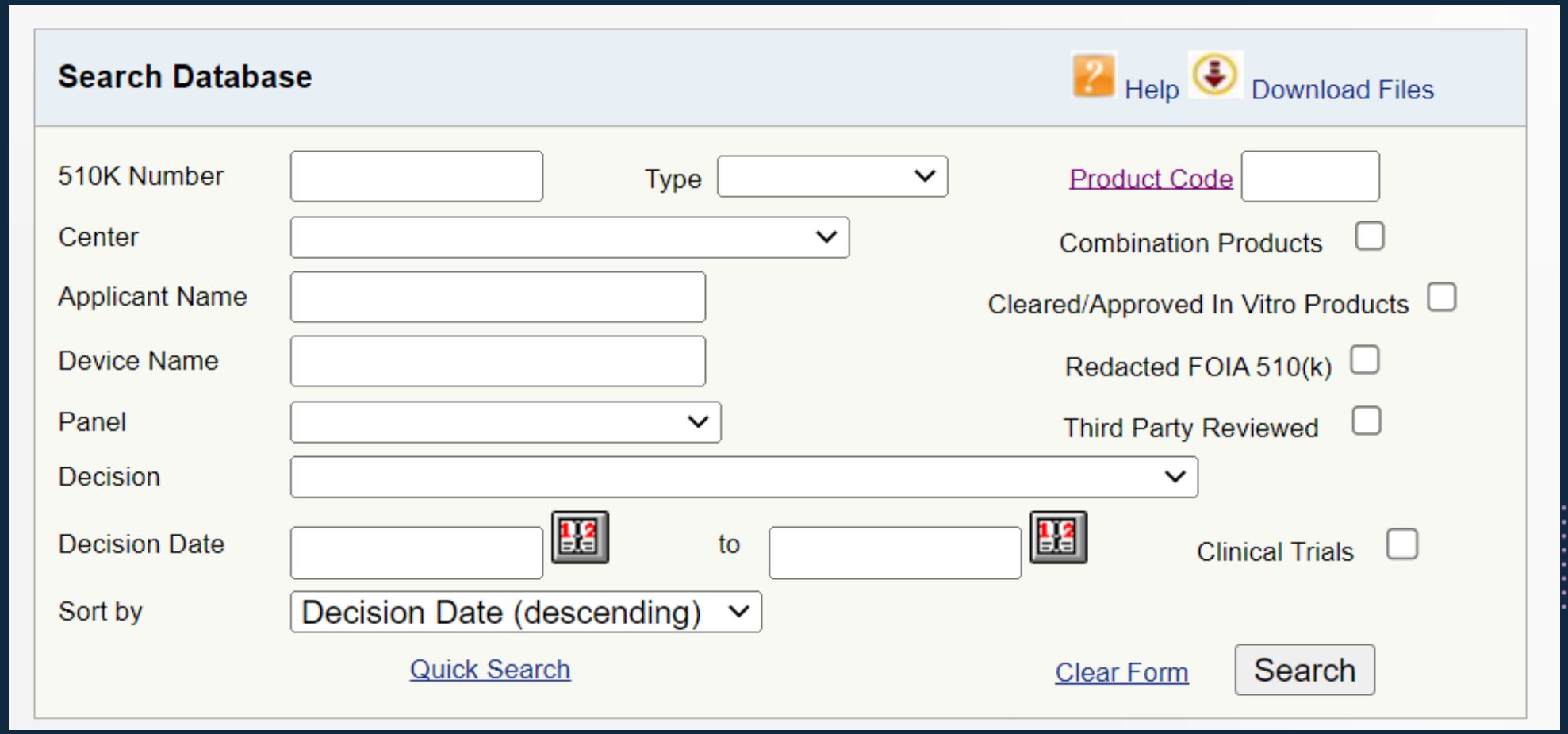
510(k) Database



https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm

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510(k) Database / Google Tip

- Word search 510(k) database:
- In the Google toolbar type “site:www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/”
- Then add a space and the keyword you want to search (e.g. “silver”)

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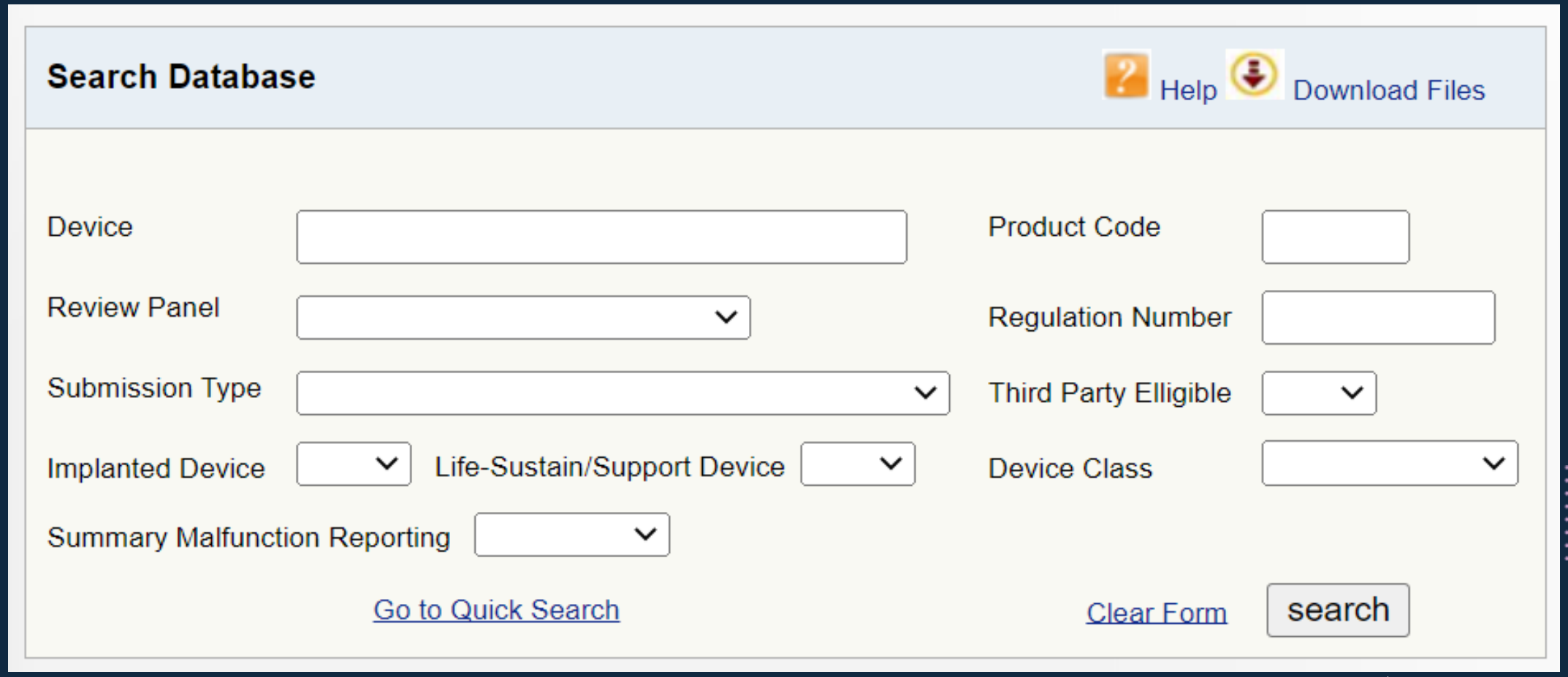
Product Code Database



https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm

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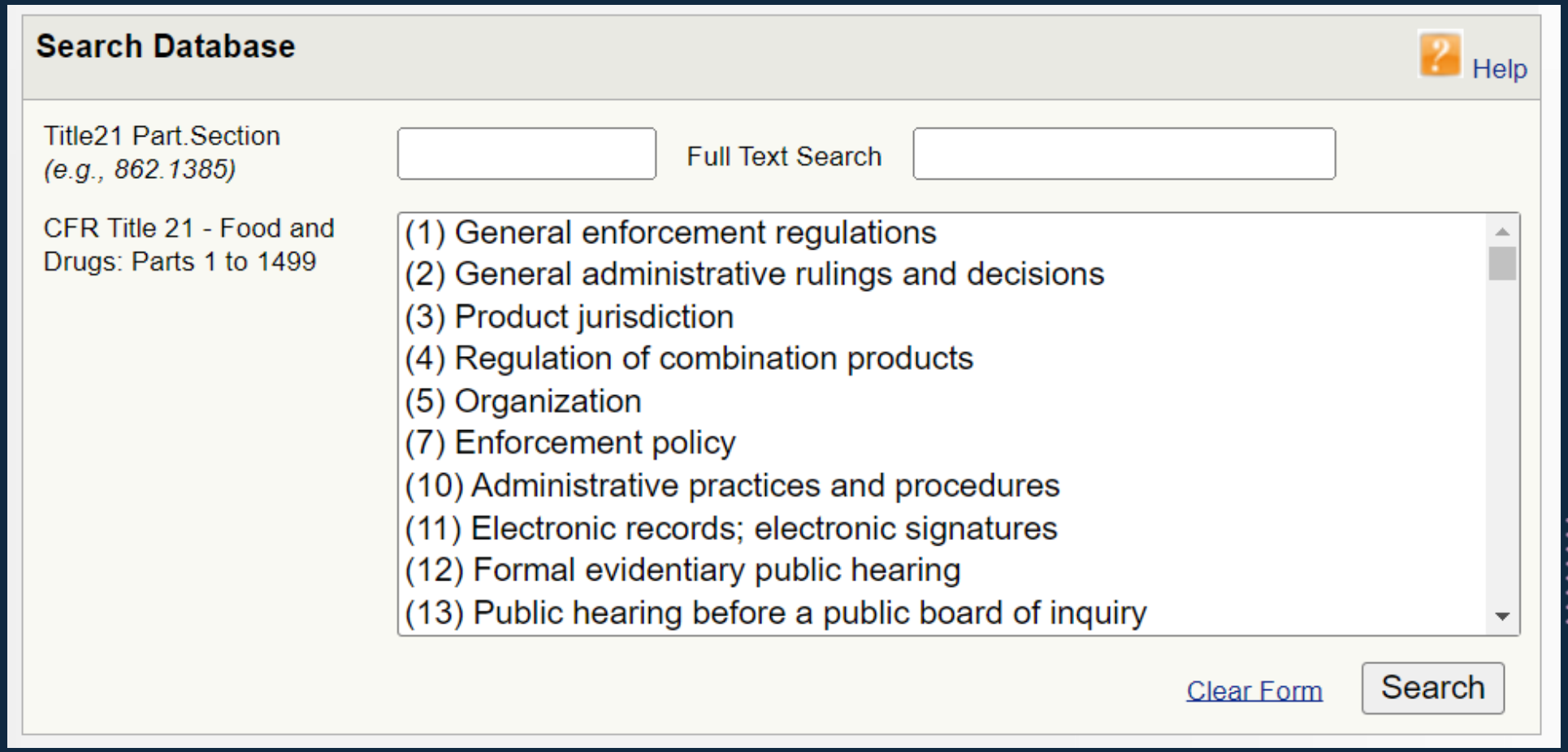
Regulation Database



https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm

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Regulation Information

New Search | Help | More About 21CFR

[Code of Federal Regulations]
[Title 21, Volume 8]
[CITE: 21CFR888.3565]

See Related Information

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H - MEDICAL DEVICES

PART 888 -- ORTHOPEDIC DEVICES

Subpart D - Prosthetic Devices

Sec. 888.3565 Knee joint patellofemorotibial metal/polymer porous-coated uncemented prosthesis.

(a) *Identification.* A knee joint patellofemorotibial metal/polymer porous-coated uncemented prosthesis is a device intended to be implanted to replace a knee joint. The device limits translation and rotation in one or more planes via the geometry of its articulating surfaces. It has no linkage across-the-joint. This generic type of device is designed to achieve biological fixation to bone without the use of bone cement. This identification includes fixed-bearing knee prostheses where the ultra high molecular weight polyethylene tibial bearing is rigidly secured to the metal tibial base plate.

(b) *Classification.* Class II (special controls). The special control is FDA's guidance: "Class II Special Controls Guidance Document: Knee Joint Patellofemorotibial and Femorotibial Metal/Polymer Porous-Coated Uncemented Prostheses; Guidance for Industry and FDA." See § 888.1 for the availability of this guidance.

[68 FR 14137, Mar. 24, 2003]

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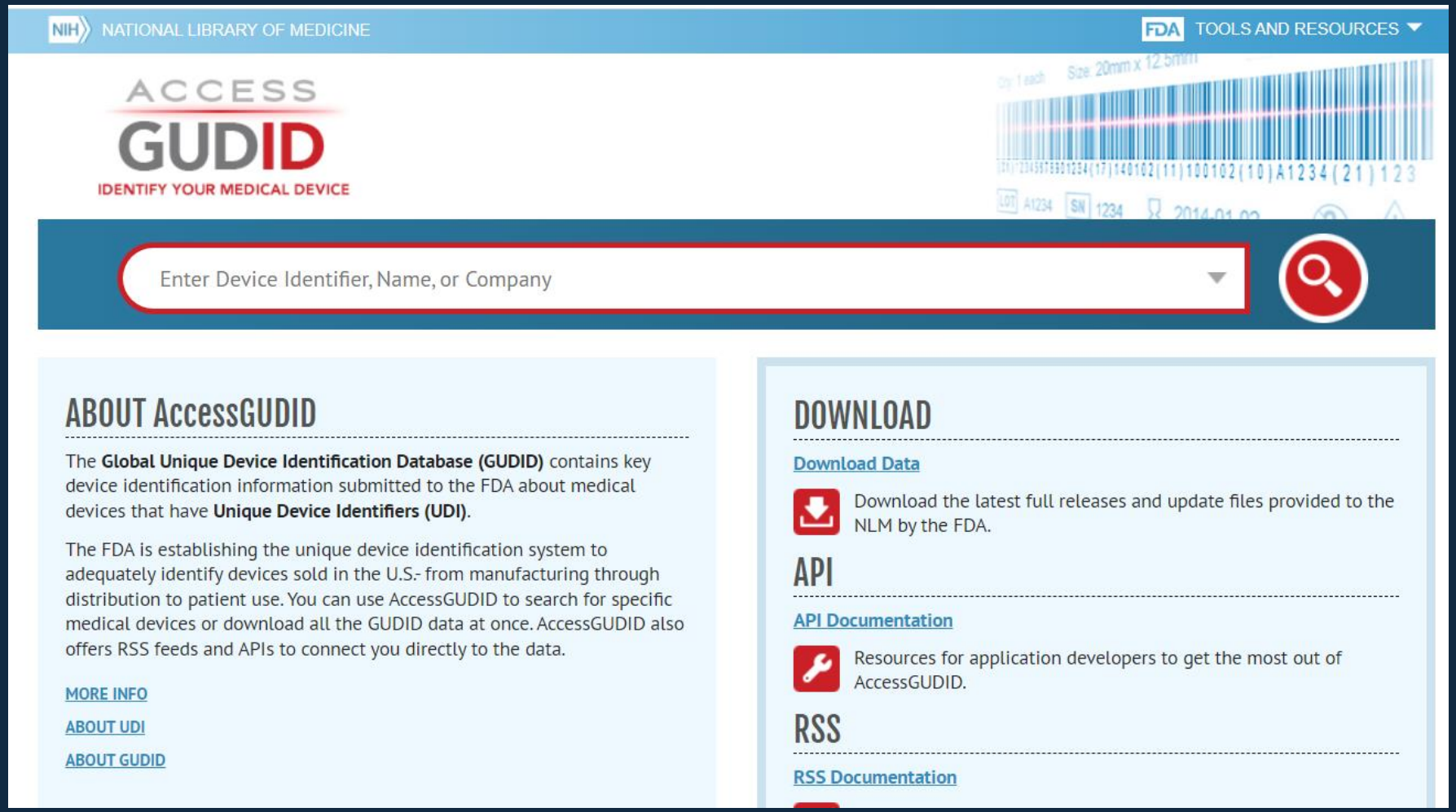
AccessGUDID Database



https://accessgudid.nlm.nih.gov/

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AccessGUDID Database - Example

DEVICE: Large Fragment Active Plating System (00866204000235)

DEVICE RECORD HISTORY | DOWNLOAD: XML | JSON | PRINT

VIEW ALL SECTIONS | CLOSE ALL SECTIONS

DEVICE IDENTIFIER (DI) INFORMATION

Brand Name: Large Fragment Active Plating System
Version or Model: 00-505-000-26
Commercial Distribution Status: Not in Commercial Distribution
Catalog Number:
Company Name: Incipio Devices
Device Description: 5mm Locking Screw, 26mm

Primary DI Number: 00866204000235
Issuing Agency: GS1
Commercial Distribution End Date: September 01, 2017
Device Count: 1
Labeler D-U-N-S® Number*: 042094056 *Terms of Use

CLOSE

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AccessGUDID Database - Example

GMDN [?]

GMDN Names and Definitions: © Copyright GMDN Agency 2015. Reproduced with Permission from the GMDN Agency.

GMDN Preferred Term Name	GMDN Definition
Hip internal fixation system	An assembly of implantable devices designed to treat fractures of the hip. It typically includes a metal plate that is held in position with fasteners such as screws and nails, or bolts, nuts and washers. The assembly is typically intended to treat stable or unstable intertrochanteric, pertrochanteric, and/or base of neck hip fractures.

CLOSE

FDA PRODUCT CODE [?]

Product Code	Product Code Name
HWC	Screw, Fixation, Bone

CLOSE

FDA PREMARKET SUBMISSION

FDA Premarket Submission Number [?]	Supplement Number [?]
K142938	000

Device Exempt from Premarket Submission: No

CLOSE

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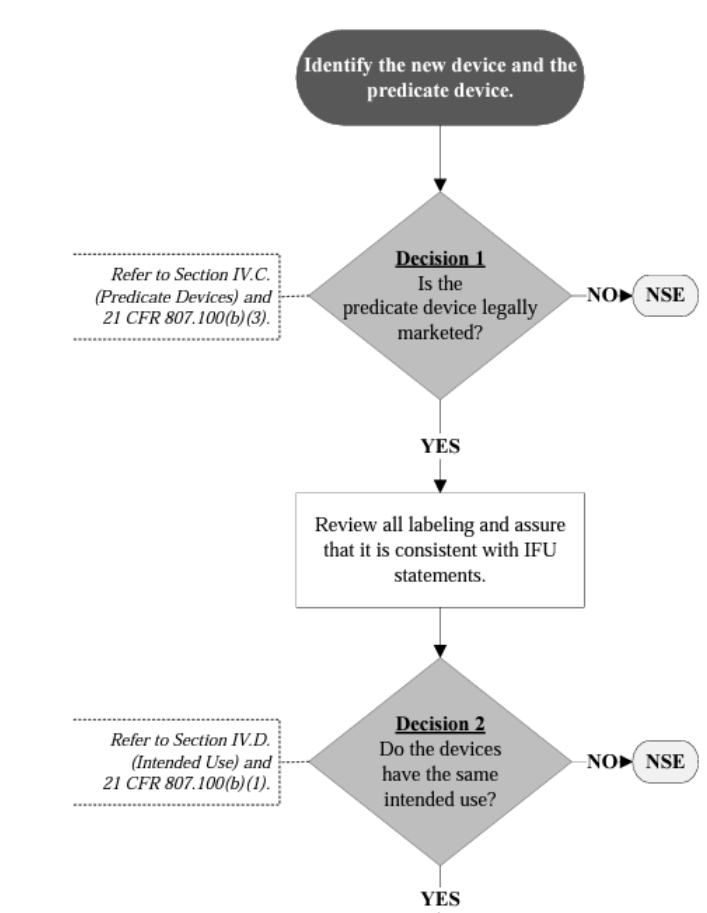
Writing Substantial Equivalence



- Identify Primary Predicate
- Review 510(k) Summary
- Intended use evaluation
- Indications evaluation

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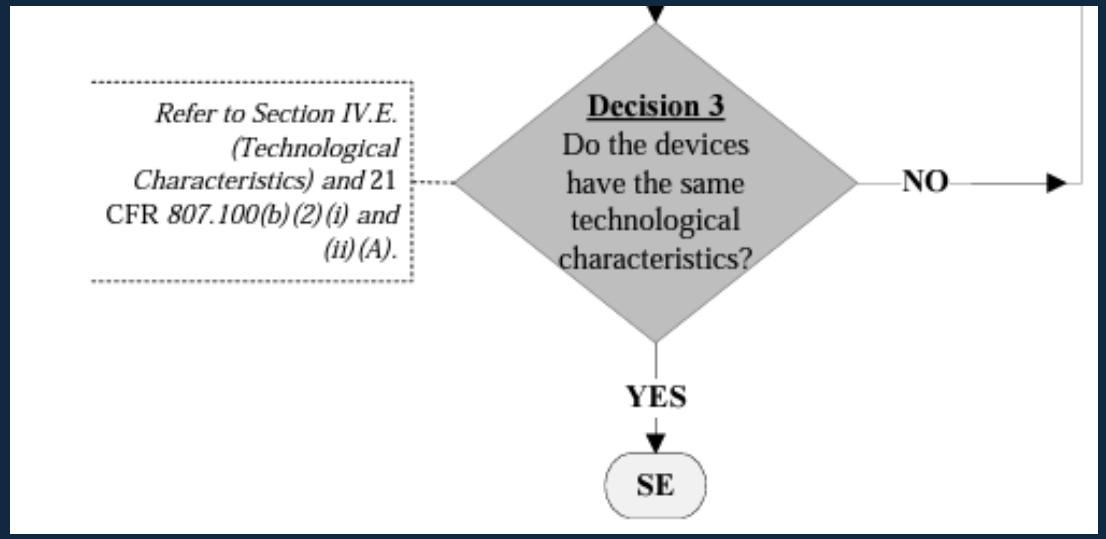
SE – Technologicial Characteristics

- Answer is almost always "No"



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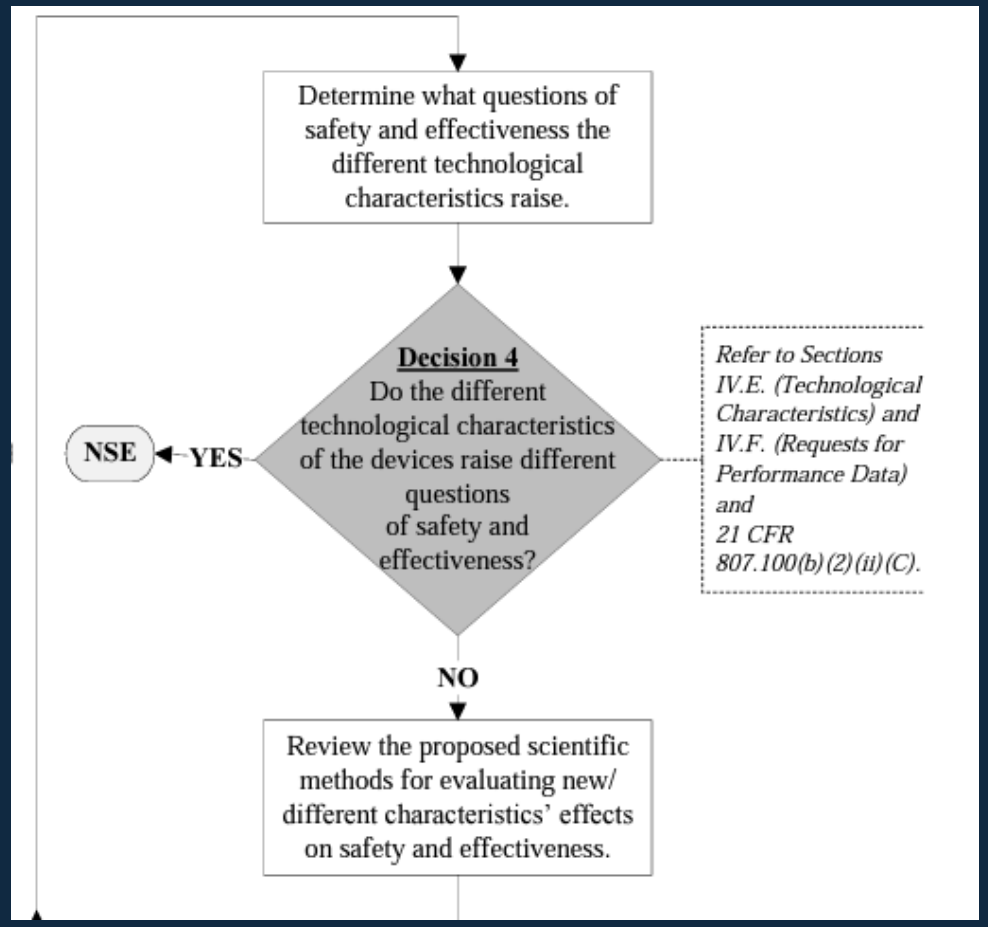
SE – Different Questions – S&E



- Evaluate previous testing required
- Evaluate risks
- What are the different technologies?

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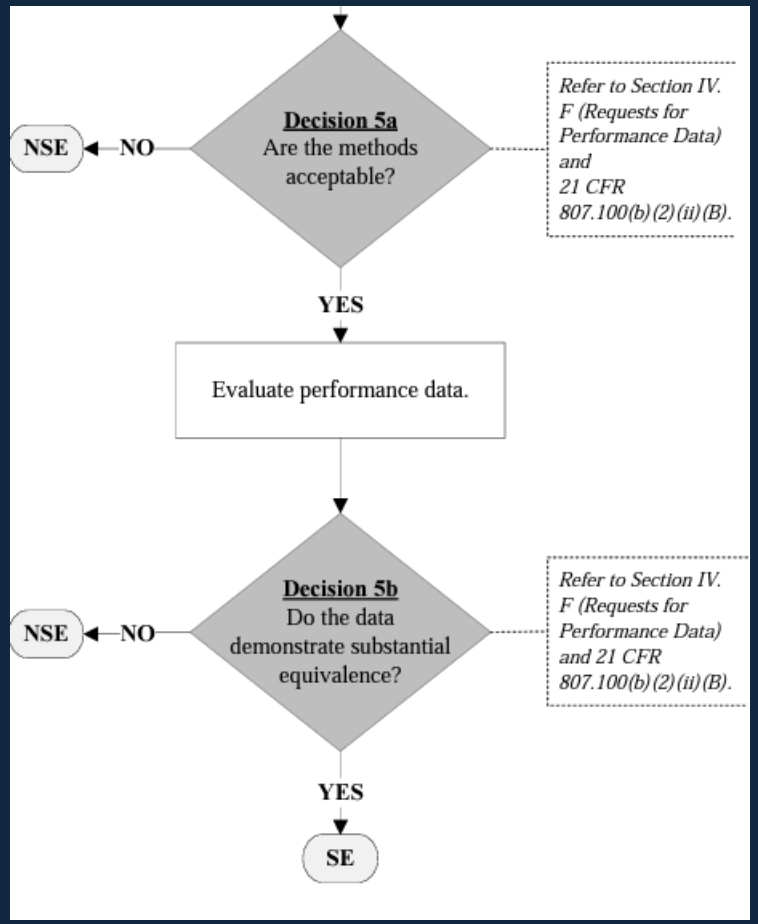
SE – Performance Data Evaluation



- 5a: Rare to state there are not acceptable methods
- 5b: Performance testing is reviewed and evaluated for equivalence

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510(k) Elements

- Cover Letter
- CDRH Coversheet
- Table of Contents
- Device Description
- Indications for use Form
- 510(k) Summary or Statement
- Truthful and Accuracy Statement
- Proposed Labeling, Labels, User Manual, Surgical Technique
- Substantial Equivalence Comparison
- Performance Testing

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510(k) – Content Example

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Assembling the 510(k)

- 510(k) Elements
  - Check against the RTA checklist or eSTAR
- Consistent Messaging
  - Check for differences or inaccuracies
- Consistent Formatting
  - Same font
  - Clear style throughout submission
  - Headings / Bookmarks
  - Table and Figures
  - Reference and footnotes

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510(k) Attachments

- Clearly reference attachments in the main 510(k) body
- Clearly name attachment
- Recommendation for Test Reports
  - Use Test Report Name, Test Report Number, and Attachment
- Organize Attachment in a clear manner
  - Order appearing in the 510(k)
  - Grouping attachments by type (e.g. Testing, Engineering drawings, labeling)

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eCopy Requirements

- FDA allows electronic submissions for 510(k)s [FOR NOW!]
- Starting October 1, 2023, all 510(k) submissions unless exempted* must be submitted as electronic submissions using eSTAR – which is different than eCopy
- eCopy can be submitted via CCP Portal or mailed in on CD or thumb drive
- Only allowed if the file meets specific naming and size requirements, e.g.,
  - Total File Size <1GB; Individual Volumes <50MB
  - File Names must begin with "001_[Description]" and go sequentially
  - NOTE – once loaded at FDA, reviewers do not see the 001 prefix, so reference accordingly.

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eCopy Resources

- eCopy requirements can still be used for all non-510(k) submission types, and there are benefits to using the traditional structure
  - Easier to navigate; easier to "tell your story"
- eCopy Guidance walks through all of the steps
- eSubmitter-eCopies Tool
  - Free, voluntary tool
  - Will ensure that file naming/sizing conventions are met
  - Will ensure no hidden software on CD/jump drive will delay your submission
  - Highly recommended – especially for larger submissions like IDEs and PMAs

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eSTAR Submissions

- electronic Submission Template And Resource (eSTAR)
- New interactive PDF form/template from CDRH
- Template includes:
  - Automation (for example, form construction and autofill)
  - Content and structure that is complementary to CDRH internal review templates
  - Integration of multiple resources (for example, guidances and databases)
  - Guided construction for each submission section
  - Automatic verification
- **October 1, 2023, all 510(k) submissions must be eSTAR**

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eSTAR Submissions (cont.)

- eSTAR ≠ eSubmitter
- eSTAR for non-IVD and IVD devices
- Location of eSTAR: https://www.fda.gov/medical-devices/how-study-and-market-your-device/voluntary-estar-program
- Relevant Guidance: Electronic Submission Template for Medical Device 510(k) Submissions (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-submission-template-medical-device-510k-submissions)

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eSTAR – Content / Structure

- Submission Type
- Cover Letter / Letter of Reference
- Submitter Information
- Pre-Submission Correspondence & Previous Interactions
- Standards
- Device Descriptions
- Indications for Use Form
- Classification
- Predicates and Substantial Equivalence
- Labeling
- Reprocessing
- Sterility
- Shelf Life
- Biocompatibility
- Software/Firmware
- Cybersecurity/Interoperability
- EMC, Electrical, Mechanical, Wireless and Thermal Safety
- Performance Testing
- References
- Administrative Documents
- AI Response

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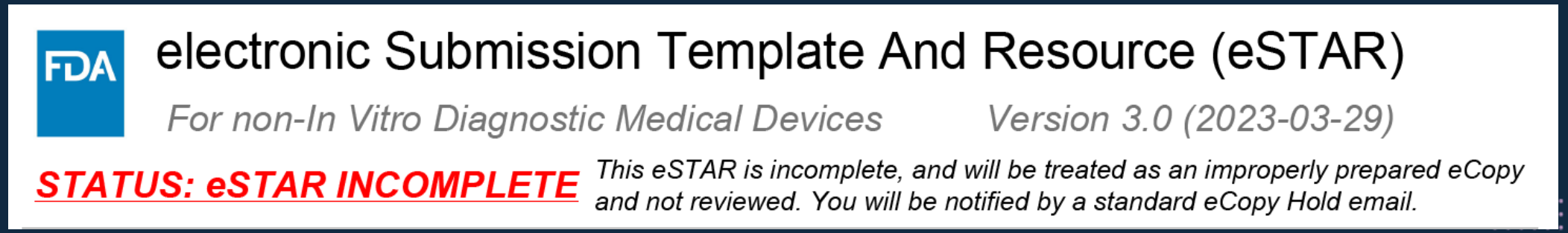
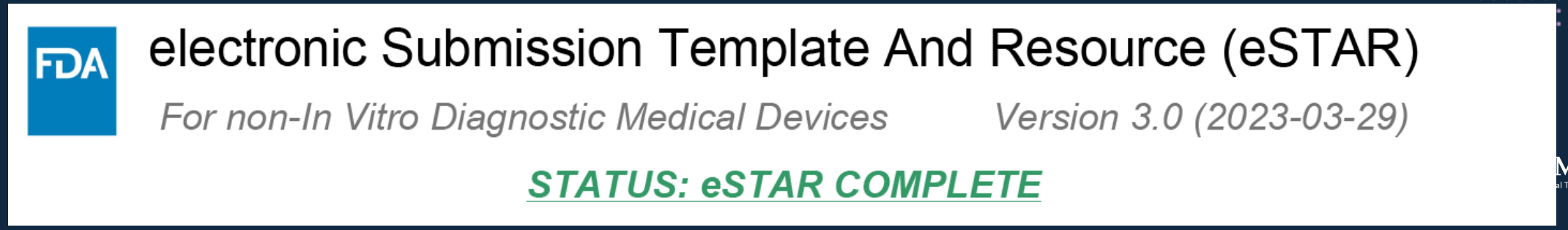
Navigating eSTAR

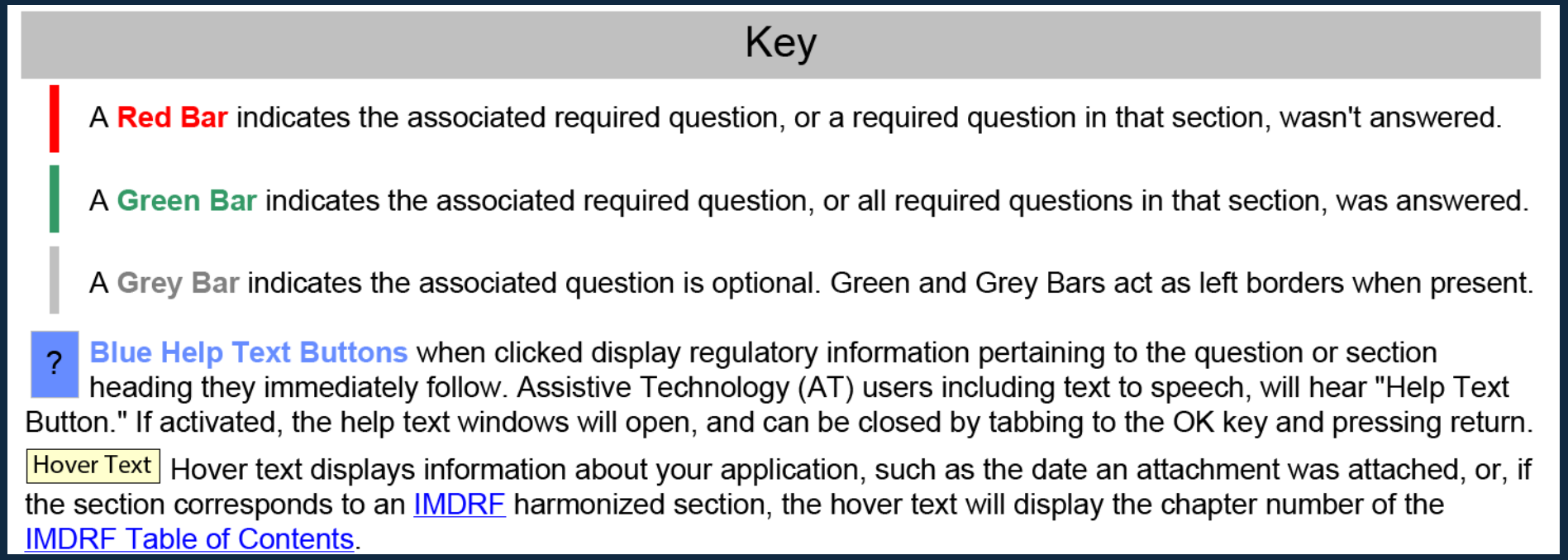
- Multiple sections
  - Dynamic sections based on what you answer
- Bookmarks
  - Note: if a section in not applicable the bookmark will not work





Navigating eSTAR

- Frequently Asked Questions (FAQ)
- Version History
- Key:



Key

A **Red Bar** indicates the associated required question, or a required question in that section, wasn't answered.

A **Green Bar** indicates the associated required question, or all required questions in that section, was answered.

A **Grey Bar** indicates the associated question is optional. Green and Grey Bars act as left borders when present.

? **Blue Help Text Buttons** when clicked display regulatory information pertaining to the question or section heading they immediately follow. Assistive Technology (AT) users including text to speech, will hear "Help Text Button." If activated, the help text windows will open, and can be closed by tabbing to the OK key and pressing return.

Hover Text Hover text displays information about your application, such as the date an attachment was attached, or, if the section corresponds to an IMDRF harmonized section, the hover text will display the chapter number of the IMDRF Table of Contents.

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eSTAR – Advantages & Disadvantages

- Advantages
  - No RTA review
  - Clearer requirements
  - Standard format
  - Known when the file is complete
  - All in one (IFU form, T&A, CDRH Form)
- Disadvantages
  - Technical Hold (RTA light?)
  - Learning curve
  - Version control
  - Not the most visually appealing document

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Advanced Medical Technology Association

eSTAR – Tips and Tricks

- Recommend Adobe Acrobat Pro
- Always download the most recent version
  - Do not rely on what was on your hard drive
  - FDA will update the eSTAR pdf
- Still need a standard template for sections
  - Either single file or multiple files format
- Attachments
  - Can be edited after attached
  - Allows for multiple file types for attachment (e.g. docx; pdf)
  - Large attachments slow down saving and opening the file

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eSTAR – Compiling

- Begin the administration steps of eSTAR
  - Recommend last step is attaching files
- Version control is key!
  - Keep yourself organized
    - Standard word templates
    - Standard folder structures
  - Recommend one owner of the eSTAR
  - Reviewers of associated sections and attachment
- First couple submission will take longer to compile

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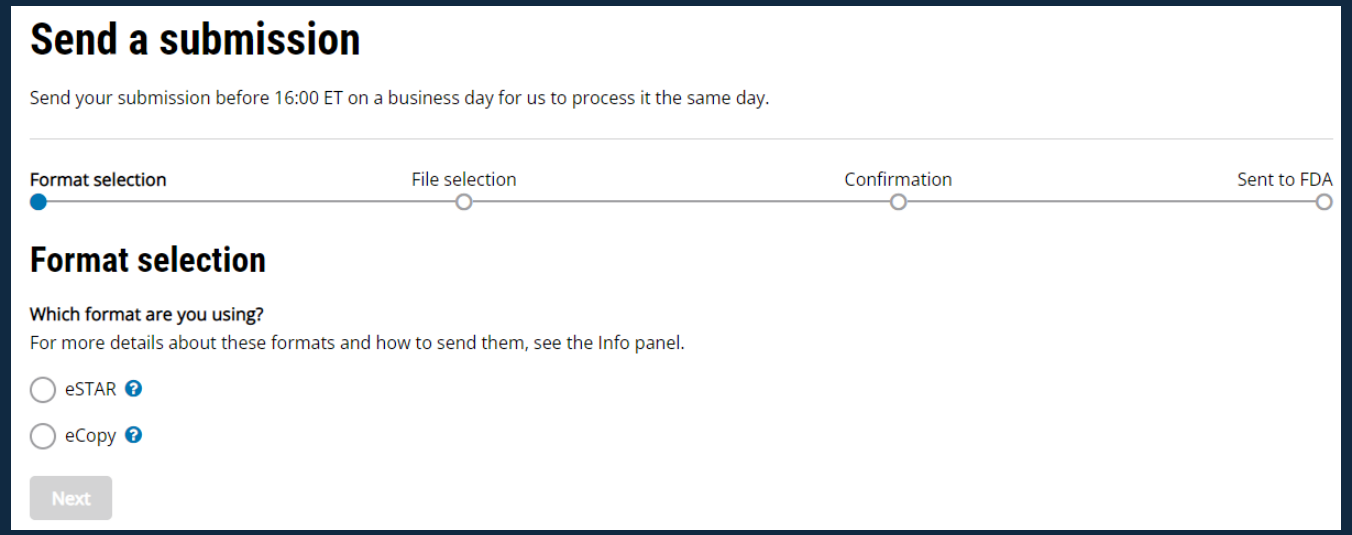
Submitting eSTAR

- Recommend FDA Customer Collaboration Portal (CCP)
  - Required starting October 1, 2023
- Create your own account: https://fda-cdrh.okta.com/signin/register
- Share status and tracking with others



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Thank you!

Dave McGurl: dmcgurl@mcra.com

Michael Nilo: michael.nilo@nilomedicalconsulting.com

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Advanced Medical Technology Association

U.S. FOOD & DRUG ADMINISTRATION

The FDA Review Process for Premarket Notification [510(k)]

AdvaMed 510(k) Workshop

May 15, 2023

Angela DeMarco, MS

Assistant Director, *510(k), 513(g), De Novo, Device Determination, Custom Devices Team*

Office of Regulatory Programs

Center for Devices and Radiological Health

Learning Objectives

MDUFA V REQUIREMENTS

THE 510(k) REVIEW PROCESS

SUB-PROGRAMS/POLICIES

HOW TO INTERACT WITH FDA DURING AND AFTER THE REVIEW PROCESS

MDUFA V REQUIREMENTS

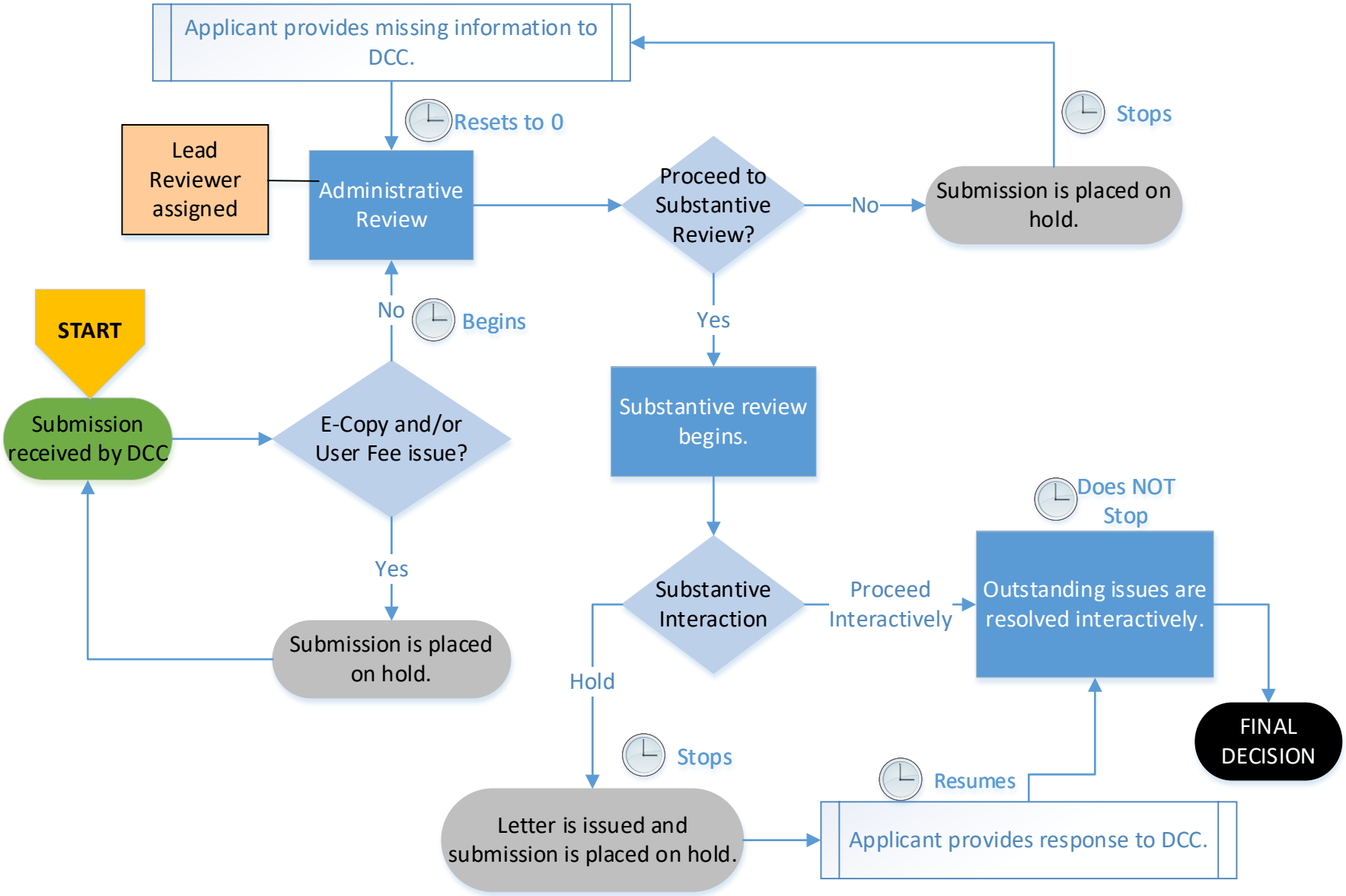
MDUFA V Review Milestones

NO CHANGES FROM MDUFA IV

- Acceptance Review (By day 15)
  - Acceptance decision
- Substantive Review (By day 60)
  - Substantive Interaction (SI) decision
- MDUFA Decision (By day 90)
  - Final decision
  - As needed, Missed MDUFA Decision (MMD) communication

THE 510(k) REVIEW PROCESS

Review Process Overview



Least Burdensome

We strive to implement the Least Burdensome principles, and expect the same from the submissions we receive.

Definition of Least Burdensome

The minimum amount of information necessary to adequately address a relevant regulatory question or issue through the most efficient manner at the right time.

- Reaffirms the statutory criteria for 510(k)
- Directs submitters and FDA reviewers to request and provide only that information required to show substantial equivalence
- Directs FDA reviewers to focus their efforts on required information in 21 CFR 807
- Congress enacted additional least burdensome provisions to the FD&C Act through the FDA Safety and Innovation Act (FDASIA) and the 21st Century Cures Act (21st Century Cures).

510(k) Preparation: Your Role

- Prepare/execute the regulatory strategy and plan
  - Prepare team for FDA questions
  - Help team determine if a 510(k) is needed for a modification to an existing device
- Coordinate preparation and review of the 510(k)
  - Assemble/write the 510(k) elements
  - Review the 510(k) prior to submitting to FDA
- Submit and confirm receipt of 510(k) documents

510(k) Review Process: Your Role

- Serve as the contact person for FDA
  - Coordinate all submission response documentation
    - Additional Information (AI) request letters, emails, or calls
    - Regulatory file maintenance
  - Serve as coordinator and lead for conference calls and meetings
- Identify individuals and resources needed for prompt responses
- Provide status updates to your management

510(k) Refuse to Accept Review

FDA completes the **Refuse to Accept (RTA)** checklist for non eSTAR submissions prior to beginning the substantive review.

Happens within the first 15 days of review.

These reviews are intended to identify:

1. Incorrect or inaccurate information as identified in the RTA checklist

2. If the review of the 510(k) can begin

RTA Guidance published April 21, 2022

The 510(k) Review

FDA Reviewers use a 510(k) review memo template.

All 510(k) reviews incorporate Least Burdensome Principles

Key elements of the review template:

- Company information including contact information
- Administrative content requirements per 21 CFR 807
- **Indications for Use / Intended Use**
- **Device Description**
- **Discussion of Technological Characteristics**
- **Product Labeling**
- **Performance Testing**
- **Discussion of Substantial Equivalence**

The 510(k) Review: Intended Use/Indications for Use

Purpose: Determine that the identified predicate is appropriate, and drives the information needed to support SE.

- Is the proposed intended use the same as the predicate(s)?
- Is it consistent throughout the submission and labeling?
  - Does the IFU make sense with the stated Device Description?
- Is data needed to support intended use and each designated indication?
- Is there new information regarding intended use or indications for this product/product type that will raise different types of questions during the review?

The 510(k) Review: Device Description

Purpose: Drives assessment of 510(k) content and supporting documentation.

- Is the Device Description clear?
  - Sufficient to understand how the device works
  - Explain materials, components, accessories, and how it interacts with other devices
  - Consistent with other parts of the submission (e.g., labelling)
- Is the device an implant?
- Does the device design use software?
- Is the device sterile?
- Is the device reusable/reprocessed single use?
- Are cleaning instructions needed and included?

The 510(k) Review: Discussion of Technological Characteristics

Purpose: To compare the subject device's characteristics to the predicate device's and explains how any differences do not render the device NSE.

- Is the primary predicate device selection, comparison, and analysis appropriate for this device?
- If multiple predicates are used, is the analysis for substantial equivalence (SE) performed for each identified predicate device?
- Are there scientific and/or clinical information/data/reports that support the SE comparison?
- Are there discrepancies between the subject and predicate devices (labeling or performance) that necessitate data sets or analysis in the performance testing sections?
- Have appropriate statistical techniques been implemented and interpreted correctly to support SE?

The 510(k) Review: Product Labeling

Purpose: Determine how the device is to be used by the end user. It also helps determine the intended use.

- Does the labeling meet the content requirements for this type of device, guidance, and/or regulations?
- Is the intended use/indications for use consistent throughout the labeling with appropriate content for each intended use and designated indication?
- Are the instructions for use adequate, comprehensive, and clearly written?
- Are the use of symbols properly addressed?
- Are the contraindications or limitations (if needed) clearly stated?
- Are scientific data/literature included to support the labeling as appropriate?

The 510(k) Review: Performance Testing

Purpose: Determine that the intended use and indications for use are supported by valid scientific evidence.

- Were appropriate data sets submitted for performance/bench, animal, and clinical testing as required for the device type?
- If manufacturing data is supplied, do processes appear to be stable and validated or verified?
- Is all labeling substantiated with data and appropriate analysis?
- Do questions remain about the science or clinical utility?
- Is the risk analysis/management complete and addresses all issues requiring mitigation?
- Are there questions of safety or effectiveness not answered by the applicant?

The 510(k) Review: Performance Testing

These are examples of the types of performance data. The requirements may differ depending on device type.
specific testing guidances associated w/these topics, and that eSTAR will walk a submitter through the appropriate questions

- Sterilization/Shelf Life/Reusability
- Software
  - e.g., Cybersecurity, Digital Health
- Electromagnetic Compatibility and Electrical, Mechanical, and Thermal Safety
- Combination product

The 510(k) Review: Performance Testing

Devices reviewed by OHT7 may have additional requirements not necessarily required by other OHTs.

- For IVD products, were CLSI (or appropriate) protocols followed with robust data analysis?

- IVD's have specific performance characteristics, which include:
  - Precision/reproducibility
  - Accuracy
  - Sensitivity
  - Analytical specificity

OHT = Office of Health Technology

The 510(k) Review: Discussion of Substantial Equivalence

Purpose: Compare the subject device to the predicate device(s). This is done sequentially during the course of review.

Does the analysis through the 510(k) flowchart lead to an SE decision?

- Is the predicate device legally marketed/does a predicate device exist?
- Same intended use?
  - If not, are there different types of questions of S&E?
- Same technological characteristics?
  - If not, are there different types of questions of S&E?
- Do acceptable scientific methods exist to assess differences?
- Do the data demonstrate substantial equivalence?

SUB-PROGRAMS/POLICIES

eSTAR

eSTAR Webpage
eSTAR Guidance published September 22, 2022

- Voluntary use right now
  - **Mandatory starting October 2023**
- Dynamic pdf template for assembling submission
- Modeled after the SMART review template used by review staff
- No RTA review

Safety and Performance Based Pathway: Overview

Final Guidance issued September 2019

- Optional program
- Expands on existing Abbreviated 510(k) Program
- Removes requirement for direct predicate comparison testing for some performance characteristics
  - You can meet FDA-identified performance criteria to demonstrate that the device is as safe and effective as predicate device
- Supports least burdensome provisions

Safety and Performance Based Pathway: Eligibility Criteria

Please note that it is a Safety and Performance Based Pathway submission in the cover letter

- Eligible device type
  - Check webpage for device-specific guidances
    - Currently, there are 9 eligible device types
- New device meets all FDA-identified performance criteria
- Performance criteria align with performance of at least one legally marketed device of the same device type

Special 510(k) Program

Final Guidance issued September 13, 2019

- The proposed change is made and submitted by the manufacturer authorized to market the existing device, **and**
- Performance data are unnecessary, or if performance data are necessary, well-established methods are available to evaluate the change, **and**
- All performance data necessary to support substantial equivalence can be reviewed in a summary or risk analysis format

Special 510(k) Program

Focus is on whether testing methods are available for the change, and whether those methods are well-established

- The change can be labeling/IFU or technology
- All methods used in subject 510(k) should be well-established, e.g.:
  - Those used in the previously-cleared 510(k)
  - Methods in a recognized consensus standard
  - Widely available and accepted methods, or those in another premarket submission
- If there is not a well-established method, FDA intends to convert the submission to a Traditional

Third Party Review Program

A list of accredited Third Party Review Organizations (TPROs) and eligible product codes are available on the webpage.

- Applicant submits their 510(k) to the TPRO for initial review
- When complete, the 510(k) is submitted to FDA by the TPRO
  - All subsequent communication with FDA will be through the TPRO
- FDA supervisory review should be conducted within 30 days of receipt
- No user fees are required to FDA

Third Party Review Program Final Guidance

What's New in Third Party?

- August 2022 transition to ORP/Div1
  - Same contact email 3P510k@fda.hhs.gov
- Training workshop held May 2023
- Coordination with EUA transition
  - Several EUA products are Third Party eligible

Making Changes During the Review Process

FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Goals
(Final October 3, 2022)

- It is possible that small changes will be made to the product during the review process
  - Always check with the review team if you are unsure

- Use FDA's changes/modifications guidances (or your internal modifications procedure) to help your decision process whether to implement the changes while the product is under review or wait until post clearance

Making Changes During the Review Process

If changes are significant, speak with FDA immediately to get guidance on next steps

- Unsolicited significant changes such as design, intended use, labeling, or technology changes that require review teams to re-start their review will typically require a new 510(k)

- As the Regulatory project leader
  - Remain aware of **all** changes to the product once submitted to FDA (keep a documented log)
  - Have an assessment process to determine what is significant to the safety and effectiveness or substantial equivalence determination for each change, and in total

Pilot Program: ASCA

ASCA Webpage

- Voluntary program aimed at:
  - Increasing consistency and predictability in assessing conformance with FDA-recognized standards
  - Enhancing the FDA's confidence in test methods and results
  - Decreasing need for additional information related to conformance with a standard
- Eligible tests: biocompatibility and EMC/electrical safety
- For more information:
  - ASCA Pilot guidance
  - ASCA@fda.hhs.gov

HOW TO INTERACT WITH FDA DURING AND AFTER THE REVIEW PROCESS

Tips when preparing a 510(k)

- Review current policies for your proposed device type
  - eSTAR template
  - Guidance documents
  - Voluntary consensus standards
- Include justifications for any deviation made
  - E.g., utilized an alternate test method, chose not to use a guidance document (not recommended)

Additional Information (AI) Request

Depending on the complexity of the questions, your submission could be placed on hold

- If there are questions during the review, you will receive notice from the lead reviewer
- Simple questions may be asked interactively via email
- AI hold letters are sent via email and contain a list of deficiencies noted by the review team.
  - These requests will be sent out around Day 60 of the review cycle.

Additional Information (AI) Request

Interactive Request	Hold Letter
• The due date is often negotiable, but typically within 2-5 days of the requested date. • Typically reserved for minor clarifications when asked before a hold. • Standard procedure for obtaining final clarifying information following a response to a hold.	• Issued around FDA Day 60 • An automatic 180-day hold is granted – you do not need to send in an extension request every 30 days. • The maximum hold time is 180 days from the date of the hold. • Typically reserved for more complex issues that require more in depth responses.

If we do not receive a response to the hold by Day 180, we consider the file withdrawn and will notify you as such.

Deficiencies within a Hold Letter

Major and Minor deficiencies are expected to be addressed in response to a hold letter.

- **Major deficiencies:** if not resolved, will preclude a favorable decision on the marketing application.
- **Minor deficiencies:** resolved in a straightforward manner, need to be addressed to meet regulatory requirements or to prevent potential misbranding or adulteration.
- **Additional considerations** are suggestions, recommendations, or requests that are not expected to preclude a favorable decision on the marketing application.

Deficiencies Guidance Document (October 26, 2022):
https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073680.pdf

Common 510(k) Hold Issues

A hold letter should not contain only Minor Deficiencies

- Clarification regarding the intended use or indications for use
  - Can include unsubstantiated claims in the labeling
- Specific or general guidance/standard not followed
  - Especially without scientific justification or prior agreement
- Data required to show substantial equivalence are incomplete, inconclusive, conflicting, lead to new questions, or new types of questions
- Statistical data analysis methods or evaluation criteria

Handling Requests for Additional Information

If you have questions or need clarification,
contact the lead reviewer ASAP prior to submitting your response.

The formal response is not an opportunity to request additional clarification.

Day-10 Call

What it IS

- Teleconference requested w/in 10 days of an AI Letter date
- Obtain clarifications about the deficiencies
- Determine need for a Submission Issue Request (SIR)

What it is NOT

- Review of additional information
- Discussion of issues unrelated to the deficiencies
- In place of a SIR

If there is still disagreement after the Day-10 Call, you must decide whether to submit a response or go to the next level

Handling Requests for Additional Information

Least Burdensome (LB) Flag

What it IS	What it is NOT
• Opportunity to address LB discrepancies in an AI letter • Opportunity for submitter to address situations when they feel they are being held to a different standard	• An Appeal Meeting • Change to 180 Response deadline

Submit the LB Flag as an email that includes a 1-2 page summary:

- Disagreement(s) limited to 2 topic areas
- Relevant prior communications
- Proposed path forward

Responding to Requests for Additional Information

- All responses are part of the official 510(k) record
- Submit formal responses (i.e., response to a hold letter) to the DCC or the portal (**not the reviewer**), referencing the original 510(k) number
  - Must have a valid eCopy or eSTAR
  - Must be a complete response - do not submit the response in sections or pieces

Deficiencies Guidance Document (October 26, 2022):
https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073680.pdf

Responding to Requests for Additional Information

- Responses should clearly identify the Section and Page in which the responses to each question can be identified.
  - E.g., “Response to Item 1 from the Additional Information Letter can be found in Section 3, page 5.”
- Answer the questions asked
  - Do not provide unsolicited information that constitutes a new indication for use or a new or different technology as this could necessitate a new 510(k)

Responding to Requests for Additional Information

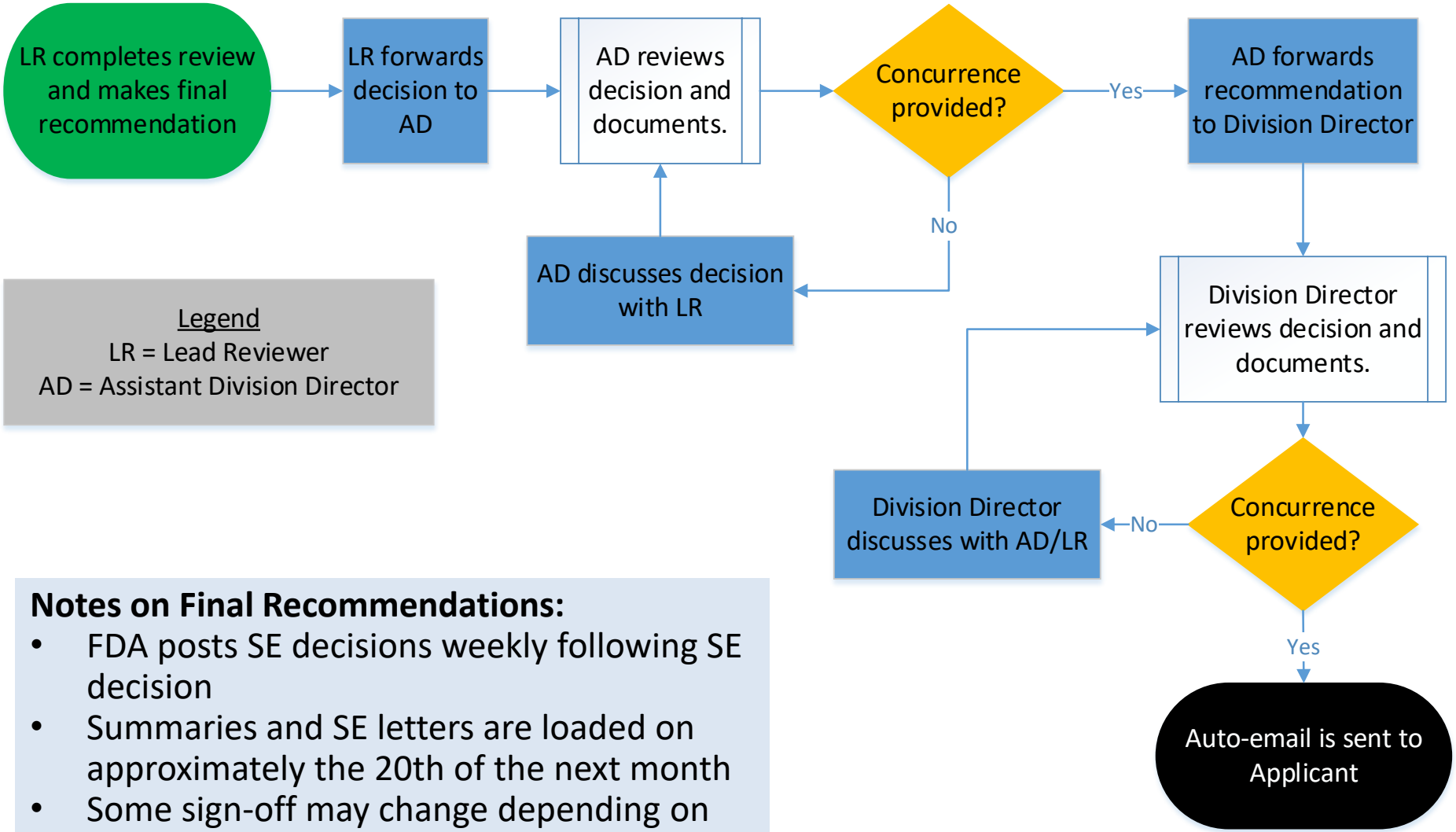
- Provide a complete response to each deficiency in a clear and comprehensive manner
  - Promissory notes for data requests do not constitute a complete response
- Expect the same level of review on the responses as with the original submission
- Be mindful of the calendar due to the MDUFA V shared Total Time to Decision (TTD) goal

Handling Post-Hold Interactions

Ensure availability during this time as additional questions will be asked interactively. Lack of response could lead to an unfavorable decision.

- All communication with the lead reviewer will be via email and/or phone.
- The lead reviewer will send interactive requests for additional information based on the responses provided.
- The time frame for a response will be dependent on the impending review deadline, information requested and time to review the response.
  - If you anticipate additional time is needed, contact the reviewer immediately.

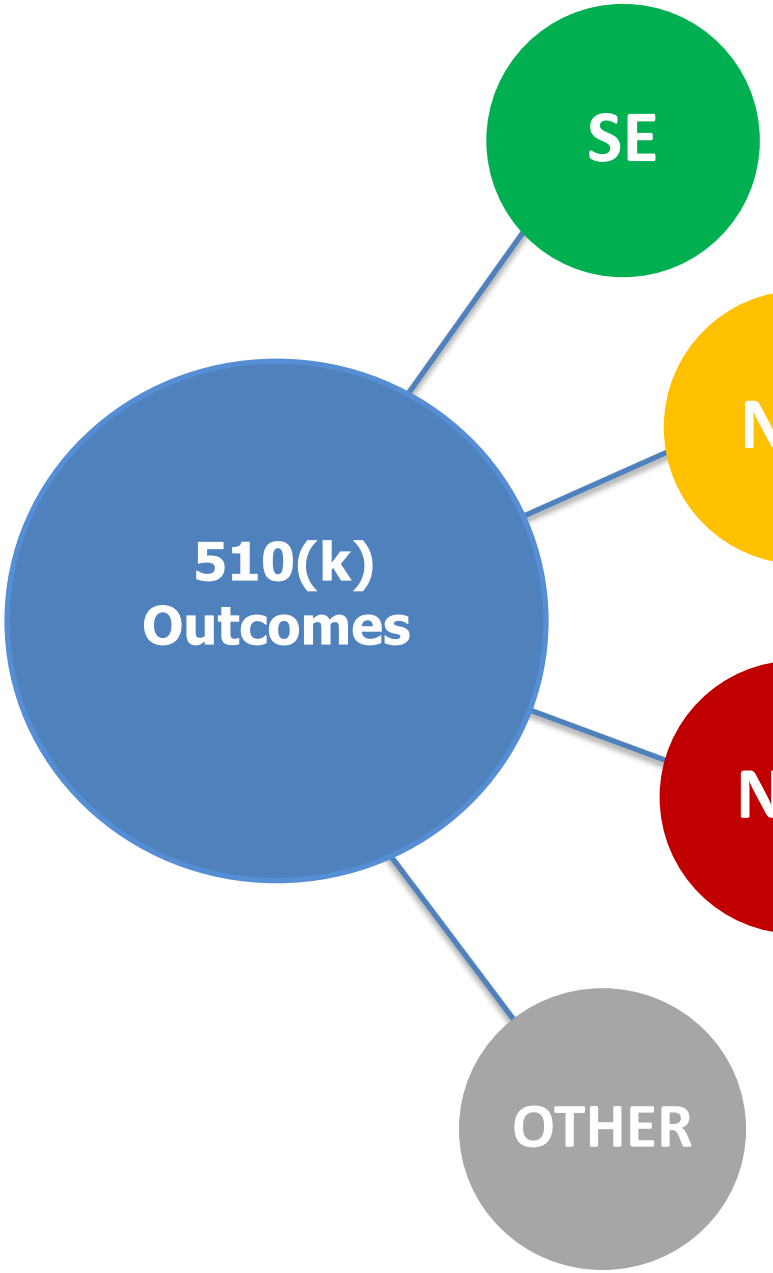
Processing a Final Recommendation



Notes on Final Recommendations:

- FDA posts SE decisions weekly following SE decision
- Summaries and SE letters are loaded on approximately the 20th of the next month
- Some sign-off may change depending on decision being rendered

Final Recommendations



- FDA Classifies and assigns regulation and product code

- Inadequate performance data and/or response
- Can't go to market yet
- Try again with a new 510(k)

- NSE for lack of predicate, new intended use, or different questions
- Can't go to market
- Possible de novo or PMA

- No 510(k) needed
- E.g., exempt device that does not exceed limitations, not a medical device

Options following an NSE Decision

- Ask clarification questions
  - Lead reviewer for technical questions
  - 510(k) Program for policy questions

- Submit a pre-submission to discuss proposed plan for new submission

- Appeal the decision
  - Consult the Ombudsman at CDRHOmbudsman@fda.hhs.gov
  - CDRH Appeals Guidance

ADDITIONAL ITEMS OF NOTE

Things to Note

- Multiple Center reviews can happen
  - CDRH/CBER
  - CDRH/CDER
- You may show the device at a trade show while it is under FDA review.
  - Label the device “Pending FDA 510(k) Review and Clearance”
  - The “pre-sale” literature cannot state an intended use, indications for use, or contain any assertion of product performance
  - Do not take orders and/or money for a device under 510(k) review even if you don’t ship it for use by the customer

Have a General Policy Question?

- Division of Industry and Consumer Education: DICE@fda.hhs.gov
- Office of Regulatory Programs / Division of Submission Support: (301)-796-5640
  - 510(k)/513(g): 510k_program@fda.hhs.gov
  - Third Party 510(k) Program: 3P510K@fda.hhs.gov
  - Device Determination: DeviceDetermination@fda.hhs.gov
  - Q-Submission, PMA, HDE, & De Novo: opeqsubmissionsupport@fda.hhs.gov


FDA
U.S. FOOD & DRUG
ADMINISTRATION

CDRH Ombudsman Program: Roles, Responsibilities, and the Appeals Process

AdvaMed Workshop

Ken Skodacek
CDRH Deputy Ombudsman
May 15, 2023

Background & Experience

20 years - Industry

10 years - CDRH

5 years - Ombuds

* Other Activities

Why did I join FDA?

What is an ombuds?

om·buds·man

/ˈämbədzmən/

noun

an official appointed to investigate individuals' complaints against maladministration, especially that of public authorities.

Ombuds Standards of Practice

Confidential

Independent

Impartial

CDRH Ombudsman Program

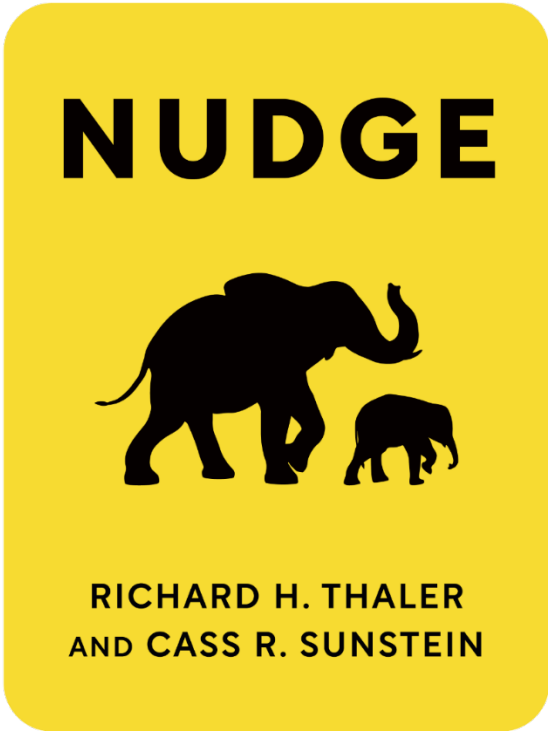
- Voluntary resource to manufacturers, consumers, & CDRH
- Direct, unrestricted access to CDRH staff at all levels
- High level of organizational, personnel, & regulatory awareness
- Encourages clear, candid, & constructive communication
- Focused on resolving differences in regulatory and/or scientific opinions, both external & internal
- Helps to resolve misunderstandings
- Ensures fairness in processes, including appeals

What is our role?

No, not this

More like this

Or this



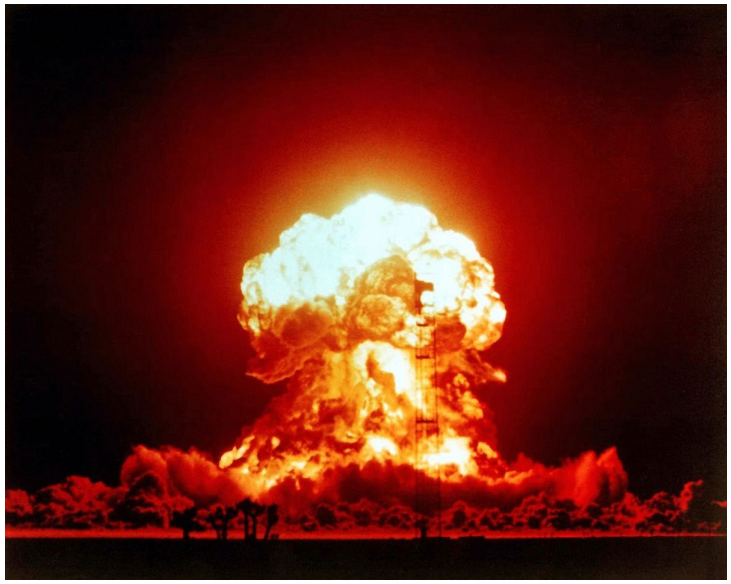
What is the “ombuds process”?

- Confidential conversation(s)
- Review of options
- Provide advice as requested

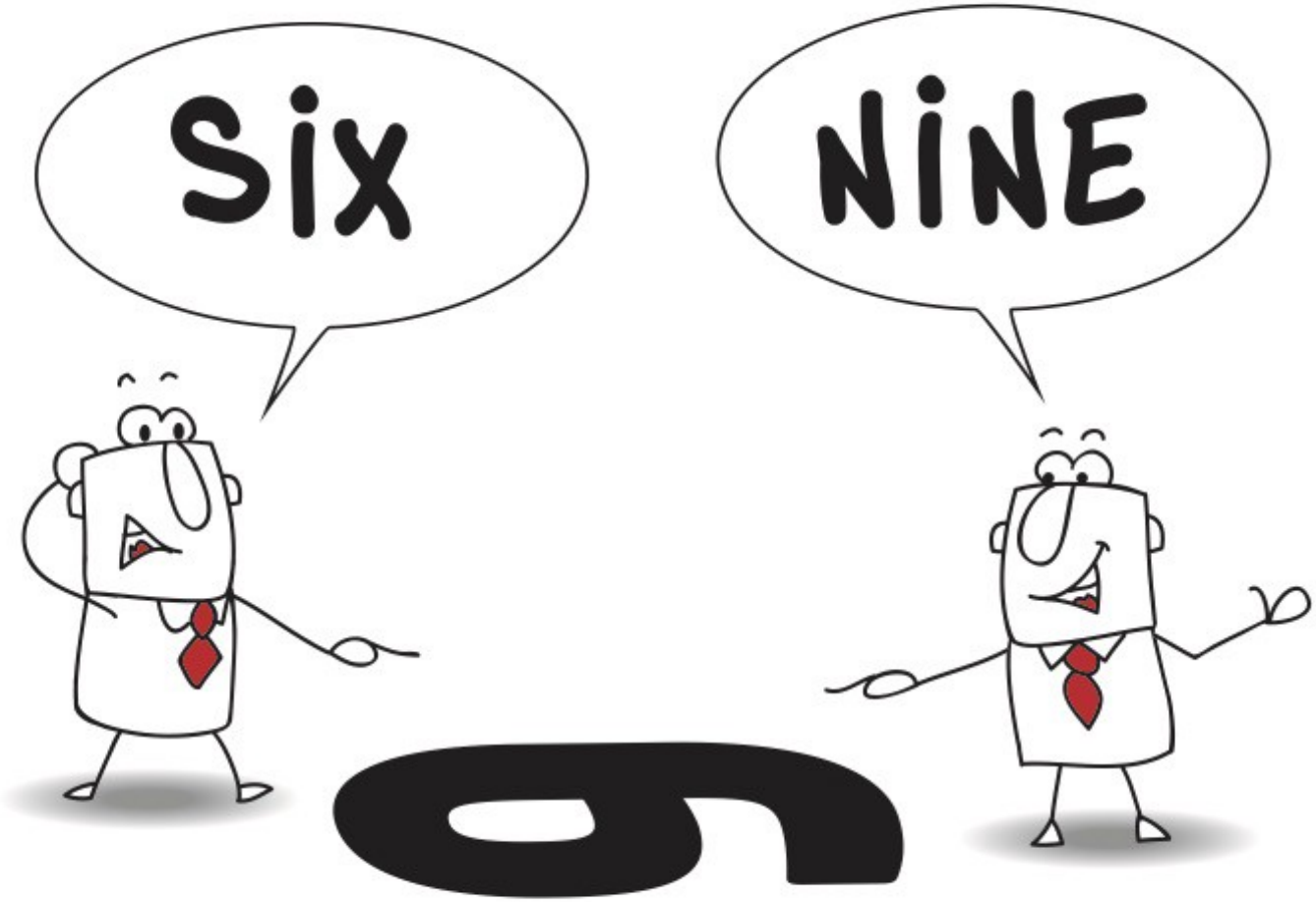
- Contact FDA staff and/or leadership
- Join internal meeting(s)
- Join external meeting(s)
- Additional follow-up conversations

CDRH Ombudsman Program is not

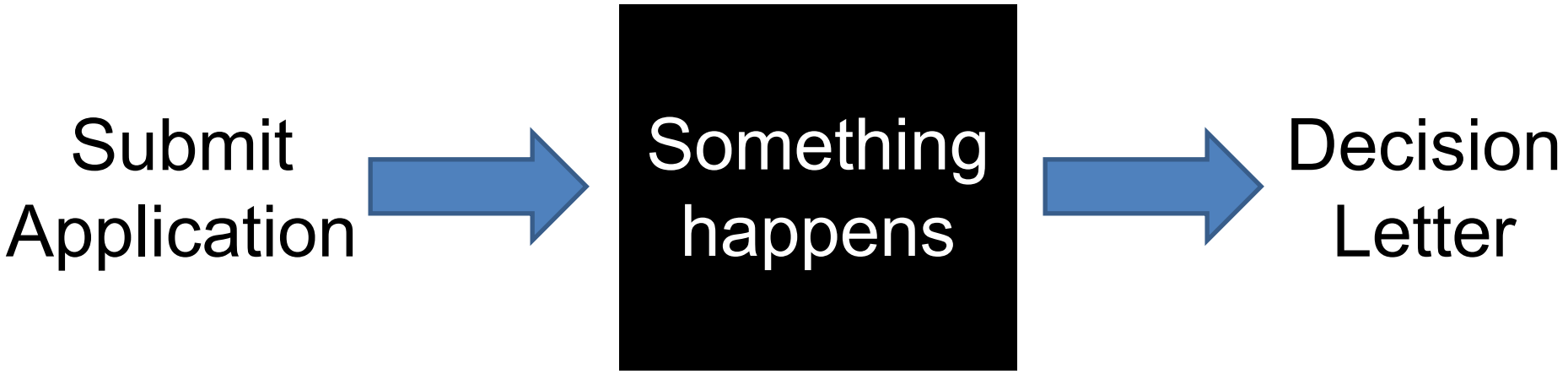
- 1st Option
- Only Option
- Nuclear Option



Expect Disagreements



Manufacturers View of the FDA Process



Unfulfilled Expectations

Beliefs vs. Supporting Data

In God we trust;

all others must bring data.

FDA Commissioner Robert Califf

Manufacturer & FDA

Manufacturer

More experience with specific device

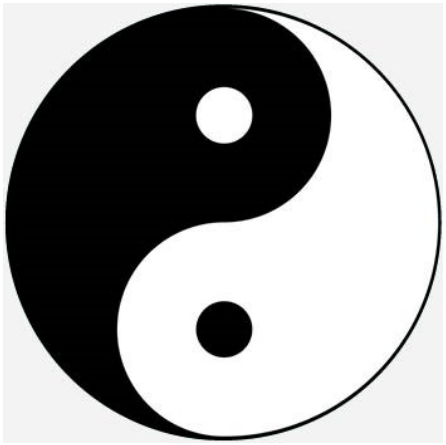
Familiarity with history

May have expert consultants (or not)

Focused on specific device

Perspective naturally influenced

Limited finances ($ in bank)



FDA

Experience with other devices

Limited perspective from submission

Specialized expertise as an organization

Juggling submissions

Small review team with fresh perspective

Limited time (statutory or MDUFA goals)

Considering contacting us?

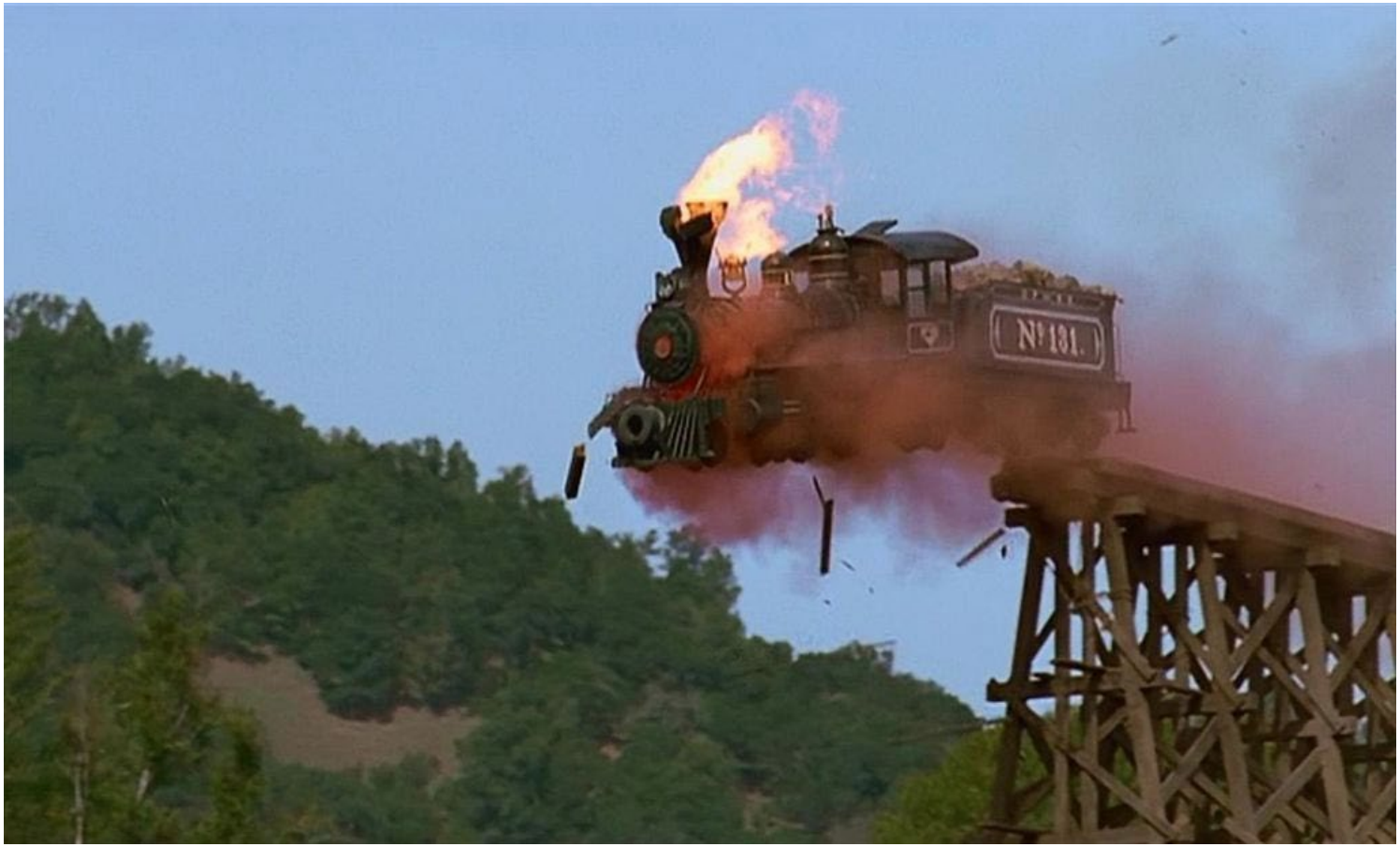
If / When

Consider Your Many Options

Does something seem “off”?

When should I contact you?

Figure 1: This is too late.



Hard Line for Regulatory Decisions

Before Final Decision	After Final Decision
Many Options	One Option

21 CFR Part 10.75 & 800.75

CDRH

FDA

"Request for Supervisory Review" – AKA "appeal"

Internal Agency Review of Decisions

- Decision of an FDA employee is subject to review by the employee's supervisor
- Review made by consultation between the employee and the supervisor or by review of the administrative file
- Interested person outside the agency may request internal agency review of a decision
- Internal agency review of a decision must be based on the information in the administrative file

Primary Appeal Resources

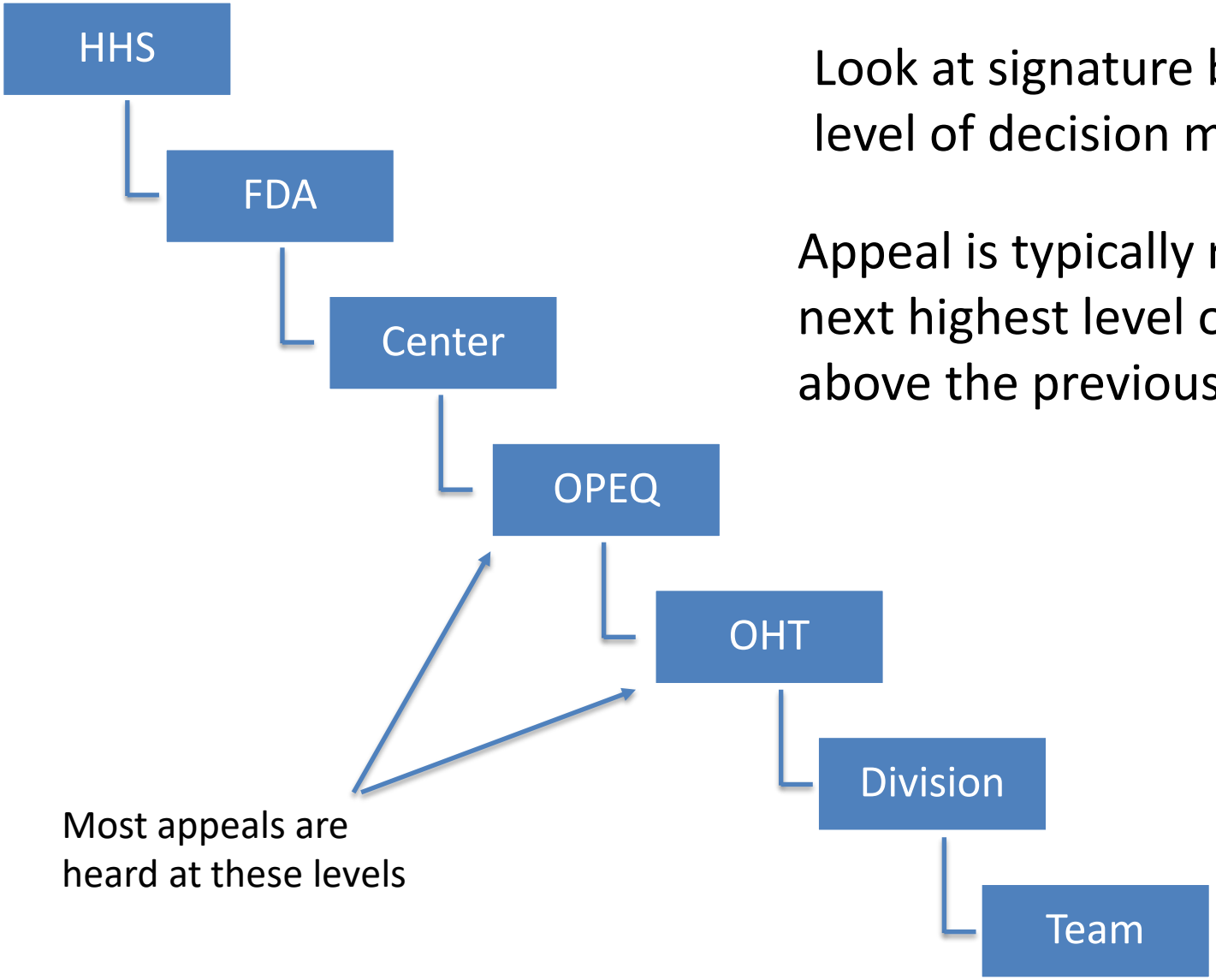
21 CFR 10.75 Internal Agency Review (FDA)

21 CFR 800.75 Request for Supervisory Review (CDRH)

CDRH Appeals Processes

CDRH Appeals Processes - Questions and Answers about 517A

Level of Appeal



Look at signature block for level of decision maker.

Appeal is typically reviewed at the next highest level of authority above the previous decision.

517A (Significant) Decisions

- 510(k): Not Substantially Equivalent; Substantially Equivalent
- PMA/HDE: Not Approvable; Approvable; Approval; Denial
- Breakthrough Devices Designation: Granted; Denied
- IDE: Disapproval; Approval; Approval with Conditions

Also refer to 21 CFR 800.75

Examples of Other Decisions

- 510(k) Requests for Additional Information
- PMA Major Deficiency Letter
- De Novo Final Decisions
- De Novo Requests for Additional Information
- HDE Requests for Additional Information
- 510(k) and PMA Refuse to Accept Letters
- 510(k) Deletions
- Postmarket Surveillance Orders (Section 522)
- CLIA Waiver Decisions
- Warning Letters
- Import Certificates
- 513(g) Letter
- PMA Refuse to File (see 814.42(d)(2))*

Requesting Substantive Summary

- Defined in 517A and guidance
- Scientific and regulatory rationale for decision
- Controversies and differences of opinion
- Consideration and application of least burdensome requirements

Potentially Insightful

We recommend that you make your request as quickly as possible as an amendment to the file, in preparation for submitting an appeal. You may also request copies of the associated review memos via FOIA as a first party, though you probably won't receive the information quickly enough to support your preparation for an appeal.

Submitting an Appeal

- Submit appeal to CDRH (e.g. to Doc Control Center as an amendment for premarket submissions)
- Opening statement: request for supervisory review per 10.75 (appeal)
- Preferred venue: meeting (telecon or in-person) or no meeting
- Summary of situation and basis for appeal
- Closing statement with specific requests
- Attachments with supporting documentation*

Appeal Timelines

You

30 days to appeal for 517A decisions

"Appeals received by the Center later than 30 days after the date of a significant decision are not eligible for review under section 10.75. FDA recommends that a 10.75 appeal of any decision be submitted within 30 days of the decision, but we will generally permit greater flexibility with respect to the timeframe of appeals of actions that are not significant decisions. Generally, appeals of other decisions received after 60 days would be untimely."

FDA

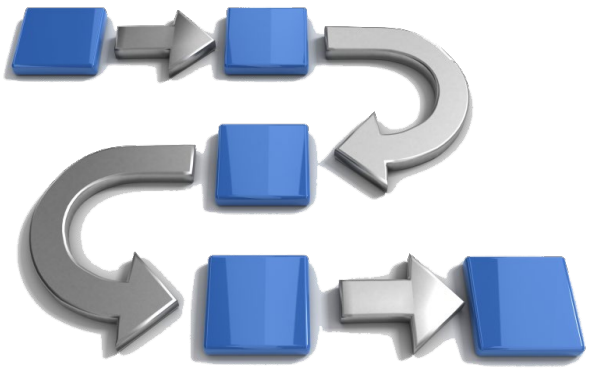
30 days to schedule meeting
+ 30 days to issue decision

OR

45 days to issue decision without a meeting

Appeal Process for CDRH

1. Receive and review request for appeal
   Accept or deny request
2. Assignment to and briefing of appeal authority
   Schedule meeting date and time
3. Preparatory meeting (internal to CDRH)
4. Meeting with applicant
5. Post-meeting discussion (internal to CDRH)
6. Preparation and review of decision letter
7. Decision letter issued by email



Appeal Meeting

- Review Authority

Focus

- Ombudsman Program
- Regulatory Advisor(s)
- Team Staff
- Team Management
- Program Staff
- Program Management

Be prepared for questions during the 1-hour meeting and be prepared to provide additional clarifying information after the meeting.

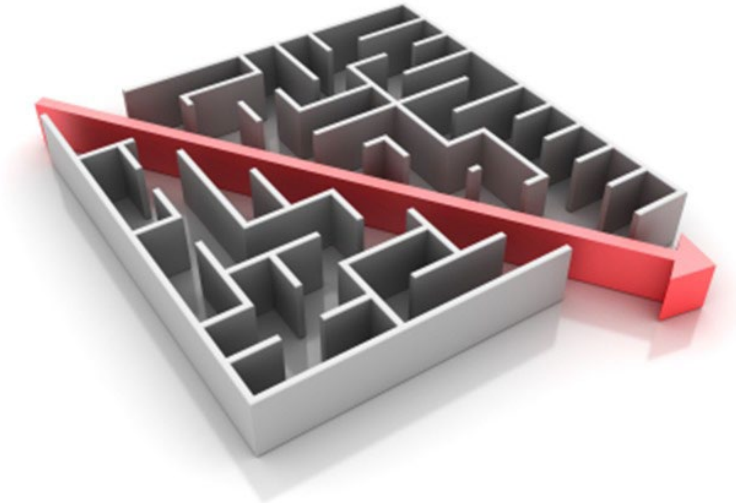
Outcomes of Appeals

A Decision Fully Overturned

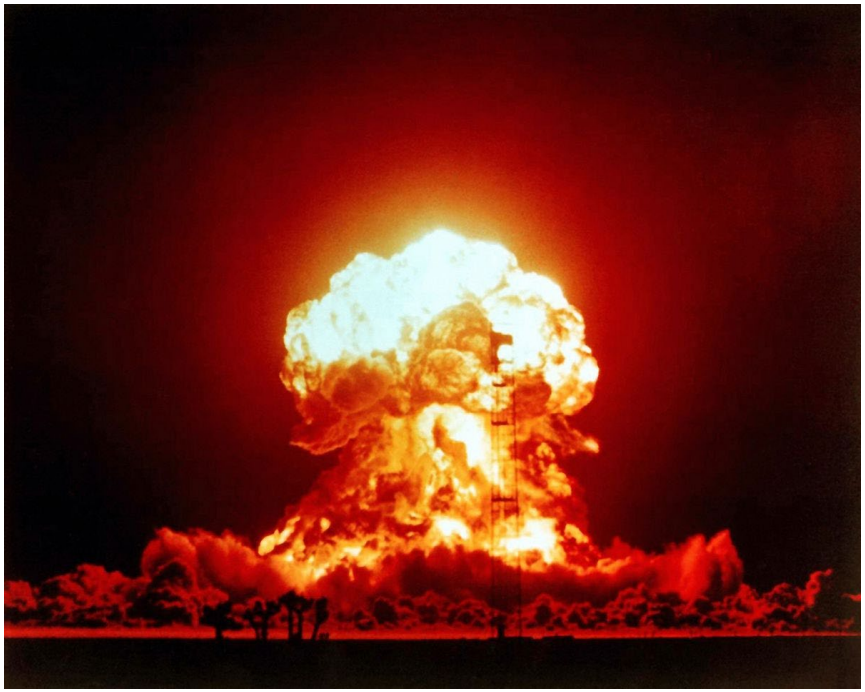
B Decision Partially Overturned

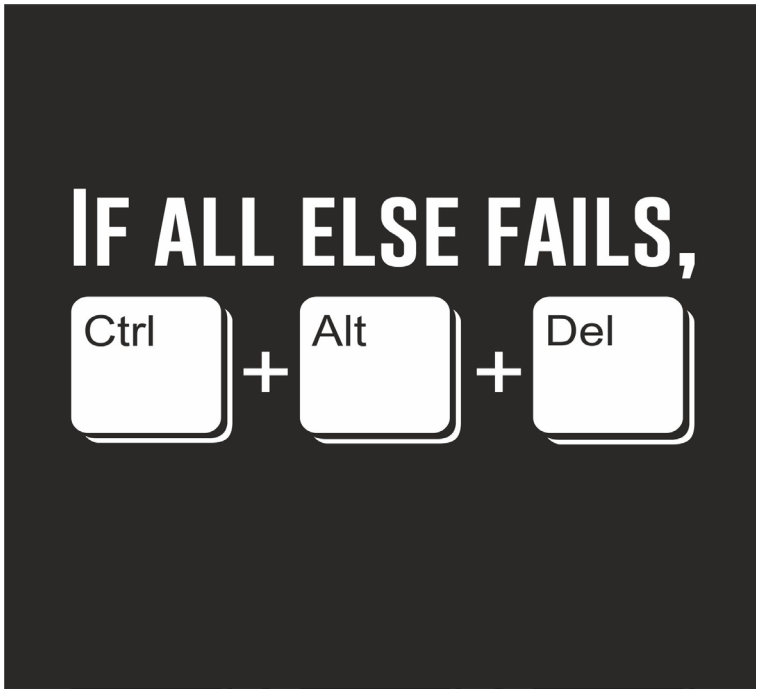
C Decision Fully Upheld

Clarity in rationale & potential paths forward



Are you considering AN APPEAL?





Non-Retaliation & Fairness

"Without question, companies are free to vigorously challenge agency positions and requirements, and to freely voice their views to the agency, the press, the public, and the Congress."

"The Center is strongly committed to ensuring that interactions with entities doing business with the Center are free from bias or retaliation at every stage, including the filing of an appeal of a Center action."

https://www.fda.gov/about-fda/office-chief-scientist/non-retaliation-policy

Insight: Other Options

ANOTHER OPTION

Informal Discussion about ***Next Steps***

Insight: Least Burdensome

Least Burdensome Provisions - Concept and Principles

Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions

Insight: Benefit/Risk

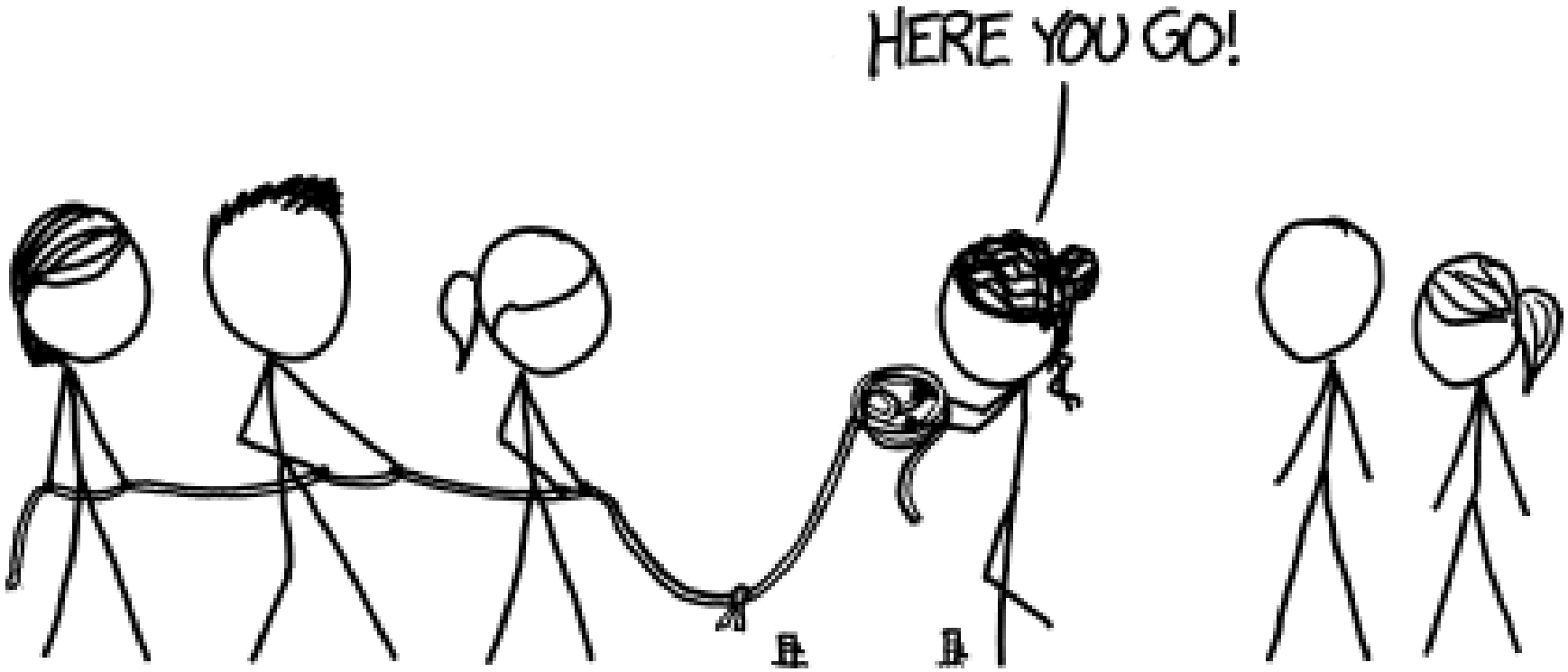
Benefit-Risk Factors to Consider When Determining Substantial Equivalence in **Premarket Notifications (510(k))** with Different Technological Characteristics

Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device **Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions** (DRAFT)

Factors to Consider When Making Benefit-Risk Determinations for Medical Device **Investigational Device Exemptions**

Factors to Consider Regarding Benefit-Risk in Medical Device **Product Availability, Compliance, and Enforcement Decisions**

Insight: Shared Goals



This is not a competition with FDA.

Insight: Support

Insight: Non-Decisions

Can I appeal feedback from a Q-Submission?

Can I appeal IDE Study Design Considerations?

Can I appeal a withdrawn submission?

Can I appeal observations from a Form 483?


TIME FOR QUESTIONS

Ken.Skodacek@fda.hhs.gov
301-796-6364
CDRH Deputy Ombudsman

Abiy.Desta@fda.hhs.gov
301-796-0293
CDRH Ombudsman

CDRHOmbudsman@fda.hhs.gov

For ORA-related matters (inspections, importation, etc.),
you can also contact Erica Katherine, ORAOmbudsman@fda.hhs.gov.

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Clearance: Launch and After

510(k) Submissions Workshop
May 15-17, 2023

Tony Blank
Tblank@AtriCure.com

What Clearance Means

- A finding that the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA).
- Issuance of a substantial equivalence determination does not mean that FDA has made a determination that the device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies.
- Allows the company to market the device for the "Intended Use" represented in the Premarket Notification

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Intended Use

- … refer to **the objective intent of the persons legally responsible for the labeling of devices**. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article.
- The FDA determines the product's "**objective intent**" by labeling claims; advertising matter; oral or written statements by manufacturers, sponsors or their representatives.

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Indications for Use

- **NOT** the same thing as “Intended Use”.
- Where “Intended Use” is quite broad, the “Indications for Use” describe the condition(s) and/or patient populations in whom the device should be used.
- It is possible to change the Indications for Use without changing the Intended Use.

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Complicating Factors

- FDA does not usually review the “official labeling” of the products submitted in 510(k) Premarket Notifications.
- FDA typically limits its review to the Intended Use described in the application
- Many 510(k) devices are cleared for general purpose rather than a particular “intended use”

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Examples

- Indications for Use: Papa's Transmission Gel is intended for general use as a non-sterile transmission media for acoustically coupling a transducer to a human body surface during external therapeutic and diagnostic ultrasound imaging procedures. It is placed on the patient's skin or on the transducer prior to initiating an ultrasound examination.

- Indications for Use: The Zinkablator System is intended for coagulation and ablation of soft tissue. It is not intended for use in cardiac procedures.

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Promotion of 510(k) cleared products

- Distribution of products for Intended Uses that have not been cleared under a 510(k) is prohibited because doing so would render the device **ADULTERATED** because the device would lack approval or clearance.
- FDA may exercise jurisdiction over products and marketers based on the CONTENT of communications if they believe the content creates a new intended use.
- Labeling of a medical device that is false and/or misleading will **MISBRAND** the device.

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What is labeling?

- Labeling consists of "all labels and other written, printed, or graphic matter" on or "accompanying" a device – FD&C Act sec. 201(m)

- The material does not physically need to accompany the device to be labeling (Kordel v. US, 335 U.S. 345, 350 (1948))

What is labeling?

- "the FDA regulations and the case law make clear that labeling under the FDCA is construed expansively, such that it may encompass nearly every form of promotional activity, including package inserts, pamphlets, mailing pieces, fax bulletins, reprints of press releases, and all other literature that supplements, explains, or is otherwise textually related to the product"
- Press releases disseminated to physicians, internal company e-mails to sales representatives leading to oral representations, blast faxes to physicians, and others by this defendant satisfied the definition of labeling under the FDC Act (U.S. v. Harkonen, 2009 WL 1578712 (N.D.Cal.) (June 4, 2009))

FDA Authority Over Labeling

- Misbranding
  - **Section 502** of the FDCA *(Food, Drug, and Cosmetic Act)*: A drug or device *shall be deemed* **misbranded** if
    - its labeling is false or misleading in any particular, or
    - its labeling fails to bear adequate directions for use *[for each intended use]*.
  - Examples of "false or misleading"
    - A failure to reveal material facts
    - Lack of fair balance
    - False advertising of a restricted device
    - Inference of FDA endorsement

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Example for discussion

- Indications for Use: The Zinkablator System is intended for coagulation and ablation of soft tissue. It is not intended for use in cardiac procedures.

- Marketing is developing a series of customer training programs with the device. Each program will have a different clinical focus. Which training programs might be problematic and why?

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Real World Example: Surgisil (April 15, 2019)

- "Your firm has a cleared 510(k) for the Perma Facial Implant "**intended for use in plastic and reconstructive surgery. The devices can be used for cosmetic augmentation and corrections in the face, including areas such as the nose, chin, and cheeks**" (K071823)."

- **"...our inspection and review of your firm's instructional videos and training materials reveal that your firm is marketing the Perma Facial Implant for augmentation of the lips, which constitutes a major change/modification to its intended use for which you lack approval."**

- "...the **Perma Facial Implant is adulterated** under section 501 (f)(1)(B) of the Act, 21 U.S.C. § 351 (f)(1)(B), because you do not have an approved application for premarket approval (PMA) in effect pursuant to section 515(a) of the Act, 21 U.S.C. § 360e(a), or an approved application for an investigational device exemption (IDE) under section 520(g) of the Act, 21 U.S.C. § 360j(g)."

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Legal Framework and Enforcement Initiatives

False Claims

- DOJ has consistently argued that off-label promotion resulting in the submission of claims to Federal Programs that do not cover off-label use violates the federal civil False Claims Act ("FCA").
- DOJ may also argue that a company's FDA submission seeking clearance for one use knowing and intending that the use will be otherwise is a false statement "tainting" and thus making actionable under the FCA all claims for reimbursement.
- Penalties for False Claims violations of $5,500 to $11,000 per claim plus treble damages (i.e., three times the amount of damages to the government), as well as exclusion from participation in Medicare/Medicaid programs.
- Numerous states have enacted false claims act laws that parallel the federal FCA.

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FTC: Promotion of 510(k) cleared products

- Under the law, claims in advertisements must be truthful, cannot be deceptive or unfair, and must be evidence-based.
- Companies must support their advertising claims with solid proof.

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Complaints

- **Definition 21 CFR 820.3(b)**
  - Any written, electronic, or oral **communication** that **alleges** deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device **after** it is released for distribution
- Typically think of complaints coming into the company via:
  - Phone lines (complaint line)
  - Service group
  - Customer facing teams (e.g., sales)
  - Social media channels
  - Lawsuits
- Key is to establish 'listening posts' to monitor for potential complaints

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General Requirement
21 CFR 820.198(a)

- **Establish** and **Maintain** procedures for receiving, reviewing, and evaluating complaints by a **Formally Designated Unit** to ensure:

  - Processing in uniform and timely manner
  - Documentation of oral complaints *upon receipt*
  - Evaluation to determine if failure investigation and/or a **medical device report (MDR)** is required

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820.198 Complaint Files

Investigations

- Review and evaluate all complaints to determine whether an investigation is necessary.
- Records of investigation shall be maintained with certain specified information as required

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820.198 Complaint Files

Investigations

- When no investigation is made, maintain a record that includes the
  - Reason no investigation was made and name of the individual responsible for the decision.

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Investigation of Failures
21 CFR 820.198(c)

- Any alleged complaint involving possible failure of a device or labeling/packaging to meet any of its specifications must be Reviewed, Evaluated, and Investigated.
- **Exception** – when an investigation has already been performed on a similar complaint
- Recurring similar complaints may not require investigation under complaint file handling but may require CAPA.

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Medical Device Reporting (MDR)
21 CFR 820.198(d)

- Complaints that are also Medical Device Reports (MDRs) must be promptly reviewed, evaluated, and investigated by designated individual(s).
- Maintain in a separate portion of the complaint files or be otherwise clearly identified.
- Keep additional records of investigation:
  - Whether device failed to meet specifications
  - Whether device was used for treatment/diagnosis
  - Relationship, if any, of device to reported incident/adverse event

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MDR's

- **For manufacturers, "MDR reportable events" are events that manufacturers become aware of that reasonably suggest that one of their marketed devices may have caused or contributed to a death or serious injury, or has malfunctioned and the malfunction of the device or a similar device that they market would be likely to cause or contribute to death or serious injury if the malfunction were to recur.**

- A "**serious injury**" is an injury or illness that [21 CFR 803.3]:
  - Is life threatening;
  - Results in permanent impairment of a body function or permanent damage to a body structure; or
  - Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

- "**Malfunction**" means the failure of a device to meet its performance specifications or otherwise perform as intended [21 CFR 803.3]. Performance specifications include all claims made in the labeling for the device.

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Characteristics of a healthy Complaint System

- Well defined methods to capture complaints;
- A system that ensures responses which are…
  - Accurate
  - Robust
  - Timely
  - Complete
- Well defined criteria for initiating, conducting and completing investigations;
- Metrics with defined acceptable/not acceptable thresholds;
- Active review to identify trends pointing to potential needs to take action to either correct or prevent a problem;
- Effective oversight of the system by management

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THANK YOU!

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Intro to De Novo

Quynh Hoang
Senior Regulatory Consultant
FDA & Life Sciences Team
Government Matters Practice

Disclaimer

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

Outline

- What is a De Novo?
- When does De Novo pathway apply?
- Why try for a De Novo?
- When De Novo may not be right for a company?
- Key Takeaways

What is a De Novo?

What is a De Novo?

De Novo ("novel") is a distinct marketing pathway for medical devices.

PATHWAY	FY2022*	
	CDRH	CBER
510(k)	3759	37
De Novo	**77**	**3**
Premarket Approval (PMA) Original PMAs and Panel-track Supplements	45	2
Humanitarian Device Exemption (HDE)**	1	0
Product Development Protocol (PDP) (3 completed since 1976)**	0	0
Device Emergency Use Authorization (EUA)***	~1000 as of May 31, 2022	-

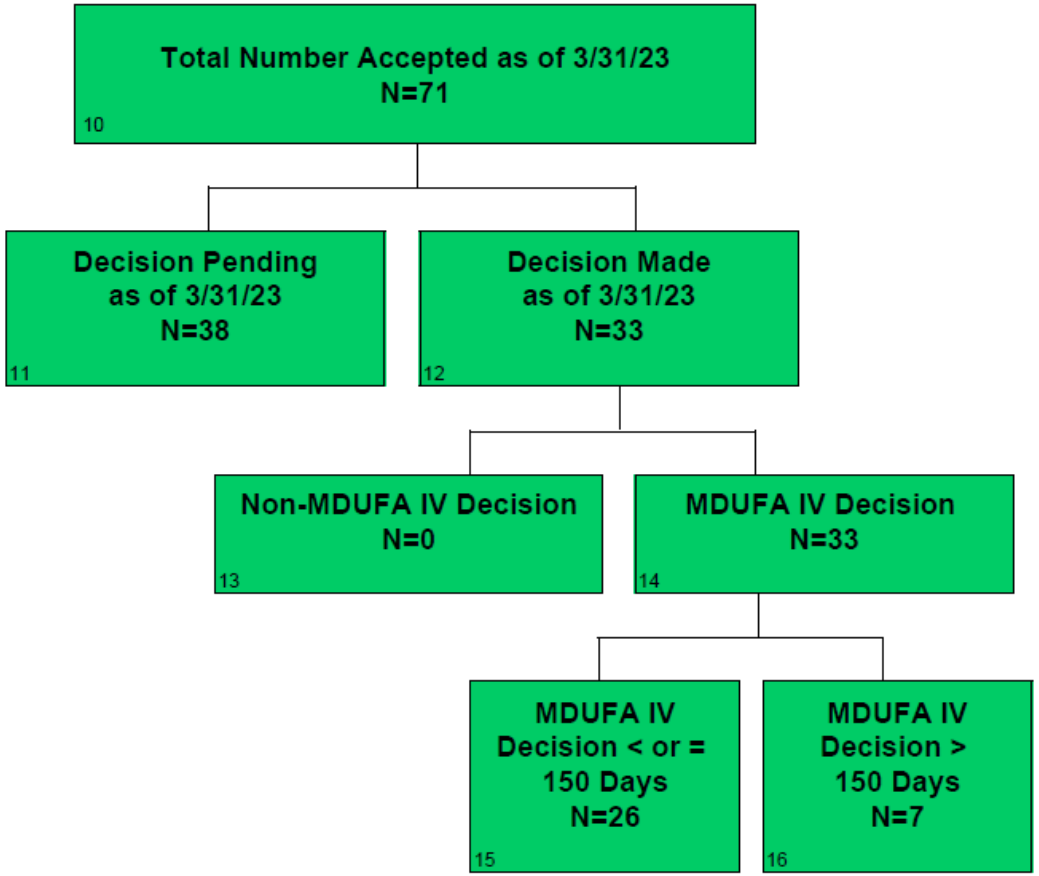
*Fiscal year 2022 is from Oct. 1, 2021 to Sept. 30, 2022. Shown are the numbers received unless otherwise noted, in MDUFA IV Performance Report dated Mar. 31, 2023

**Number approved since pathway is not covered by User Fee Reports (number approved is usually smaller than number submitted.)

***Dr. Shuren on FDA Voices, May 31, 2022

What is a De Novo?

CDRH FY2022 De Novos (from MDUFA IV Performance Report dated Mar. 31, 2023)



What is a De Novo?

De Novo ("novel") pathway brief history:

1. Prior to 1997, a device that received a Not Substantially Equivalent (NSE) determination was automatically assigned to the PMA pathway.

2. Congress added De Novo pathway (it's FDCA 513(f)(2)):
   a. For NSE 510(k) submissions, via FDA Modernization Act (FDAMA) of 1997; and,
   b. For Direct De Novos (submissions not preceded by NSE 510(k)s), via FDA Safety and Innovation Act (FDASIA) of 2012.

3. FDA:
   a. Tried various approaches in implementing the De Novo submission since 1997 (e.g., for each granted De Novo, FDA issued a Special Control Guidance Document); and,
   b. Codified the latest approach in 2018 (21 CFR Part 860).

When does De Novo pathway apply?

When does De Novo pathway apply?

De Novo ("novel") pathway may be used when:

1. No PMA-approved device for same intended use and technology;
2. No predicate for same intended use and technology (i.e., 510(k) is not an option); and,
3. Novel device is Low to Moderate Risk
   (i.e., risks can be mitigated by:
   a. General Controls for a De Novo device to be classified in Class 1; or
   b. General Controls and Special Controls for a De Novo device to be classified in Class 2).

When does De Novo pathway apply?

General and Special Controls

1. General Controls (apply to every medical device, unless the CFR for the device-type specifies exemption(s)):
   a. [No] Adulterated Device (FDCA 501);
   b. [No] Misbranded Device (FDCA 502);
   c. etc. (FDCA 510, 516, 518, 519, and 520).

2. Special Controls (specific to each device-type)
   What must be done to confirm the safety and performance of the device-type:
   a. Technological characteristics for the proposed intended use are well understood such that bench/animal/clinical testing can be defined; AND,
   b. Clinical data, if needed, demonstrate reasonable safety and reasonable effectiveness.

When does De Novo pathway apply?

Examples of Special Controls:

- "Clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use and include the following…"
- "All patient-contacting components of the device must be demonstrated to be biocompatible."
- "Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life."
- "Labeling must include the following:
  i. Instruction for use, including specific instructions regarding device selection and placement;
  ii. A detailed summary of the clinical performance testing with the device, including procedure and device-related complications or adverse events; and
  iii. A shelf life."

Why try for a De Novo?

Why try for a De Novo?

When there is:

- No PMA-approved device for same intended use and technology; and,
- No predicate for same intended use and technology (i.e., 510(k) is not an option),

FDA leaves it to the applicant to decide whether to submit a De Novo or PMA.

Why try for a De Novo?

Comparing to the PMA pathway, De Novo pathway will require:

1. Less clinical data?	*Not likely*
2. Less pre-clinical (bench/animal) data?	*Not likely*
3. Less details in labeling?	*Not likely*
4. Shorter FDA review time?	*Not likely*
5. Less money?	*See next slide*

Why try for a De Novo?

Compared to the PMA pathway, De Novo pathway will require less money over the life span of the device:

PURPOSE	PMA			DE NOVO	
	Type of submission	Standard	Small business*	Standard	Small business*
New/Novel Device	ORIGINAL	$441,547	$110,387	$132,464	$33,116
Change to indications	PANEL-TRACK SUPPLEMENT	$353,238	$88,309	New Indications: 510(k)	
Manufacturing Change(s) (no fee for site change)	30-DAY NOTICE	$7,065	$3,532	Follows 510(k) Process	
	135-DAY SUPPLEMENT	No fee (already paid with the 30-day notice)			
Minor Design and/or Labeling Changes	REAL-TIME SUPPLEMENT	$30,908	$7,727		
Design and/or Labeling Change(s)	180-DAY SUPPLEMENT	$66,232	$16,558		
Periodic Reporting	ANNUAL REPORT	$15,454	$3,864	Not applicable	

Shown are FY2023 user fees
*Requires a Small Business Designation

When De Novo may not be right for a company?

When De Novo may not be right for a company?

Though its novel device appears to qualify for De Novo pathway, a company may still choose the PMA pathway because:

- Company does not want to spend its resources to set up the 510(k) path for the subsequent me-too devices from competitors; or,

- Company wants to limit the number of competing me-too devices by setting the marketing pathway for the device-type to the more costly PMA.

Key Takeaways

Key Takeaways

- De Novo pathway requires the applicant to show the risks and performance of the novel device to be respectively mitigated and assured by:
  - General Controls if seeking a Class 1 designation; or,
  - General and [Identified] Special Controls if seeking a Class 2 designation.

- There are pros and cons with choosing the De Novo pathway. Confirm that it's right for your business.

Thanks!

Quynh Hoang
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FDA and Life Sciences

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Regulatory Strategy for De Novo & Preparing the De Novo Submission

PRESENTED BY: Neeta Sharma, Holly Drake

Advamed De Novo Workshop| May 16, 2023

Presenter Background

- **Neeta Sharma**
  - **Current Role:** Dexcom, Inc., Vice President, Regulatory Affairs
  - **Experience:** 20 years Regulatory Affairs and Quality Assurance
    - Devices for Cardiovascular , Orthopedics, Diabetes (Class I and Class II medical devices), SaMD,
    - **Linkedin:** **https://www.linkedin.com/in/neeta-sharma-2653121/**

- **Holly Chico Drake**
  - **Current Role:** Dexcom, Inc., Director, Regulatory Affairs
  - **Experience:** 11 years Regulatory Affairs and 6 years Clinical Affairs
    - Devices for Diabetes (PMA including Panel-Track, De Novo, 510(k), Class I and II, 510(k) exempt)
  - **Linkedin:** https://www.linkedin.com/in/holly-chico-drake/

- ***Disclaimer:*** *The opinions expressed in this presentation and on the following slides are solely those of the presenter and do not represent those of Dexcom, Inc. Presentations are intended for educational purposes only and do not replace independent professional judgement. Dexcom, Inc. does not endorse or approve, and assumes no responsibility for the content, accuracy or completeness of information presented.*

Learning Objectives

- Regulatory Strategy for De Novo (30 minutes)
  - Key eligibility criteria
  - Benefit-risk analysis

- Preparing the De Novo Submission (30 Minutes)
  - Content
  - Assembling the submission
  - Managing expectations and impact to business functions
  - Case Examples

- Q&A (15 minutes)

De Novo ("from the beginning")

- The De Novo process provides a pathway to **classify novel medical devices** for which **general controls alone, or general and special controls,** provide **reasonable assurance of safety and effectiveness** for the intended use, but for which there is **no legally marketed predicate device**.

Key Eligibility Criteria

HOW TO DETERMINE IF THE DE NOVO PATHWAY IS THE RIGHT ROAD TO MARKET

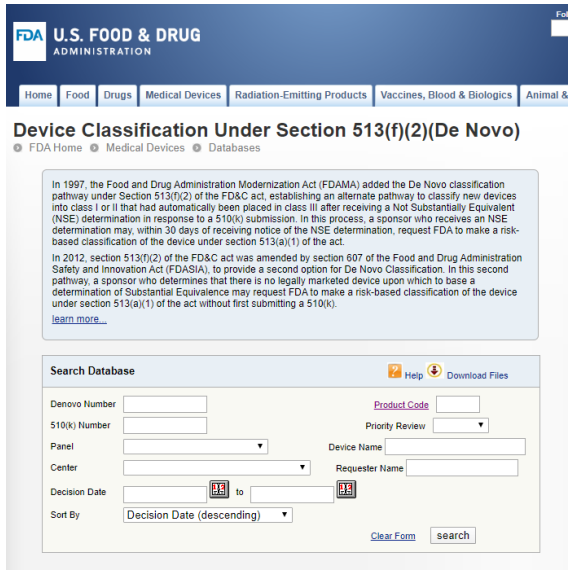
Key Eligibility of the Device

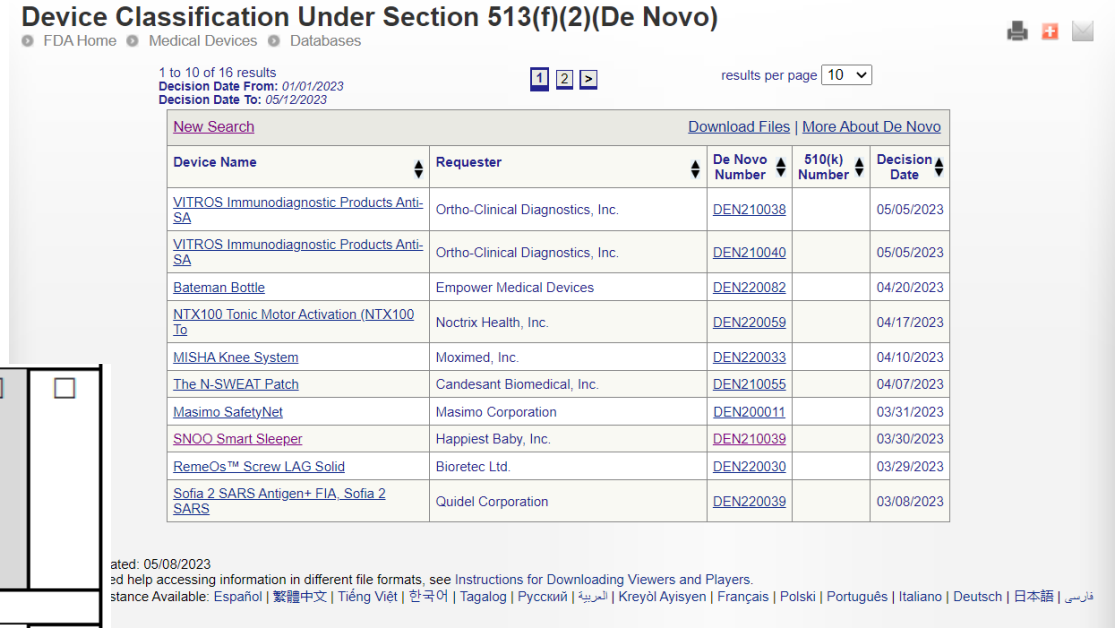
- ❑ Acceptance Review for De Novo Classification Requests
  - ✓ Complete the checklists in FDA Guidance
- ❑ **Risk profile** is well understood (low or medium risk)
  - ✓ Can **general and special controls** provide reasonable assurance of S&E?

- ❑ **Novel** device type
  - ✓ Does not fall within existing classification regulation
  - ✓ Predicate device does not exist
  - ✓ New intended use
  - ✓ Different question of safety and effectiveness

Do your research

- #5: Review product classification database
  - Search Keywords
  - Filter for relevancy
  - Examine intended use and technological characteristics
- Consider submitting a pre-sub





5. Is the device is eligible on its face for De Novo classification? If substantive review is required to determine whether the device is eligible for De Novo classification (e.g., research to determine whether a predicate device exists, an existing classification regulation exists for the same device type, or an approved PMA(s) exists for the same device type), this item can be left blank. If the device type is not eligible for De Novo classification, mark "No."	☐	☐	☐
Comments:			

Risks, Benefits, Controls

Identified Risks	Mitigation Measures
Patient harm due to…	*Clinical data*
Risk due to…	*Training*
Risk due to…	*Testing of…*

Identify the risks

- How could use of the device lead to harm?
- What new risks are introduced by novel technology or new application?
- Practical Steps
  - Reference FDA guidance and ISO 14971
  - Cross-functional hazard analysis meetings
  - Research risks associated with similar device types
  - Review risks described in previous Summary of Safety and Effectiveness Data (SSEDs)
  - Conduct literature search for risks mentioned in research publications for novel technology

Identify the Mitigations

Mitigation Measures

Example 1: Electrocardiograph software for over-the-counter use (DEN180044)

Apple unveils Watch Series 4 with FDA-approved ECG

This is the first FDA clearance for Apple and pushes the Watch further into healthcare than ever before.

By Jonah Comstock | September 12, 2018 | 02:48 PM

Note: Since De Novo is not a PMA, the FDA recommends using marketing language like "granted De Novo" or "granted marketing authorization" rather than "FDA approved."

The ECG app is a software-only mobile medical application intended for use with the Apple Watch to create, record, store, transfer, and display a single channel electrocardiogram (ECG) similar to a Lead I ECG. The ECG app determines the presence of atrial fibrillation (AFib) or sinus rhythm on a classifiable waveform. The ECG app is not recommended for users with other known arrhythmias.

The ECG app is intended for over-the-counter (OTC) use. The ECG data displayed by the ECG app is intended for informational use only. The user is not intended to interpret or take clinical action based on the device output without consultation of a qualified healthcare professional. The ECG waveform is meant to supplement rhythm classification for the purposes of discriminating AFib from normal sinus rhythm and not intended to replace traditional methods of diagnosis or treatment.

The ECG app is not intended for use by people under 22 years old.

Electrocardiograph software for over-the-counter use. An electrocardiograph software device for over-the-counter use creates, analyzes, and displays electrocardiograph data, and can provide information for identifying cardiac arrhythmias. This device is not intended to provide a diagnosis.

Contact	C/O Biologics Consulting Group 400 N Washington St., Suite 100 Alexandria, VA 22314 Donna-Bea Tillman
Reclassification Order	Reclassification Order
FDA Review	Decision Summary
Type	Direct

Example 1: Electrocardiograph software for over-the-counter use (DEN180044)

Table 1 – Identified Risks to Health and Mitigation Measures

Identified Risks to Health	Mitigation Measures
Poor quality ECG signal resulting in failure to detect arrhythmia	Clinical performance testing Human factors testing Labeling
Misinterpretation and/or over-reliance on device output, leading to: • Failure to seek treatment despite acute symptoms • Discontinuing or modifying treatment for chronic heart condition	Human factors testing Labeling
False negative resulting in failure to identify arrhythmia and delay of further evaluation or treatment	Clinical performance testing Software verification, validation, and hazard analysis Non-clinical performance testing Labeling
False positive resulting in additional unnecessary medical procedures	Clinical performance testing Software verification, validation, and hazard analysis Non-clinical performance testing Labeling

In combination with the general controls of the FD&C Act, the electrocardiograph software for over-the-counter use is subject to the following special controls:

1. Clinical performance testing under anticipated conditions of use must demonstrate the following:
   a. The ability to obtain an ECG of sufficient quality for display and analysis; and
   b. The performance characteristics of the detection algorithm as reported by sensitivity and either specificity or positive predictive value.

2. Software verification, validation, and hazard analysis must be performed. Documentation must include a characterization of the technical specifications of the software, including the detection algorithm and its inputs and outputs.

3. Non-clinical performance testing must validate detection algorithm performance using a previously adjudicated data set.

4. Human factors and usability testing must demonstrate the following:
   a. The user can correctly use the device based solely on reading the device labeling; and
   b. The user can correctly interpret the device output and understand when to seek medical care.

5. Labeling must include:
   a. Hardware platform and operating system requirements;
   b. Situations in which the device may not operate at an expected performance level;
   c. A summary of the clinical performance testing conducted with the device;
   d. A description of what the device measures and outputs to the user; and
   e. Guidance on interpretation of any results.

Special Controls Development

Performance criteria

Benefit/Risk Conclusion

Conclude the probable benefits outweigh the probable risks

State whether risks can be mitigated by general controls and identified special controls

Other inputs to consider:

Example: Infant Supine Sleep System (DEN210039)

Note: Since De Novo is not a PMA, the FDA recommends using marketing language like "granted De Novo" or "granted marketing authorization" rather than "FDA approved."

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your De Novo request for classification of the SNOO Smart Sleeper, an over-the-counter device under 21 CFR Part 801 Subpart C with the following indications for use:

> The SNOO Smart Sleeper bassinet plus the SNOO Sleep Sack are jointly intended to facilitate a supine position during sleep. Infants who are placed in a supine sleep position are at lower risk of SIDS/SUID. The device is intended for home use by caregivers of infants from birth to 6 months of age, who are not yet able to roll over consistently.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the SNOO Smart Sleeper, and substantially equivalent devices of this generic type, into Class II under the generic name infant supine sleep system.

FDA identifies this generic type of device as:

> **Infant supine sleep system**. An infant supine sleep system is a device intended to facilitate a supine position during sleep for use in infants that are not yet able to roll over consistently. Infants placed in a supine sleep position are at lower risk of sudden infant death syndrome (SIDS) or sudden unexpected infant death (SUID).

Example: Infant Supine Sleep System (DEN210039)

Risk to Health	Mitigation Measures
Increased risk of death, including from inadequate securement or inadequate positioning of the infant	Clinical data Postmarket surveillance Non-clinical performance testing Labeling
Inappropriate securement leading to • Injuries, contusions, or bruising • Entrapment • Respiratory compromise or suffocation • Gastroesophageal reflux • Plagiocephaly ("flat head syndrome") • Death	Clinical data Postmarket surveillance Labeling
Inappropriate or inadequate securement due to device degradation over time (wear and tear, laundering)	Non-clinical performance testing Labeling
Inappropriate use or inadequate securement due to use error and/or improper fit	Clinical data Human factors assessment Labeling
Injury due to unstable device (tipping, rocking, improper placement)	Non-clinical performance testing Labeling
Infection	Labeling
Adverse tissue reaction (e.g., dermatitis)	Biocompatibility evaluation Labeling

In combination with the general controls of the FD&C Act, the infant supine sleep system is subject to the following special controls:

(1) Premarket clinical information and, as determined by FDA, postmarket surveillance data acquired under anticipated conditions of use must be collected to fulfill the following:
  (i) Demonstrate that the device holds the infant on the back;
  (ii) Provide data on adverse events (including deaths and injuries) and malfunctions to demonstrate the device can be safely used in the intended use population; and
  (iii) Provide data to demonstrate that use of the device does not increase the rate of SIDS/SUID in the intended use population.

(2) Human factors testing must demonstrate that the user can safely and correctly use the device.

(3) The patient-contacting components of the device must be demonstrated to be biocompatible.

(4) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following must be conducted:
  (i) Testing to ensure the mechanical and structural stability of the device and demonstrate that the device does not present a tipping hazard due to mechanical failures; and
  (ii) Material compatibility testing to demonstrate that the cleaning instructions provided by the manufacturer do not cause crazing, cracking, or deterioration of the device.

(5) Labeling must include:
  (i) Unless clinical performance data demonstrates that it can be removed or modified, a prominent warning that the device has not been demonstrated to reduce the risk of SIDS/SUID. Such warning must appear prominently on all labeling;
  (ii) A summary of available clinical information with the device, including a discussion of adverse events;
  (iii) A warning that the device is only indicated for use with infants who cannot consistently roll over;
  (iv) Instructions to ensure proper fit;
  (v) Instructions for cleaning the device; and
  (vi) Information regarding safe sleep practices to ensure the safe use of the device, including:
    (A) Recommendations for safe sleep environments; and
    (B) The level of supervision necessary to monitor a sleeping infant.

Contents of a De Novo request

- A De Novo request should include all the content elements necessary for acceptance of the De Novo request, listed in **Appendix A** of the "Acceptance Review for De Novo Classification Request" guidance document.

- Best practice to complete the checklist as you plan submission and provide a copy in your submission

Elements of a Complete De Novo Request
(Section 513(f)(2) of the FD&C Act and 21 CFR Part 860, Subpart D, unless otherwise indicated)

- Any "No" answer can result in a "Refuse to Accept" decision; however, FDA staff has discretion to determine whether missing items are needed to ensure that the request is administratively complete to allow the request to be accepted or to request missing checklist items interactively from requesters during the RTA review.
- Each element on the checklist should be addressed within the request. The requester may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present ("Yes"). An assessment of the rationale will be considered during the review of the request.

Elements of a Complete De Novo Request

Check "Yes" if item is present, "N/A" if it is not needed, and "No" if it is not included but needed. ***Requesters including the checklist with their De Novo request should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**	**Yes**	**No**	**N/A**	***Page #**
A. Organizational Elements				
1. De Novo request contains a Table of Contents. Each section should be labeled (e.g., headings or tabs designating Device Description section, Classification Information and Supporting Data, etc.).	☐	☐		

Required content for a De Novo request (21 CFR 860.220)

Starting with the basics…

- A **coversheet** clearly identifying the request as a "Request for Evaluation of Automatic Class III Designation" under 513(f)(2) De Novo request.
- **Administrative Information**, such as the device's intended use, prescription use or over-the-counter use designated, etc.
- **Device Description**, which includes but is not limited to technology, proposed conditions of use, accessories, and components.

Required content for a De Novo request (21 CFR 860.220)

What else is applicable? Go back to the identified risks and required mitigations

- Classification Information and Supporting Data
  - The **classification being recommended** under section 513 of the Federal Food, Drug, and Cosmetic Act (FD&C Act);
  - A **complete discussion of why general controls or general and special controls provide reasonable assurance of the safety and effectiveness of the device**, and what special controls, if proposing a class II designation, would allow the Agency to conclude there is reasonable assurance the device is safe and effective for its intended use;
  - **Clinical data (if applicable)** that are relevant to support reasonable assurance of the safety and effectiveness of the device. For information on acceptance of clinical data, refer to the FDA's guidance document entitled "Acceptance of Clinical Data to Support Medical Device Applications and Submissions: Frequently Asked Questions.";

Required content for a De Novo request (21 CFR 860.220)

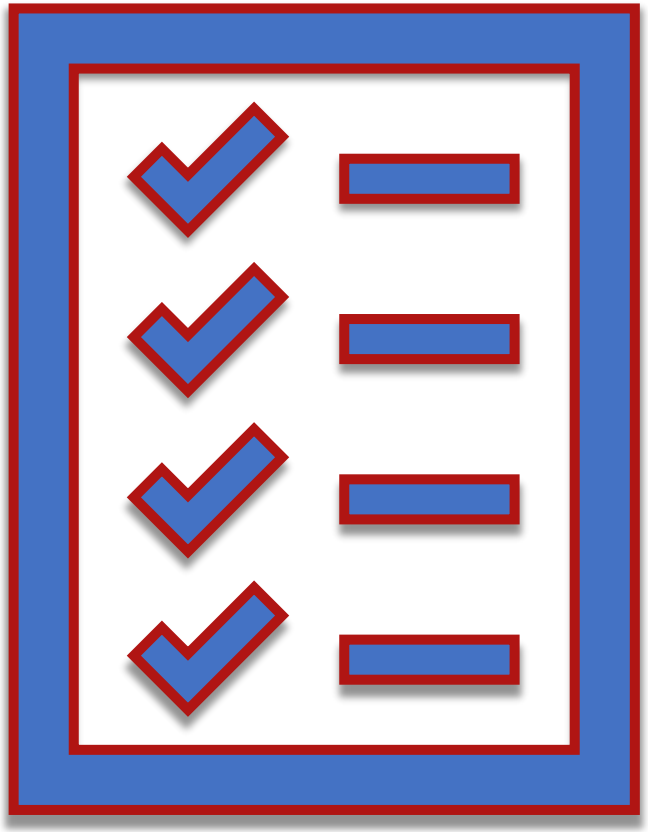
What else is applicable? Go back to the identified risks and required mitigations

- **Non-clinical data including bench performance testing.** For information regarding the content and format of bench testing information, please see the FDA's guidance document, "Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions.";
- **Information** on the reprocessing and **sterilization, shelf life, biocompatibility, software, electrical safety and electromagnetic compatibility, animal study, literature** (if applicable); and
- **A description of the probable benefits** of the device when compared to the probable or anticipated risks when the device is used as intended. For information on assessing the benefits and risks of the device, refer to the FDA's guidance entitled "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications."

Assembling Your submission

- **Use Acceptance Checklist** as a guide to order of submission contents
- Refer to **eCopy guidance** for volume and file organization
- **Good practices** for any type of submission
  - Section headers match checklist headers
  - Use bookmarks and hyperlinks
  - Page numbering
  - Tables to summarize key test reports and results
  - Reference subject specific guidance to organize contents (e.g. Software guidance, biocompatibility, etc.)

Managing expectations and impact to business functions



Chat Question:

How much is the user fee in US Dollars for a De Novo Classification Request?

1. About $1300
2. About $13,000
3. About $130,000
4. Same as a PMA

Align on Strategy

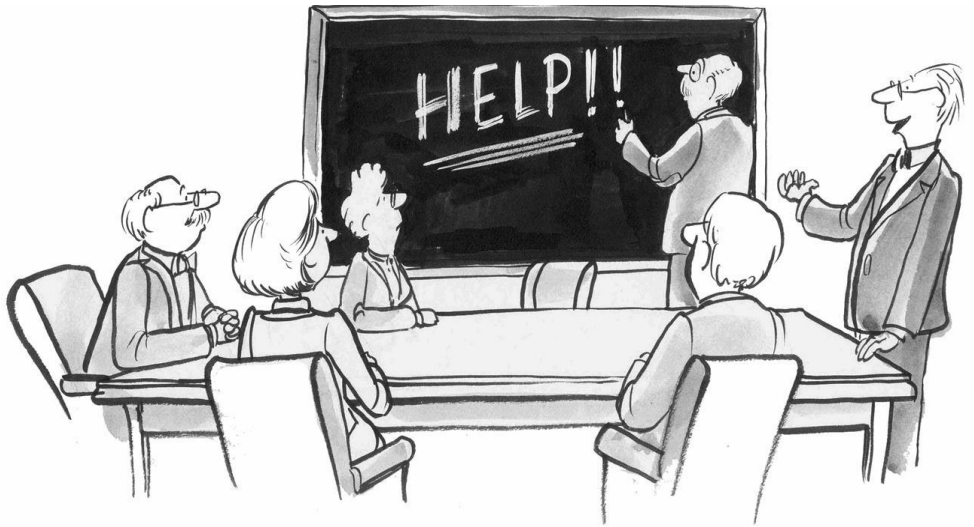
- Understand Leadership Perspective
  - PMA viewed as barrier to market
  - 510(k) viewed as quick entry to market for competitors

- Explain potential benefits of 510(k)
  - Shorter review times
  - More changes via internal documentation and change control procedure
  - Enables more frequent iterations
  - Establishes company as lead in category (first predicate on the market)

Who is impacted?

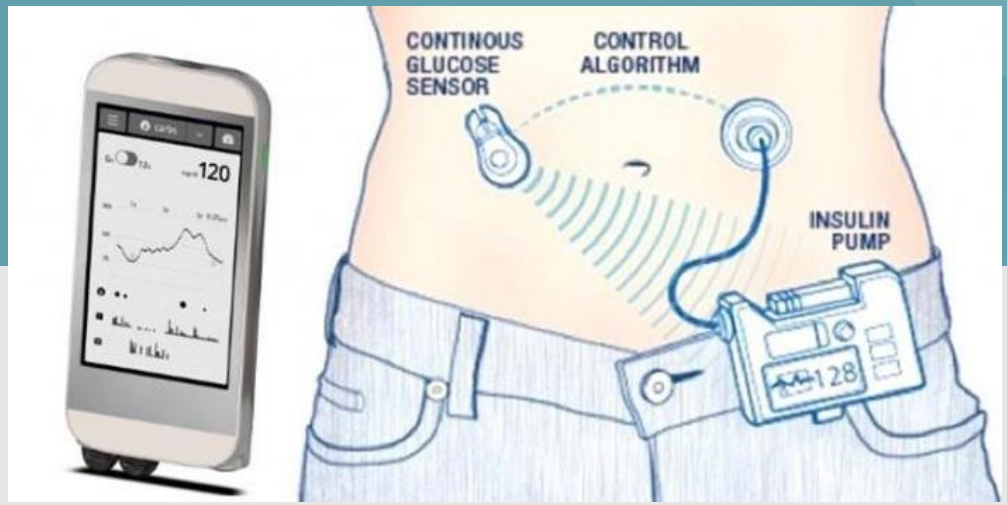
Training for Success in the 510(k) World

- **Cross functional teams**
  - Training sessions – PMA to 510(k), Change Control
  - Prepare FAQ – Understanding new device type
    - Specific intended use
    - Claims
    - Performance data
    - Special controls
  - Revise procedures as necessary
- **RA Department**
  - 510(k) Class II Basics and Change control, including LTF preparation
  - Update internal procedures - 510(k) change assessment
  - Submission templates - Special 510(k), Traditional 510(k)
  - Effect of regulatory changes on Partners
  - Advertising and Promotional Labeling Review
  - Send to workshops/trainings
  - Hire different expertise



"We like to greet our Regulatory Compliance hires with one word."

Case Examples: De Novo Pathway to Advance Diabetes Care

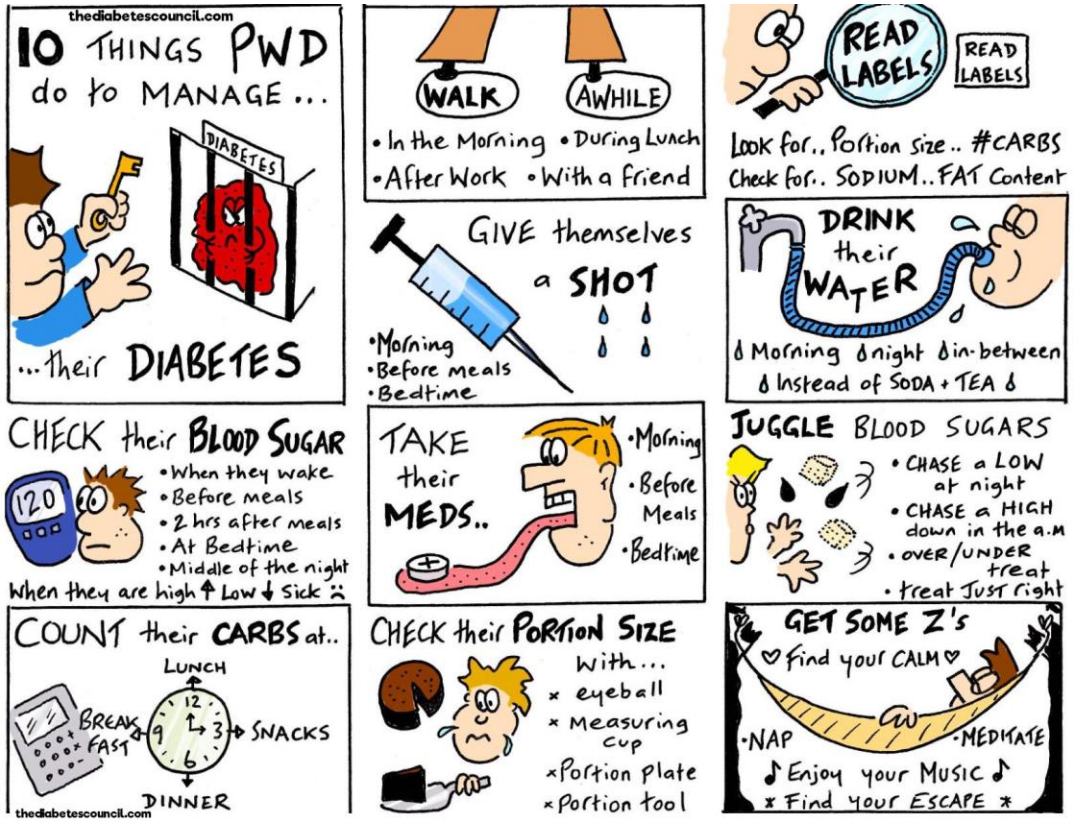


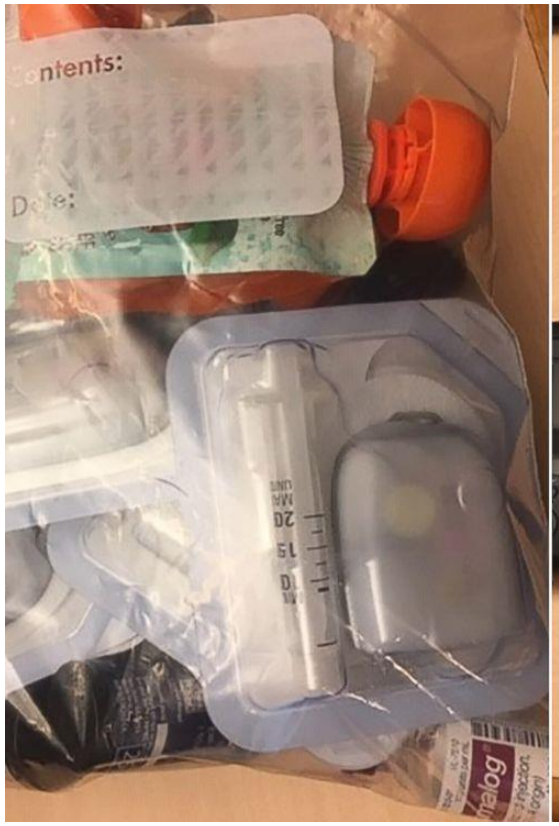
Components of an “Artificial Pancreas”

iCGM

ACE Pump

iController

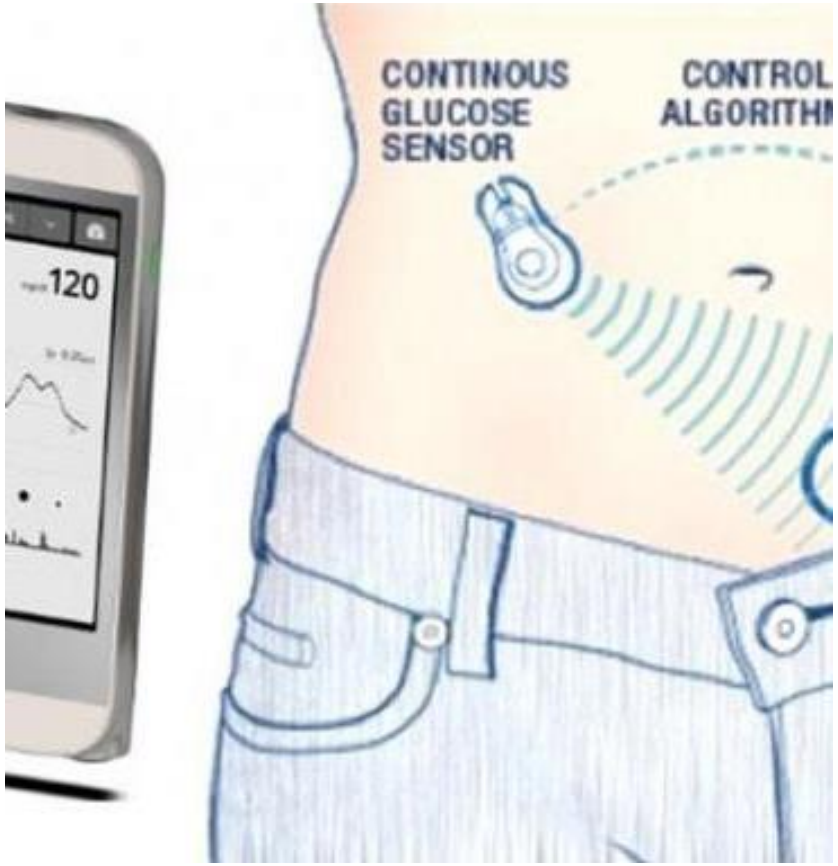




Daily Struggle for People with Diabetes
So many tools to juggle

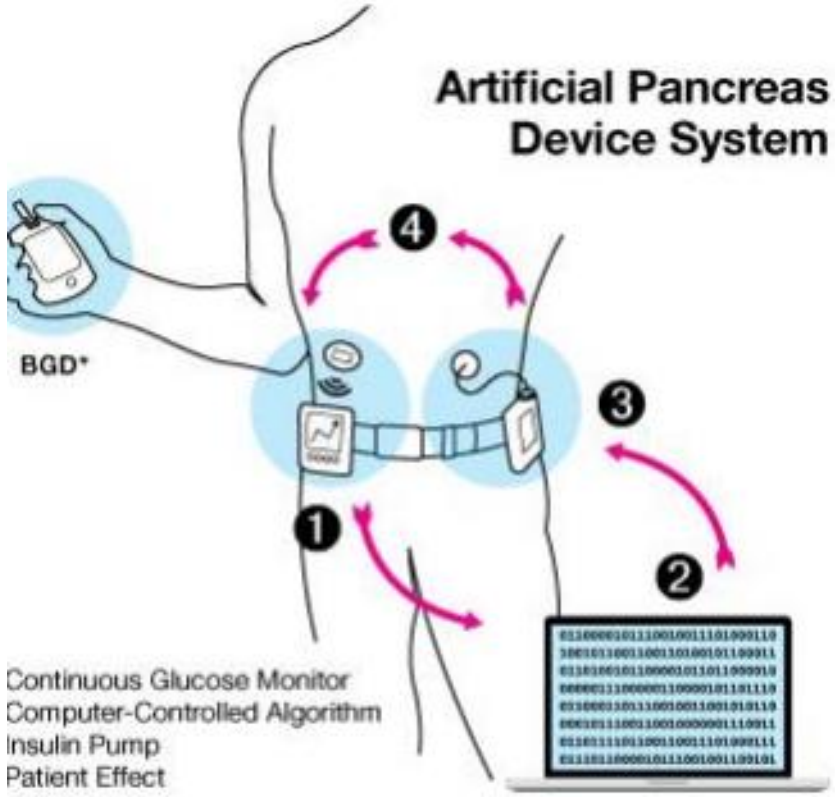
FDA helps to fulfill vision of “Artificial Pancreas”

- Components by different manufacturers
- PMA pathways inhibiting timely access to novel technology
  - FDA reviewers faced with many CGMs and sensor-augmented pumps



FDA Integral Partner to Vision

- Component specific risks
  - Sensor glucose accuracy
  - Pump infusion accuracy
  - Algorithm
- Risks as a result of integration
- Special controls for each
- Make it “plug and play”



Step 1: iCGM (DEN170088)

FDA Search Menu

IN THIS SECTION: Press Announcements

← Press Announcements

FDA NEWS RELEASE

FDA authorizes first fully interoperable continuous glucose monitoring system, streamlines review pathway for similar devices

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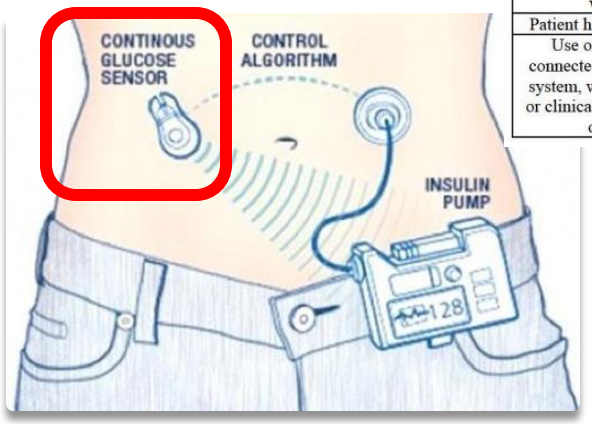
For Immediate Release: March 27, 2018

The U.S. Food and Drug Administration today permitted marketing of the Dexcom G6 integrated continuous glucose monitoring (iCGM) system for determining blood glucose (sugar) levels in children aged two and older and adults with diabetes. This is the first type of continuous glucose monitoring system permitted by the agency to be used as part of an integrated system with other compatible medical devices and electronic interfaces, which may include automated insulin dosing systems, insulin pumps, blood glucose meters or other electronic devices used for diabetes management. Today's authorization also classifies this new type of device in class II and subjects it to certain criteria called special controls. This enables developers of future iCGM systems to bring their

fda.gov/.../fda-authorizes-first-fully-interoperable-continuous-gl...

Identified Risk	Special Control
Inaccurate values lead to inappropriate treatment decisions	Clinical Performance

Identified Risks to Health	Mitigations Measures
Clinical action based on falsely high or falsely low inaccurate glucose values or inaccurate alerts may lead to inappropriate treatment decisions.	General Controls and special controls (1), (2), (3), (4), (5), (6), and (7)
Clinical action in pediatric patients based on falsely high or falsely low inaccurate values or inaccurate alerts due to poorer or different iCGM performance in pediatric populations.	General Controls and special controls (1), (2), (3), (4), (5), (6), and (7)
The inability to make appropriate treatment decisions when glucose values are unavailable due to sensor signal drop-out or loss of communication with digitally connected devices.	General Controls and special controls (1)(vii), (2), (3), (6), and (7)
Patient harm due to insecure transmission of data.	General Controls and special control (2)
Use of an iCGM as part of another digitally connected medical device system, such as an AID system, when the iCGM has inadequate analytical or clinical performance to support the intended use of the digitally connected device.	General Controls and special controls (2), (6), and (7)



Step 2: ACE pump (DEN180058)

FDA

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IN THIS SECTION: Press Announcements

← Press Announcements

FDA NEWS RELEASE

FDA authorizes first interoperable insulin pump intended to allow patients to customize treatment through their individual diabetes management devices

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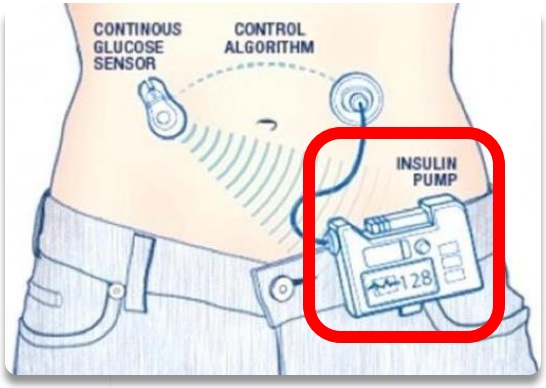
For Immediate Release: February 14, 2019

Español

The U.S. Food and Drug Administration today permitted marketing of the Tandem Diabetes Care t:Slim X2 insulin pump with interoperable technology (interoperable t:Slim X2) for delivering insulin under the skin for children and adults with diabetes. This new type of insulin pump, referred to as an alternate controller enabled (ACE) infusion pump, or ACE insulin pump, is the first interoperable pump, meaning it can be used with different components that make up diabetes therapy systems, allowing patients to tailor their diabetes management to their individual device preferences. Diabetes therapy systems may be comprised of an ACE insulin pump and other compatible medical devices, including automated insulin dosing (AID) systems, continuous glucose monitors (CGMs), blood glucose meters or other electronic devices used for diabetes management.



Identified Risk	Mitigation Measures
Patient harm due to inadequate drug delivery accuracy that leads to over infusion or under infusion of drug.	Basal and bolus drug delivery accuracy validation testing Device use life reliability testing Design mitigations to prevent cross-channeling Validated and traceable risk control measures for identified hazards
Patient harm due to undetected pump occlusions that pose risk of under infusion of drug.	Hazard detection (e.g., drug occlusion) validation testing
Patient harm due to incompatibility between the drug and the pump that may lead to over infusion or under infusion of drug, or exposure to harmful substances leached from pump materials into the infused drug solution.	Drug compatibility testing
Inability to provide appropriate treatment due to loss of communication with digitally connected alternate pump controller devices.	Validated communication specifications, processes, and procedures with digitally connected devices
Commands from the digitally connected alternate pump controller devices that conflict with existing pump commands may lead to unintended over or under infusion of drug.	Validated communication specifications, processes, and procedures with digitally connected devices Validated failsafe design features
Conflicting interfaces resulting in over or under delivery.	Validated communication specifications, processes, and procedures with digitally connected devices Validated failsafe design features
Patient harm due to insecure transmission of data.	Validated communication specifications, processes, and procedures with digitally connected devices
Patient harm due to inability to determine source of dosing error when used in an integrated system.	Validated data logging capability
Patient harm due to exposure to hazardous and non-biocompatible materials or pathogens.	Biocompatibility testing Validation of reprocessing procedures
Patient harm due to data transmission interference/electromagnetic disturbance.	Electrical safety, electromagnetic compatibility, and radio frequency wireless safety testing
Patient harm due to incorrect use of pump, operational, and/or use-related errors.	Human Factors testing Transparent pump performance descriptions in labeling

Step 3: AID Controller (DEN190034)

FDA

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IN THIS SECTION: Press Announcements

← Press Announcements

FDA NEWS RELEASE

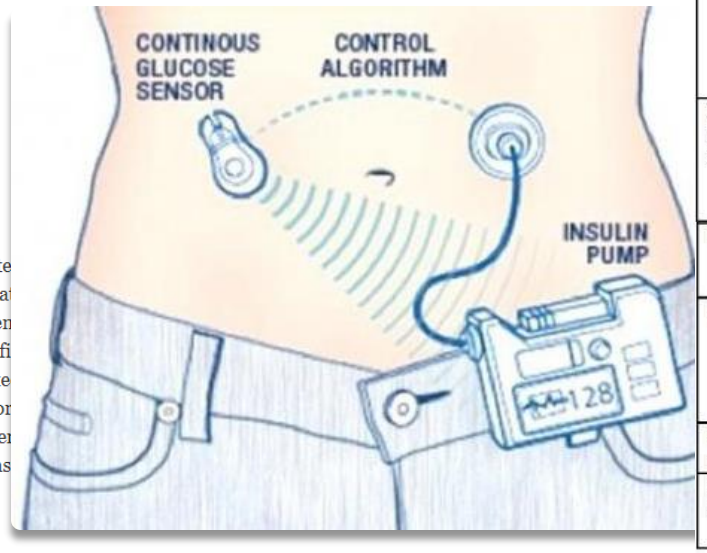
FDA authorizes first interoperable, automated insulin dosing controller designed to allow more choices for patients looking to customize their individual diabetes management device system

Share Tweet LinkedIn Email Print

For Immediate Release: December 13, 2019

Español

The U.S. Food and Drug Administration today authorized marketing of the Tandem Diabete
Control-IQ Technology, an interoperable automated glycemic controller device that automat
adjusts insulin delivery to a person with diabetes by connecting to an alternate controller-en
insulin pump (ACE pump) and integrated continuous glucose monitor (iCGM). This is the fi
controller that can be used with other diabetes devices that are also designed to be integrate
customizable diabetes management system for automated insulin delivery. This FDA author
paves the way for iCGMs and ACE pumps to be used with an interoperable automated glycer
controller as a complete automated insulin dosing (AID) system. AID systems typically cons
pump, CGM and software to control the system of compatible devices.



Identified Risk	Mitigation Measures
Patient harm due to inappropriate drug delivery	Clinical data demonstrating device performance Certain software validation testing User training plan Certain drug compatibility information in labeling
Risk due to poorer or different performance in pediatric populations	Clinical data demonstrating device performance in pediatric population Certain warning statements and precautions in labeling
Risk due to the inability of the controller to handle different pharmacokinetic/pharmacodynamic characteristics of the drugs	Clinical data demonstrating device performance Drug compatibility information in labeling User training plan Human factors testing
Risk due to lack of compatibility of connected devices	Certain validation of communication specifications, processes, and procedures with digitally connected devices Limitations on interoperable devices
Risk of connected devices having inadequate performance to allow safe use of the controller	Specifications for performance of connected devices Certain validation of communication specifications, processes, and procedures with digitally connected devices Limitations on interoperable devices
Failure to report device malfunctions or adverse events to the device manufacturer	Plans and procedures for assigning post-market responsibilities.
Risk of latent flaws in software	Robust software validation testing Certain validation of communication specifications, processes, and procedures with digitally connected devices Certain verification and validation of risk control measures
Failure to provide appropriate treatment due to loss of communication with connected devices	Certain verification and validation of risk control measures Certain validation of communication specifications, processes, and procedures with digitally connected devices
Risk due to insecure transmission of data	Certain validation of communication specifications, processes, and procedures with digitally connected devices
Failure to correctly operate the device	Human factors testing User training plan Compatible devices listed in labeling Certain warning statements and precautions in labeling
Failure to correctly determine the root cause of device malfunctions	Certain verification and validation of logging capability
Risk due to data transmission interference/electromagnetic disturbance	Certain verification and validation of electrical safety, electromagnetic compatibility, and radio frequency wireless testing

FDA Cleared iCGMs, iControllers and ACE Pumps – 2023

iCGMs Integrated Continuous Glucose Monitor	iControllers Interoperable Automated Glycemic Controller	ACE Pumps Alternate Controller-Enabled Insulin Pump
Dexcom G6	Tandem Control-IQ Technology	Tandem t:slim X2
Dexcom G7	Omnipod 5 Controller	Omnipod 5
FreeStyle Libre 2	Tidepool Loop	
FreeStyle Libre 3		

Summary

De Novo Pathway is more accessible than ever

Do your research - know your device risk profile

Consult with business leadership on strategy

Train your staff and manage change

Regulatory Strategy for De Novo & Preparing the De Novo Submission

PRESENTED BY: Neeta Sharma, Holly Drake

Advamed De Novo Workshop| May 16, 2023

Presenter Background

- **Neeta Sharma**
  - **Current Role:** Dexcom, Inc., Vice President, Regulatory Affairs
  - **Experience:** 20 years Regulatory Affairs and Quality Assurance
    - Devices for Cardiovascular , Orthopedics, Diabetes (Class I and Class II medical devices), SaMD,
    - **Linkedin:** **https://www.linkedin.com/in/neeta-sharma-2653121/**

- **Holly Chico Drake**
  - **Current Role:** Dexcom, Inc., Director, Regulatory Affairs
  - **Experience:** 11 years Regulatory Affairs and 6 years Clinical Affairs
    - Devices for Diabetes (PMA including Panel-Track, De Novo, 510(k), Class I and II, 510(k) exempt)
  - **Linkedin:** https://www.linkedin.com/in/holly-chico-drake/

- ***Disclaimer:*** *The opinions expressed in this presentation and on the following slides are solely those of the presenter and do not represent those of Dexcom, Inc. Presentations are intended for educational purposes only and do not replace independent professional judgement. Dexcom, Inc. does not endorse or approve, and assumes no responsibility for the content, accuracy or completeness of information presented.*

Learning Objectives

- Regulatory Strategy for De Novo (30 minutes)
  - Key eligibility criteria
  - Benefit-risk analysis

- Preparing the De Novo Submission (30 Minutes)
  - Content
  - Assembling the submission
  - Managing expectations and impact to business functions
  - Case Examples

- Q&A (15 minutes)

De Novo ("from the beginning")

- The De Novo process provides a pathway to **classify novel medical devices** for which **general controls alone, or general and special controls,** provide **reasonable assurance of safety and effectiveness** for the intended use, but for which there is **no legally marketed predicate device**.

Key Eligibility Criteria

HOW TO DETERMINE IF THE DE NOVO PATHWAY IS THE RIGHT ROAD TO MARKET

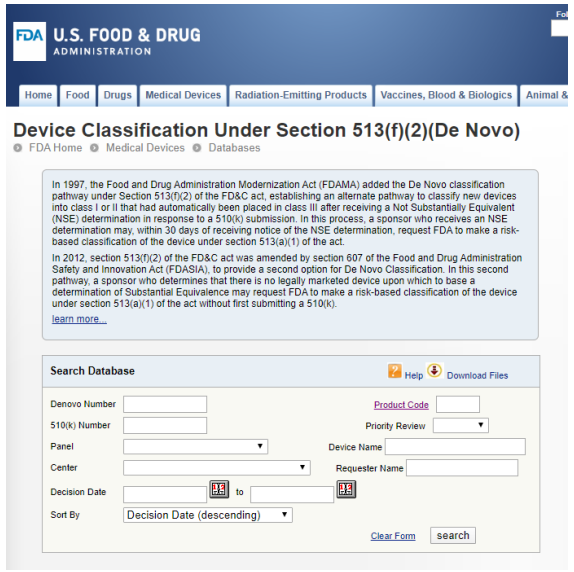
Key Eligibility of the Device

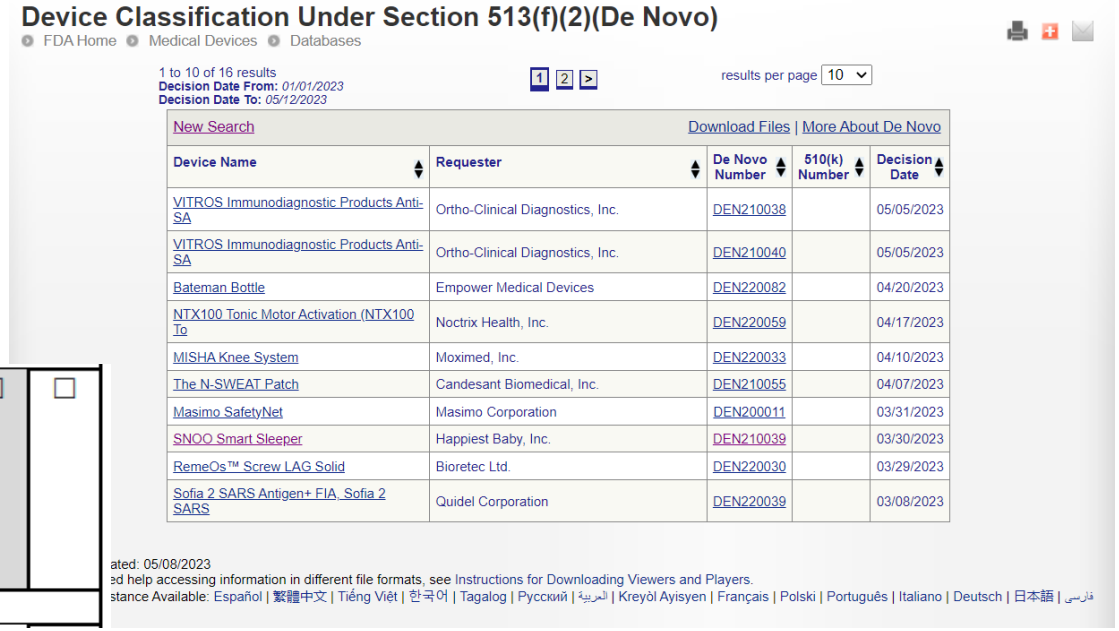
- ❑ Acceptance Review for De Novo Classification Requests
  - ✓ Complete the checklists in FDA Guidance
- ❑ **Risk profile** is well understood (low or medium risk)
  - ✓ Can **general and special controls** provide reasonable assurance of S&E?

- ❑ **Novel** device type
  - ✓ Does not fall within existing classification regulation
  - ✓ Predicate device does not exist
  - ✓ New intended use
  - ✓ Different question of safety and effectiveness

Do your research

- #5: Review product classification database
  - Search Keywords
  - Filter for relevancy
  - Examine intended use and technological characteristics
- Consider submitting a pre-sub





5. Is the device is eligible on its face for De Novo classification? If substantive review is required to determine whether the device is eligible for De Novo classification (e.g., research to determine whether a predicate device exists, an existing classification regulation exists for the same device type, or an approved PMA(s) exists for the same device type), this item can be left blank. If the device type is not eligible for De Novo classification, mark "No."	☐	☐	☐
Comments:			

Risks, Benefits, Controls

Identified Risks	Mitigation Measures
Patient harm due to…	*Clinical data*
Risk due to…	*Training*
Risk due to…	*Testing of…*

Identify the risks

- How could use of the device lead to harm?
- What new risks are introduced by novel technology or new application?
- Practical Steps
  - Reference FDA guidance and ISO 14971
  - Cross-functional hazard analysis meetings
  - Research risks associated with similar device types
  - Review risks described in previous Summary of Safety and Effectiveness Data (SSEDs)
  - Conduct literature search for risks mentioned in research publications for novel technology

Identify the Mitigations

Mitigation Measures

Example 1: Electrocardiograph software for over-the-counter use (DEN180044)

Apple unveils Watch Series 4 with FDA-approved ECG

This is the first FDA clearance for Apple and pushes the Watch further into healthcare than ever before.

By Jonah Comstock | September 12, 2018 | 02:48 PM

Note: Since De Novo is not a PMA, the FDA recommends using marketing language like "granted De Novo" or "granted marketing authorization" rather than "FDA approved."

The ECG app is a software-only mobile medical application intended for use with the Apple Watch to create, record, store, transfer, and display a single channel electrocardiogram (ECG) similar to a Lead I ECG. The ECG app determines the presence of atrial fibrillation (AFib) or sinus rhythm on a classifiable waveform. The ECG app is not recommended for users with other known arrhythmias.

The ECG app is intended for over-the-counter (OTC) use. The ECG data displayed by the ECG app is intended for informational use only. The user is not intended to interpret or take clinical action based on the device output without consultation of a qualified healthcare professional. The ECG waveform is meant to supplement rhythm classification for the purposes of discriminating AFib from normal sinus rhythm and not intended to replace traditional methods of diagnosis or treatment.

The ECG app is not intended for use by people under 22 years old.

Electrocardiograph software for over-the-counter use. An electrocardiograph software device for over-the-counter use creates, analyzes, and displays electrocardiograph data, and can provide information for identifying cardiac arrhythmias. This device is not intended to provide a diagnosis.

Contact	C/O Biologics Consulting Group 400 N Washington St., Suite 100 Alexandria, VA 22314 Donna-Bea Tillman
Reclassification Order	Reclassification Order
FDA Review	Decision Summary
Type	Direct

Example 1: Electrocardiograph software for over-the-counter use (DEN180044)

Table 1 – Identified Risks to Health and Mitigation Measures

Identified Risks to Health	Mitigation Measures
Poor quality ECG signal resulting in failure to detect arrhythmia	Clinical performance testing Human factors testing Labeling
Misinterpretation and/or over-reliance on device output, leading to: • Failure to seek treatment despite acute symptoms • Discontinuing or modifying treatment for chronic heart condition	Human factors testing Labeling
False negative resulting in failure to identify arrhythmia and delay of further evaluation or treatment	Clinical performance testing Software verification, validation, and hazard analysis Non-clinical performance testing Labeling
False positive resulting in additional unnecessary medical procedures	Clinical performance testing Software verification, validation, and hazard analysis Non-clinical performance testing Labeling

In combination with the general controls of the FD&C Act, the electrocardiograph software for over-the-counter use is subject to the following special controls:

1. Clinical performance testing under anticipated conditions of use must demonstrate the following:
   a. The ability to obtain an ECG of sufficient quality for display and analysis; and
   b. The performance characteristics of the detection algorithm as reported by sensitivity and either specificity or positive predictive value.

2. Software verification, validation, and hazard analysis must be performed. Documentation must include a characterization of the technical specifications of the software, including the detection algorithm and its inputs and outputs.

3. Non-clinical performance testing must validate detection algorithm performance using a previously adjudicated data set.

4. Human factors and usability testing must demonstrate the following:
   a. The user can correctly use the device based solely on reading the device labeling; and
   b. The user can correctly interpret the device output and understand when to seek medical care.

5. Labeling must include:
   a. Hardware platform and operating system requirements;
   b. Situations in which the device may not operate at an expected performance level;
   c. A summary of the clinical performance testing conducted with the device;
   d. A description of what the device measures and outputs to the user; and
   e. Guidance on interpretation of any results.

Special Controls Development

Performance criteria

Benefit/Risk Conclusion

Conclude the probable benefits outweigh the probable risks

State whether risks can be mitigated by general controls and identified special controls

Other inputs to consider:

Example: Infant Supine Sleep System (DEN210039)

Note: Since De Novo is not a PMA, the FDA recommends using marketing language like "granted De Novo" or "granted marketing authorization" rather than "FDA approved."

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your De Novo request for classification of the SNOO Smart Sleeper, an over-the-counter device under 21 CFR Part 801 Subpart C with the following indications for use:

> The SNOO Smart Sleeper bassinet plus the SNOO Sleep Sack are jointly intended to facilitate a supine position during sleep. Infants who are placed in a supine sleep position are at lower risk of SIDS/SUID. The device is intended for home use by caregivers of infants from birth to 6 months of age, who are not yet able to roll over consistently.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the SNOO Smart Sleeper, and substantially equivalent devices of this generic type, into Class II under the generic name infant supine sleep system.

FDA identifies this generic type of device as:

> **Infant supine sleep system**. An infant supine sleep system is a device intended to facilitate a supine position during sleep for use in infants that are not yet able to roll over consistently. Infants placed in a supine sleep position are at lower risk of sudden infant death syndrome (SIDS) or sudden unexpected infant death (SUID).

Example: Infant Supine Sleep System (DEN210039)

Risk to Health	Mitigation Measures
Increased risk of death, including from inadequate securement or inadequate positioning of the infant	Clinical data Postmarket surveillance Non-clinical performance testing Labeling
Inappropriate securement leading to • Injuries, contusions, or bruising • Entrapment • Respiratory compromise or suffocation • Gastroesophageal reflux • Plagiocephaly ("flat head syndrome") • Death	Clinical data Postmarket surveillance Labeling
Inappropriate or inadequate securement due to device degradation over time (wear and tear, laundering)	Non-clinical performance testing Labeling
Inappropriate use or inadequate securement due to use error and/or improper fit	Clinical data Human factors assessment Labeling
Injury due to unstable device (tipping, rocking, improper placement)	Non-clinical performance testing Labeling
Infection	Labeling
Adverse tissue reaction (e.g., dermatitis)	Biocompatibility evaluation Labeling

In combination with the general controls of the FD&C Act, the infant supine sleep system is subject to the following special controls:

(1) Premarket clinical information and, as determined by FDA, postmarket surveillance data acquired under anticipated conditions of use must be collected to fulfill the following:
  (i) Demonstrate that the device holds the infant on the back;
  (ii) Provide data on adverse events (including deaths and injuries) and malfunctions to demonstrate the device can be safely used in the intended use population; and
  (iii) Provide data to demonstrate that use of the device does not increase the rate of SIDS/SUID in the intended use population.

(2) Human factors testing must demonstrate that the user can safely and correctly use the device.

(3) The patient-contacting components of the device must be demonstrated to be biocompatible.

(4) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following must be conducted:
  (i) Testing to ensure the mechanical and structural stability of the device and demonstrate that the device does not present a tipping hazard due to mechanical failures; and
  (ii) Material compatibility testing to demonstrate that the cleaning instructions provided by the manufacturer do not cause crazing, cracking, or deterioration of the device.

(5) Labeling must include:
  (i) Unless clinical performance data demonstrates that it can be removed or modified, a prominent warning that the device has not been demonstrated to reduce the risk of SIDS/SUID. Such warning must appear prominently on all labeling;
  (ii) A summary of available clinical information with the device, including a discussion of adverse events;
  (iii) A warning that the device is only indicated for use with infants who cannot consistently roll over;
  (iv) Instructions to ensure proper fit;
  (v) Instructions for cleaning the device; and
  (vi) Information regarding safe sleep practices to ensure the safe use of the device, including:
    (A) Recommendations for safe sleep environments; and
    (B) The level of supervision necessary to monitor a sleeping infant.

Contents of a De Novo request

- A De Novo request should include all the content elements necessary for acceptance of the De Novo request, listed in **Appendix A** of the "Acceptance Review for De Novo Classification Request" guidance document.

- Best practice to complete the checklist as you plan submission and provide a copy in your submission

Elements of a Complete De Novo Request
(Section 513(f)(2) of the FD&C Act and 21 CFR Part 860, Subpart D, unless otherwise indicated)

- Any "No" answer can result in a "Refuse to Accept" decision; however, FDA staff has discretion to determine whether missing items are needed to ensure that the request is administratively complete to allow the request to be accepted or to request missing checklist items interactively from requesters during the RTA review.
- Each element on the checklist should be addressed within the request. The requester may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present ("Yes"). An assessment of the rationale will be considered during the review of the request.

Elements of a Complete De Novo Request

Check "Yes" if item is present, "N/A" if it is not needed, and "No" if it is not included but needed. ***Requesters including the checklist with their De Novo request should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**	**Yes**	**No**	**N/A**	***Page #**
A. Organizational Elements				
1. De Novo request contains a Table of Contents. Each section should be labeled (e.g., headings or tabs designating Device Description section, Classification Information and Supporting Data, etc.).	☐	☐		

Required content for a De Novo request (21 CFR 860.220)

Starting with the basics…

- A **coversheet** clearly identifying the request as a "Request for Evaluation of Automatic Class III Designation" under 513(f)(2) De Novo request.
- **Administrative Information**, such as the device's intended use, prescription use or over-the-counter use designated, etc.
- **Device Description**, which includes but is not limited to technology, proposed conditions of use, accessories, and components.

Required content for a De Novo request (21 CFR 860.220)

What else is applicable? Go back to the identified risks and required mitigations

- Classification Information and Supporting Data
  - The **classification being recommended** under section 513 of the Federal Food, Drug, and Cosmetic Act (FD&C Act);
  - A **complete discussion of why general controls or general and special controls provide reasonable assurance of the safety and effectiveness of the device**, and what special controls, if proposing a class II designation, would allow the Agency to conclude there is reasonable assurance the device is safe and effective for its intended use;
  - **Clinical data (if applicable)** that are relevant to support reasonable assurance of the safety and effectiveness of the device. For information on acceptance of clinical data, refer to the FDA's guidance document entitled "Acceptance of Clinical Data to Support Medical Device Applications and Submissions: Frequently Asked Questions.";

Required content for a De Novo request (21 CFR 860.220)

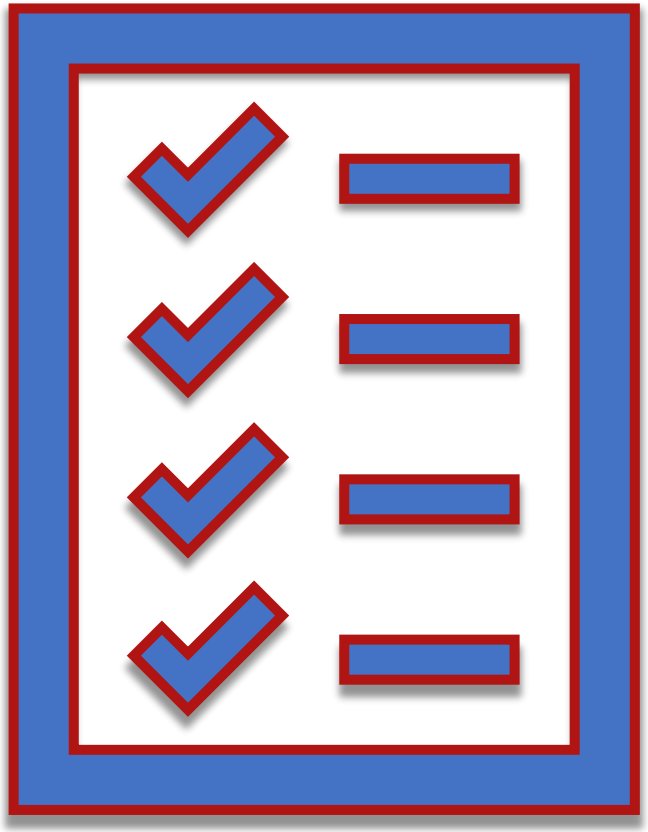
What else is applicable? Go back to the identified risks and required mitigations

- **Non-clinical data including bench performance testing.** For information regarding the content and format of bench testing information, please see the FDA's guidance document, "Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions.";
- **Information** on the reprocessing and **sterilization, shelf life, biocompatibility, software, electrical safety and electromagnetic compatibility, animal study, literature** (if applicable); and
- **A description of the probable benefits** of the device when compared to the probable or anticipated risks when the device is used as intended. For information on assessing the benefits and risks of the device, refer to the FDA's guidance entitled "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications."

Assembling Your submission

- **Use Acceptance Checklist** as a guide to order of submission contents
- Refer to **eCopy guidance** for volume and file organization
- **Good practices** for any type of submission
  - Section headers match checklist headers
  - Use bookmarks and hyperlinks
  - Page numbering
  - Tables to summarize key test reports and results
  - Reference subject specific guidance to organize contents (e.g. Software guidance, biocompatibility, etc.)

Managing expectations and impact to business functions



Chat Question:

How much is the user fee in US Dollars for a De Novo Classification Request?

1. About $1300
2. About $13,000
3. About $130,000
4. Same as a PMA

Align on Strategy

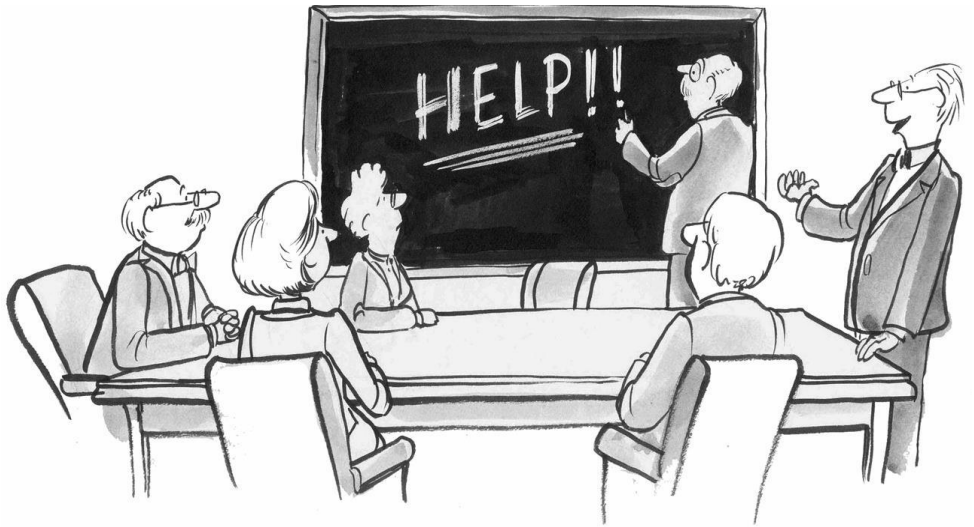
- Understand Leadership Perspective
  - PMA viewed as barrier to market
  - 510(k) viewed as quick entry to market for competitors

- Explain potential benefits of 510(k)
  - Shorter review times
  - More changes via internal documentation and change control procedure
  - Enables more frequent iterations
  - Establishes company as lead in category (first predicate on the market)

Who is impacted?

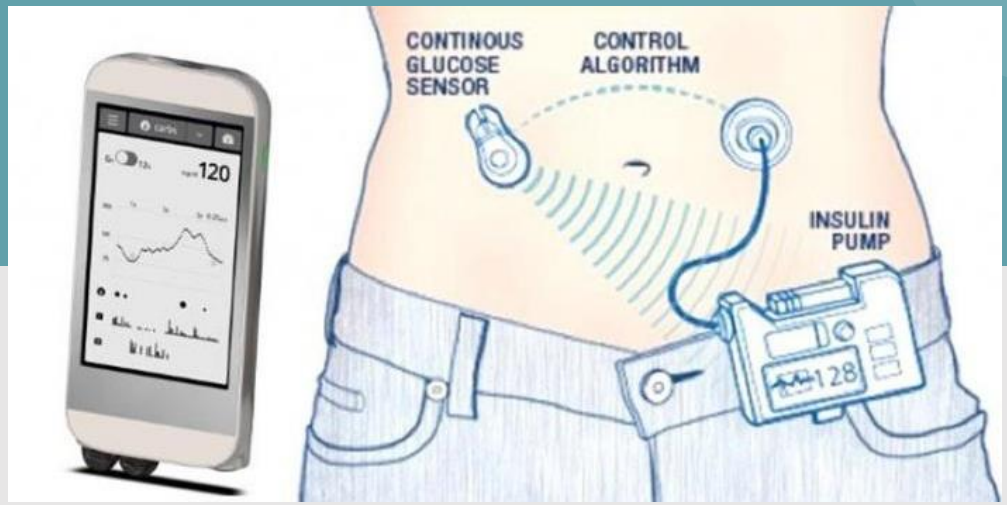
Training for Success in the 510(k) World

- **Cross functional teams**
  - Training sessions – PMA to 510(k), Change Control
  - Prepare FAQ – Understanding new device type
    - Specific intended use
    - Claims
    - Performance data
    - Special controls
  - Revise procedures as necessary
- **RA Department**
  - 510(k) Class II Basics and Change control, including LTF preparation
  - Update internal procedures - 510(k) change assessment
  - Submission templates - Special 510(k), Traditional 510(k)
  - Effect of regulatory changes on Partners
  - Advertising and Promotional Labeling Review
  - Send to workshops/trainings
  - Hire different expertise



"We like to greet our Regulatory Compliance hires with one word."

Case Examples: De Novo Pathway to Advance Diabetes Care

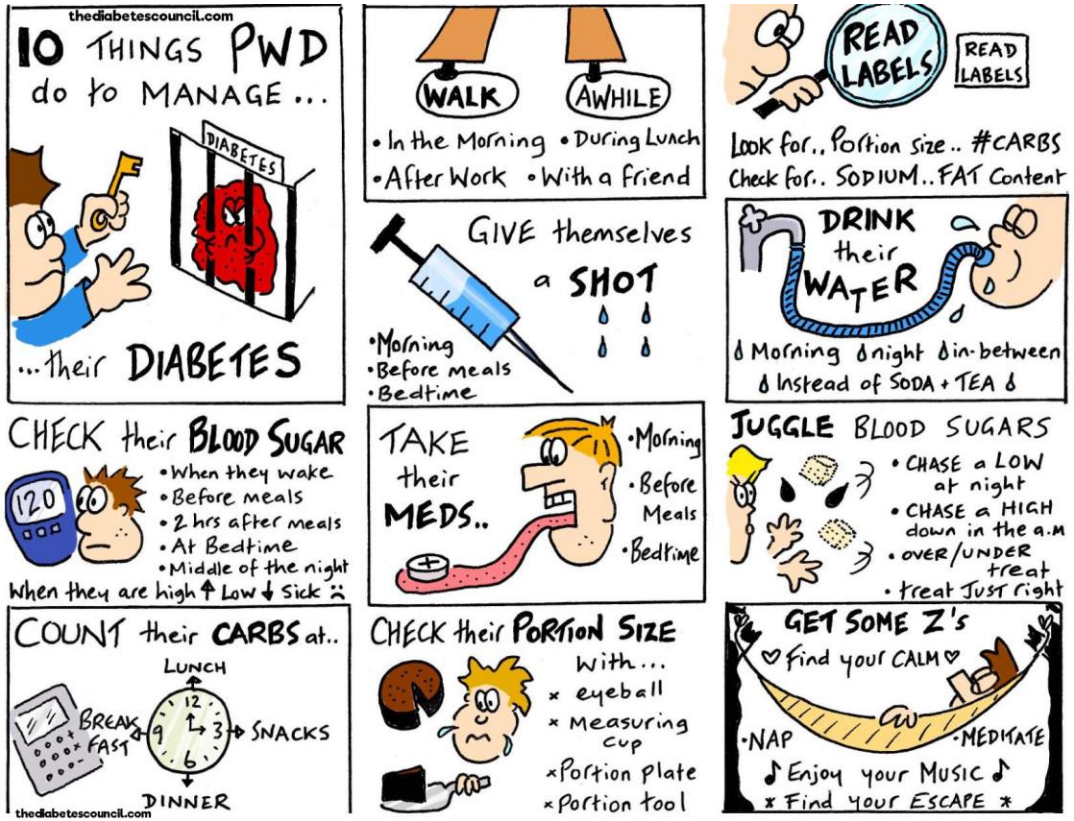


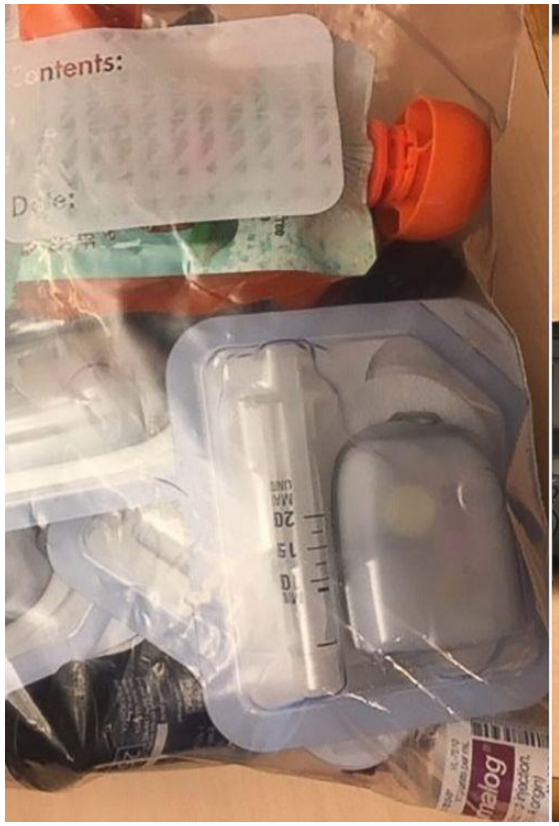
Components of an “Artificial Pancreas”

iCGM

ACE Pump

iController

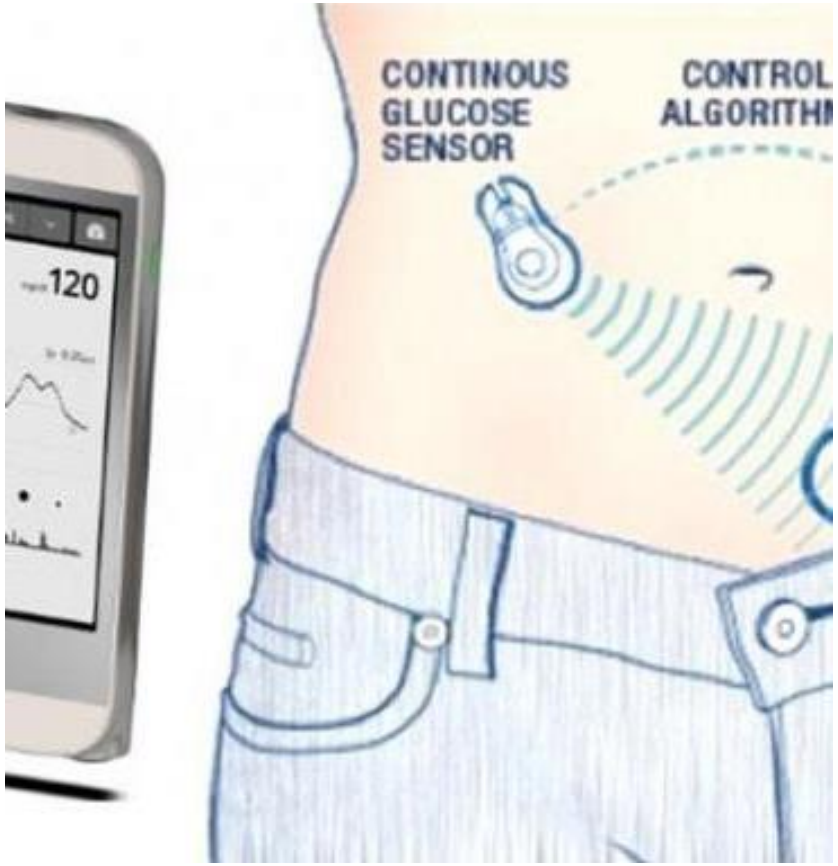




Daily Struggle for People with Diabetes
So many tools to juggle

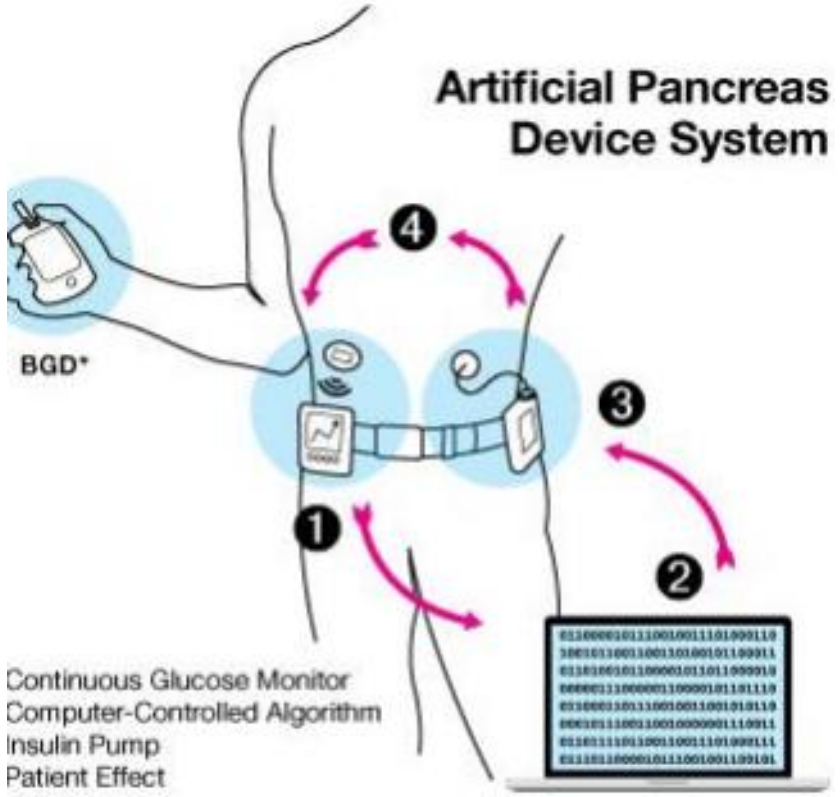
FDA helps to fulfill vision of “Artificial Pancreas”

- Components by different manufacturers
- PMA pathways inhibiting timely access to novel technology
  - FDA reviewers faced with many CGMs and sensor-augmented pumps



FDA Integral Partner to Vision

- Component specific risks
  - Sensor glucose accuracy
  - Pump infusion accuracy
  - Algorithm
- Risks as a result of integration
- Special controls for each
- Make it “plug and play”



Step 1: iCGM (DEN170088)

FDA Search Menu

IN THIS SECTION: Press Announcements

← Press Announcements

FDA NEWS RELEASE

FDA authorizes first fully interoperable continuous glucose monitoring system, streamlines review pathway for similar devices

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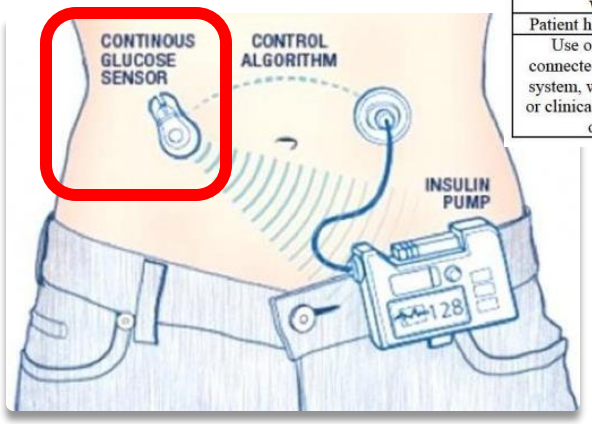
For Immediate Release: March 27, 2018

The U.S. Food and Drug Administration today permitted marketing of the Dexcom G6 integrated continuous glucose monitoring (iCGM) system for determining blood glucose (sugar) levels in children aged two and older and adults with diabetes. This is the first type of continuous glucose monitoring system permitted by the agency to be used as part of an integrated system with other compatible medical devices and electronic interfaces, which may include automated insulin dosing systems, insulin pumps, blood glucose meters or other electronic devices used for diabetes management. Today's authorization also classifies this new type of device in class II and subjects it to certain criteria called special controls. This enables developers of future iCGM systems to bring their

fda.gov/.../fda-authorizes-first-fully-interoperable-continuous-gl...

Identified Risk	Special Control
Inaccurate values lead to inappropriate treatment decisions	Clinical Performance

Identified Risks to Health	Mitigations Measures
Clinical action based on falsely high or falsely low inaccurate glucose values or inaccurate alerts may lead to inappropriate treatment decisions.	General Controls and special controls (1), (2), (3), (4), (5), (6), and (7)
Clinical action in pediatric patients based on falsely high or falsely low inaccurate values or inaccurate alerts due to poorer or different iCGM performance in pediatric populations.	General Controls and special controls (1), (2), (3), (4), (5), (6), and (7)
The inability to make appropriate treatment decisions when glucose values are unavailable due to sensor signal drop-out or loss of communication with digitally connected devices.	General Controls and special controls (1)(vii), (2), (3), (6), and (7)
Patient harm due to insecure transmission of data.	General Controls and special control (2)
Use of an iCGM as part of another digitally connected medical device system, such as an AID system, when the iCGM has inadequate analytical or clinical performance to support the intended use of the digitally connected device.	General Controls and special controls (2), (6), and (7)



Step 2: ACE pump (DEN180058)

FDA

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← Press Announcements

FDA NEWS RELEASE

FDA authorizes first interoperable insulin pump intended to allow patients to customize treatment through their individual diabetes management devices

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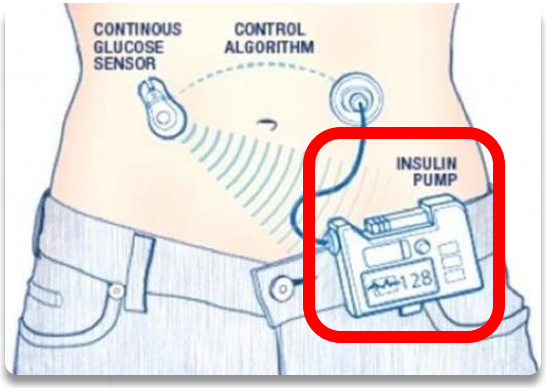
For Immediate Release: February 14, 2019

Español

The U.S. Food and Drug Administration today permitted marketing of the Tandem Diabetes Care t:Slim X2 insulin pump with interoperable technology (interoperable t:Slim X2) for delivering insulin under the skin for children and adults with diabetes. This new type of insulin pump, referred to as an alternate controller enabled (ACE) infusion pump, or ACE insulin pump, is the first interoperable pump, meaning it can be used with different components that make up diabetes therapy systems, allowing patients to tailor their diabetes management to their individual device preferences. Diabetes therapy systems may be comprised of an ACE insulin pump and other compatible medical devices, including automated insulin dosing (AID) systems, continuous glucose monitors (CGMs), blood glucose meters or other electronic devices used for diabetes management.



Identified Risk	Mitigation Measures
Patient harm due to inadequate drug delivery accuracy that leads to over infusion or under infusion of drug.	Basal and bolus drug delivery accuracy validation testing Device use life reliability testing Design mitigations to prevent cross-channeling Validated and traceable risk control measures for identified hazards
Patient harm due to undetected pump occlusions that pose risk of under infusion of drug.	Hazard detection (e.g., drug occlusion) validation testing
Patient harm due to incompatibility between the drug and the pump that may lead to over infusion or under infusion of drug, or exposure to harmful substances leached from pump materials into the infused drug solution.	Drug compatibility testing
Inability to provide appropriate treatment due to loss of communication with digitally connected alternate pump controller devices.	Validated communication specifications, processes, and procedures with digitally connected devices
Commands from the digitally connected alternate pump controller devices that conflict with existing pump commands may lead to unintended over or under infusion of drug.	Validated communication specifications, processes, and procedures with digitally connected devices Validated failsafe design features
Conflicting interfaces resulting in over or under delivery.	Validated communication specifications, processes, and procedures with digitally connected devices Validated failsafe design features
Patient harm due to insecure transmission of data.	Validated communication specifications, processes, and procedures with digitally connected devices
Patient harm due to inability to determine source of dosing error when used in an integrated system.	Validated data logging capability
Patient harm due to exposure to hazardous and non-biocompatible materials or pathogens.	Biocompatibility testing Validation of reprocessing procedures
Patient harm due to data transmission interference/electromagnetic disturbance.	Electrical safety, electromagnetic compatibility, and radio frequency wireless safety testing
Patient harm due to incorrect use of pump, operational, and/or use-related errors.	Human Factors testing Transparent pump performance descriptions in labeling

Step 3: AID Controller (DEN190034)

FDA

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← Press Announcements

FDA NEWS RELEASE

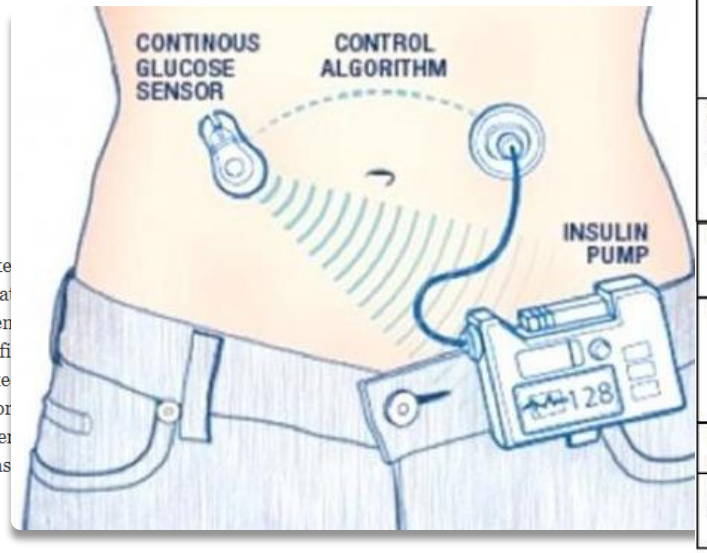
FDA authorizes first interoperable, automated insulin dosing controller designed to allow more choices for patients looking to customize their individual diabetes management device system

Share Tweet LinkedIn Email Print

For Immediate Release: December 13, 2019

Español

The U.S. Food and Drug Administration today authorized marketing of the Tandem Diabete
Control-IQ Technology, an interoperable automated glycemic controller device that automat
adjusts insulin delivery to a person with diabetes by connecting to an alternate controller-en
insulin pump (ACE pump) and integrated continuous glucose monitor (iCGM). This is the fi
controller that can be used with other diabetes devices that are also designed to be integrate
customizable diabetes management system for automated insulin delivery. This FDA author
paves the way for iCGMs and ACE pumps to be used with an interoperable automated glycer
controller as a complete automated insulin dosing (AID) system. AID systems typically cons
pump, CGM and software to control the system of compatible devices.



Identified Risk	Mitigation Measures
Patient harm due to inappropriate drug delivery	Clinical data demonstrating device performance Certain software validation testing User training plan Certain drug compatibility information in labeling
Risk due to poorer or different performance in pediatric populations	Clinical data demonstrating device performance in pediatric population Certain warning statements and precautions in labeling
Risk due to the inability of the controller to handle different pharmacokinetic/pharmacodynamic characteristics of the drugs	Clinical data demonstrating device performance Drug compatibility information in labeling User training plan Human factors testing
Risk due to lack of compatibility of connected devices	Certain validation of communication specifications, processes, and procedures with digitally connected devices Limitations on interoperable devices
Risk of connected devices having inadequate performance to allow safe use of the controller	Specifications for performance of connected devices Certain validation of communication specifications, processes, and procedures with digitally connected devices Limitations on interoperable devices
Failure to report device malfunctions or adverse events to the device manufacturer	Plans and procedures for assigning post-market responsibilities.
Risk of latent flaws in software	Robust software validation testing Certain validation of communication specifications, processes, and procedures with digitally connected devices Certain verification and validation of risk control measures
Failure to provide appropriate treatment due to loss of communication with connected devices	Certain verification and validation of risk control measures Certain validation of communication specifications, processes, and procedures with digitally connected devices
Risk due to insecure transmission of data	Certain validation of communication specifications, processes, and procedures with digitally connected devices
Failure to correctly operate the device	Human factors testing User training plan Compatible devices listed in labeling Certain warning statements and precautions in labeling
Failure to correctly determine the root cause of device malfunctions	Certain verification and validation of logging capability
Risk due to data transmission interference/electromagnetic disturbance	Certain verification and validation of electrical safety, electromagnetic compatibility, and radio frequency wireless testing

FDA Cleared iCGMs, iControllers and ACE Pumps – 2023

iCGMs Integrated Continuous Glucose Monitor	iControllers Interoperable Automated Glycemic Controller	ACE Pumps Alternate Controller-Enabled Insulin Pump
Dexcom G6	Tandem Control-IQ Technology	Tandem t:slim X2
Dexcom G7	Omnipod 5 Controller	Omnipod 5
FreeStyle Libre 2	Tidepool Loop	
FreeStyle Libre 3		

Summary

De Novo Pathway is more accessible than ever

Do your research - know your device risk profile

Consult with business leadership on strategy

Train your staff and manage change

AdvaMed Virtual Event
510(k) and **De Novo** Submissions Workshop

Peter J. Yang, PhD, RAC
De Novo Program Lead
OPEQ/ORP/Division of Submission Support
CDRH/FDA

Agenda

- Learn how to use the Pre-Submission process
- Learn what FDA does during the De Novo review process
- Recap changes in the De Novo final rule
- Learn what happens after a De Novo request has been granted

What Is a De Novo Request?

- Intended for **new types of devices** that are low-to-moderate risk that are otherwise automatically classified into class III
- Request to classify the device into class I or class II based on **reasonable assurance of safety and effectiveness** (**not substantial equivalence**)
- If granted:
  - FDA **creates a new classification regulation**
  - the new device type is regulated through 510(k), if class II
  - the De Novo device serves as the first predicate device of its kind

DE NOVO PRE-SUBMISSIONS

De Novo Pre-Submission Topics

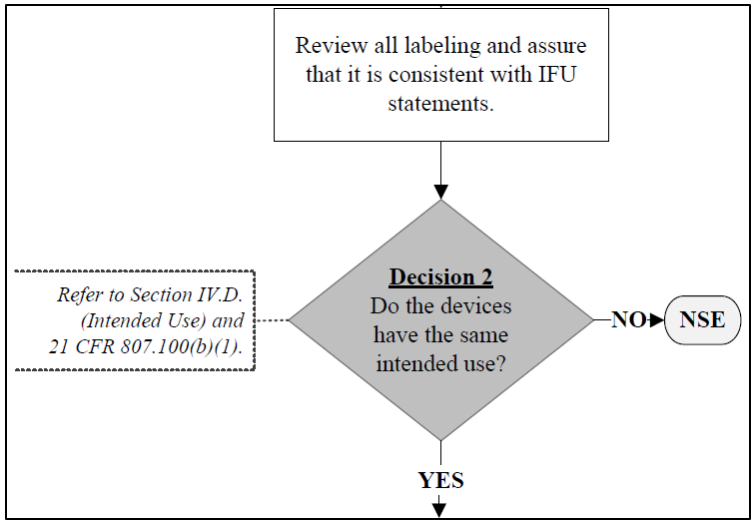
- Get feedback on whether your device is eligible for De Novo classification
- Get feedback on study designs for clinical studies and non-clinical testing
- Get feedback on FDA's concerns regarding risks to health

Is the Product Eligible for De Novo?

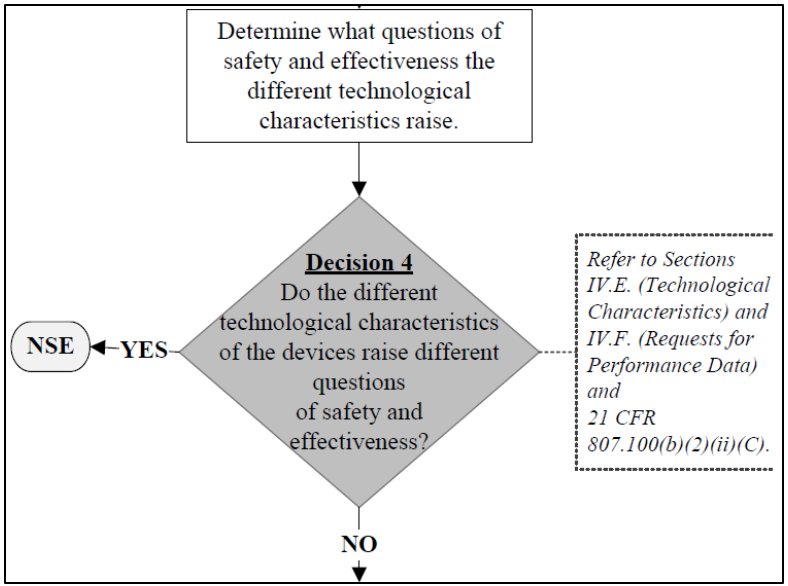
- **Must be a medical device (Section 201(h) of FD&C Act)**
- **Must not fit into any existing classification regulation**
  - Doesn't fit into existing Class I/II regulation, i.e., no predicate device (would be NSE)
    - Includes unclassified preamendment devices
  - Doesn't fit into existing Class III regulation
- **No approved PMA(s) for same device type**

(What Do We Mean By NSE?)

510(k) Program Guidance, Section IV.A.3; Appendix A – 510(k) Flowchart



Intended use



Technological characteristics

De Novo Eligibility Considerations

- Review pathway is generally dictated by a device's stated intended use and technology.
- Consider the following:
  - What devices has FDA reviewed in this space?
  - Does my device represent a new intended use or difference in technological characteristics, relative to existing legally marketed devices?
  - What is FDA's feedback on my device's regulatory pathway?

Pre-Subs and Planning Clinical Studies

- Get FDA's feedback and input on:
  - Study design and protocol
  - Patient population choices, including any important inclusion/exclusion criteria
  - Primary and secondary effectiveness endpoints, safety endpoints
  - Results and how to define study success
  - Areas of uncertainty in establishing benefits and risks of the device

Pre-Subs and FDA's Feedback on Risks

- Get FDA's feedback and input on:
  - Any risks of the device that have not been already addressed in your proposal for clinical and non-clinical testing
  - Your proposal for special controls (if class II) to mitigate those risks

FDA REVIEW OF DE NOVOS

MDUFA V User Fees and Performance

User Fees

- Standard fee = 30% of PMA user fee
- Small business fee = 25% of standard fee

Performance Goals

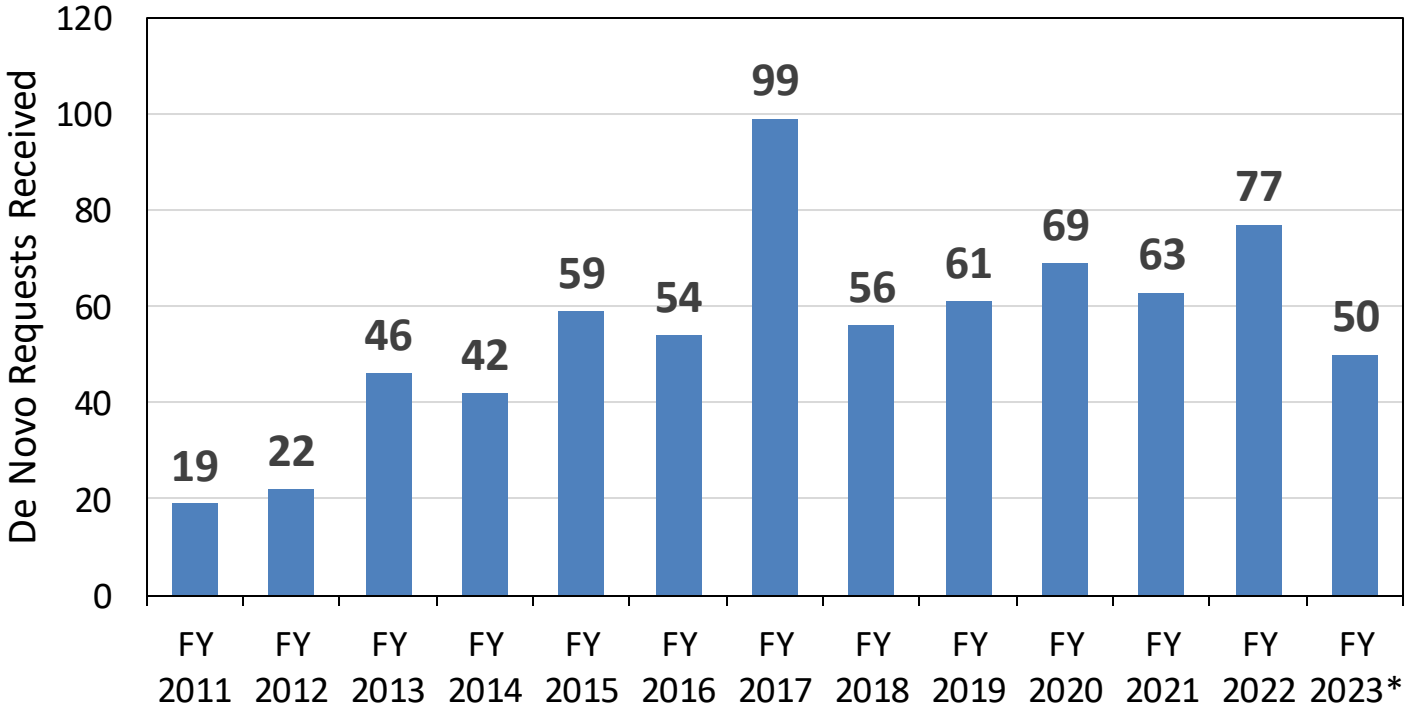
- Based on 150 FDA days
  - Different than statutory deadline of 120 FDA days
- Based on % of De Novo requests reaching final decision (grant, decline, withdraw)
- Performance goals increase if FY 2023 and FY 2024 goals are met

FY	Final Decision by Day 150
FY 2023	70% (same as FY 2022 goal)
FY 2024	70%
FY 2025	70%
FY 2026	70% (80% if FY 2023 goal is met)
FY 2027	70% (80% if FY 2023 goal is met; 90% if FY 2024 goal is met)

FY 2023 De Novo User Fee: $132,464
FY 2023 Small Business User Fee: $33,116

MDUFA: Medical Device User Fee Amendments

De Novos Received In CDRH



* As of 3/31/2023; As of 5/12/2023: 63

Overview of Review Process

- Verification of submission receipt and user fee receipt
- Acceptance review/technical screening within 15 days
  - Substantive review proceeds if file is accepted
- Substantive interaction mid-review
  - Proceed interactively (i.e. via email) without stopping the FDA review clock
  - Issue request for additional information ("AI letter") and the FDA review clock is put on hold
    - Submit response within 180 days
- Agency interacts via email throughout, as resources permit, and renders final decision, ideally within 150 FDA days

Classification Requirements

1. Determine if probable benefits outweigh probable risks
2. Identify probable risks to health for the device/product
3. Determine level of control needed:
   - general controls only = class I
   - general controls + special controls = class II

Together, these provide reasonable assurance of safety and effectiveness.

Benefit-Risk Assessment

- Based on totality of evidence in the De Novo request
- Assessment of probable benefits
- Assessment of probable risks
- Assessment of additional factors, for example:
  - Uncertainty
  - Patient perspectives
  - Addressing unmet medical need
- See FDA guidance document "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications"

New Classification Regulation

- Number (e.g., 21 CFR 878.XXXX)
- Name (name of device type)
- Identification
  - Intended use(s)
  - Key technological characteristics
  - Describes what FDA believes to be a single device type with a shared intended use and technology

Risk/Mitigation Table (Class II)

Identified Risks to Health	Mitigation Measures
Infection	Reprocessing validation Labeling
Adverse tissue reaction	Biocompatibility evaluation
???	???
???	???

- **Risk to Health:** Written from the patient's perspective
- **Mitigation Measures:** Categories of testing or other requirements which, together, mitigate a particular risk to health
- Risks and mitigations will be dependent on a device's intended use and technology

Special Controls (Class II)

- Each special control maps back to Risk/Mitigation Table
- Will be legally required for all devices of the same type
- Will be written into the new classification regulation
- De Novo device must meet its own special controls

Proposing Special Controls

- The Federal Food, Drug, and Cosmetic Act requires that you propose special controls (if proposing class II).
- Adopt FDA's conventions for writing Risk/Mitigation tables and special controls.
- Generalize special controls for devices in a regulation, not just to your device.
- Consider what would be least burdensome.
- Remember that FDA makes the final decision.

DE NOVO PROGRAM BACKGROUND

De Novo History and Evolution

- FDAMA (1997) — *Created De Novo pathway*
  - FDASIA (2012) — *Added Direct De Novo option*
    - 21st Century Cures (2016) — *Added combination products (21 CFR 3.2(e))*
      - FDARA (2017) — *Added user fees; resulted in new guidances*
        - De Novo RTA — *Final guidance issued September 2019*
          - De Novo Final Rule — *In effect January 3, 2022*

What Is the De Novo Final Rule?

- Adds new regulations to the Code of Federal Regulations (CFR) that govern the De Novo review process
- 21 CFR 860: Medical device classification procedures
- De Novo regulations now placed at **21 CFR 860 Subpart D**

21 CFR 860 Subpart D Overview

- 21 CFR 860 Subpart D: 860.200 – 860.260
  - 860.200: Purpose and applicability.
  - 860.210: De Novo request format.
  - 860.220: De Novo request content.
  - 860.230: Accepting a De Novo request.
  - 860.240: Procedures for review of a De Novo request.
  - 860.250: Withdrawal of a De Novo request.
  - 860.260: Granting or declining a De Novo request.

De Novo Regulation Distinctives

- Specifies submission content requirements
- Codifies acceptance review process
- Adds specific inspection authority
- Outlines specific reasons for declining a De Novo, including reasons related to eligibility, inspections, and non-clinical and clinical data deficiencies

21 CFR 860.220: De Novo request content.

- Table of contents
- Administrative information
- Regulatory history
- Device name
- Indications for use
- Device description
- Alternative practices and procedures
- Classification summary
- Summary of risks and mitigations
- Proposed special controls
- Classification recommendation
- Standards
- Summary of studies
- Benefit and risk considerations
- Technical sections:
  - Non-clinical testing
  - Software
  - Clinical testing
- Other information
  - Bibliography
  - Other information reasonably known to the requester
  - Other information to support reasonable assurance of safety and effectiveness
- Samples (if requested)
- Labeling

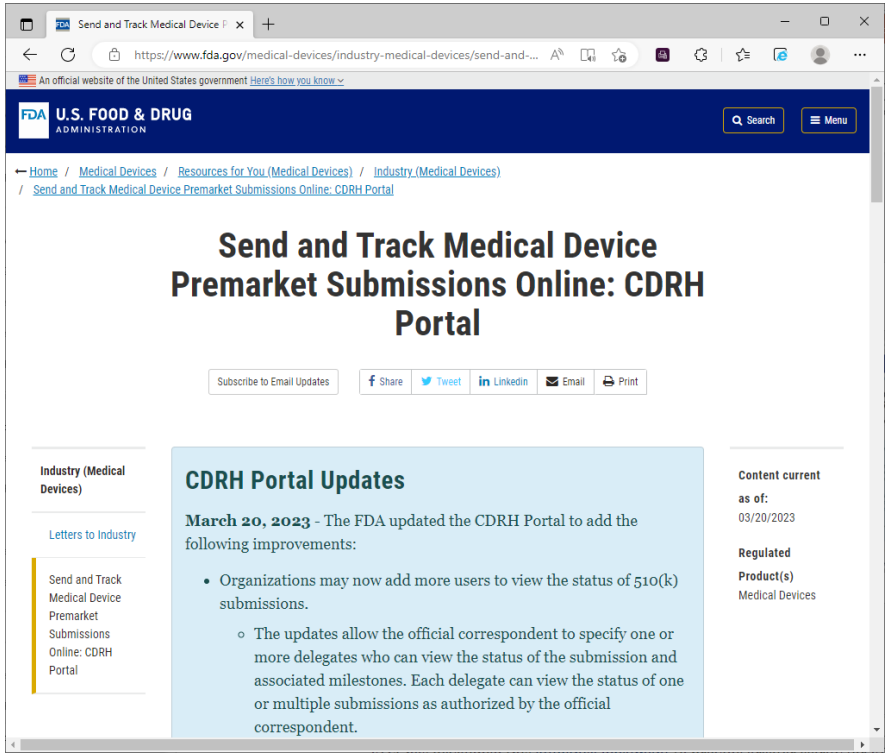
Blue text: De Novo classification-specific elements

Electronic Submission Template And Resource (eSTAR)

- Official De Novo eSTAR available as a complex PDF form
- RTA requirements are automated within eSTAR
- eSTAR files will be screened for technical completeness
- See the Voluntary eSTAR Program webpage

Use the CDRH Portal

- Send medical device submissions to CDRH electronically instead of through the mail
- All submissions are processed by our Document Control Center (DCC) during normal business hours
- You can submit eSTAR or eCopy submissions
- 510(k) submissions require eSTAR starting October 1, 2023, but De Novo eSTAR is voluntary until further notice



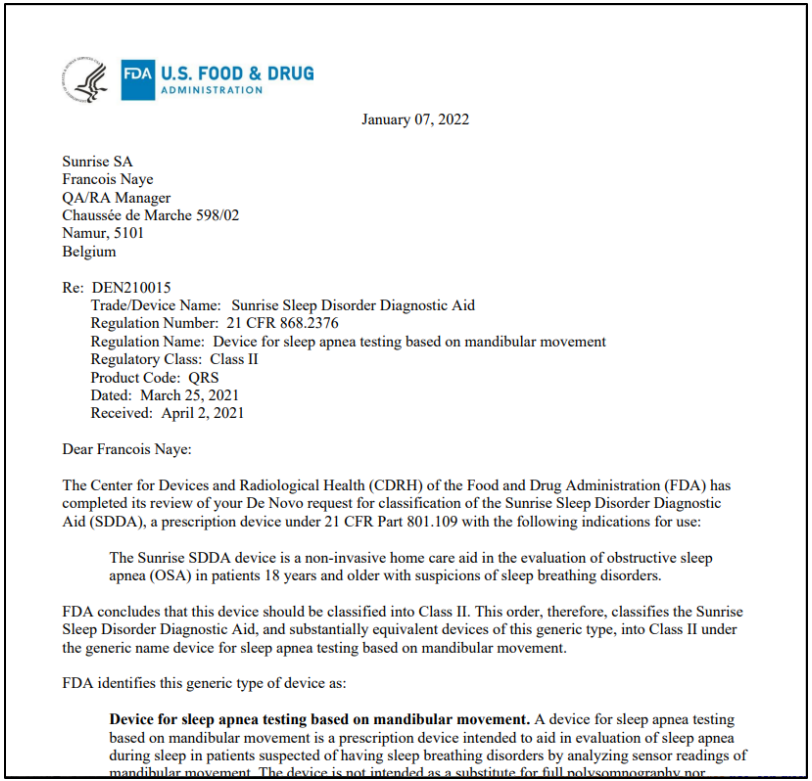
AFTER A DE NOVO HAS BEEN GRANTED

When a De Novo Is Granted

- FDA sends and publishes letter on web site:
  - New device may be legally marketed
    - Subject to applicable requirements
  - New classification regulation is established
  - New device may be used as a predicate device
- FDA publishes Decision Summary
- FDA publishes notice in Federal Register to update the Code of Federal Regulations (CFR)

Granting Order (Classification Order)

- Issuance of a granting order creates the regulation
- Granting order includes:
  - Indications for use
  - Regulation identification
  - Risk/Mitigation Table (if class II)
  - Special controls (if class II)



U.S. FOOD & DRUG ADMINISTRATION

January 07, 2022

Sunrise SA
Francois Naye
QA/RA Manager
Chaussée de Marche 598/02
Namur, 5101
Belgium

Re: DEN210015
Trade/Device Name: Sunrise Sleep Disorder Diagnostic Aid
Regulation Number: 21 CFR 868.2376
Regulation Name: Device for sleep apnea testing based on mandibular movement
Regulatory Class: Class II
Product Code: QRS
Dated: March 25, 2021
Received: April 2, 2021

Dear Francois Naye:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your De Novo request for classification of the Sunrise Sleep Disorder Diagnostic Aid (SDDA), a prescription device under 21 CFR Part 801.109 with the following indications for use:

The Sunrise SDDA device is a non-invasive home care aid in the evaluation of obstructive sleep apnea (OSA) in patients 18 years and older with suspicions of sleep breathing disorders.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the Sunrise Sleep Disorder Diagnostic Aid, and substantially equivalent devices of this generic type, into Class II under the generic name device for sleep apnea testing based on mandibular movement.

FDA identifies this generic type of device as:

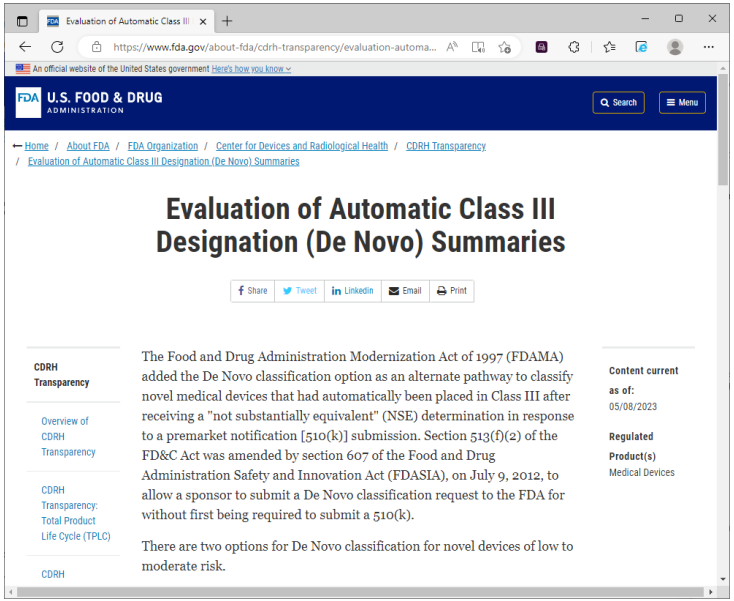
Device for sleep apnea testing based on mandibular movement. A device for sleep apnea testing based on mandibular movement is a prescription device intended to aid in evaluation of sleep apnea during sleep in patients suspected of having sleep breathing disorders by analyzing sensor readings of mandibular movement. The device is not intended as a substitute for full polysomnography nor

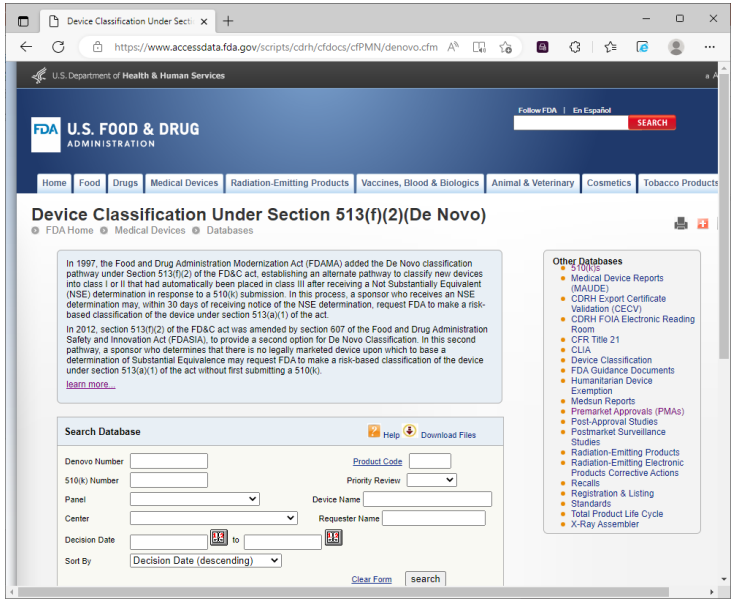
Decision Summary

- The granting order and Decision Summary contain:
  - New regulation (number, name, and identification)
  - Risk/Mitigation Table (if class II)
  - Special controls (if class II)
  - Non-clinical and clinical data summaries
  - Benefit-risk discussion
- The Decision Summary:
  - Provides transparency into FDA's decision making
  - Facilitates future 510(k) submissions
- Decision Summaries are redacted for company confidential information

De Novo Databases

- De Novo Transparency Web Page
- De Novo Searchable Database
- Provides access to both granting orders and Decision Summaries





Postmarket Requirements and Changes

- No special postmarket requirements for granted De Novos, unless otherwise specified
- Upon granting, 510(k) policies apply, including:
  - Deciding when to submit a 510(k) for a change to the De Novo device
  - Other companies can now use the De Novo device as a predicate device for their own 510(k)s

How to Refer to De Novo Requests

- Terminology
  - 510(k)s are “cleared”
  - PMAs are “approved”
  - De Novo requests are “granted”
- You can use the following terms:
  - “The FDA authorized marketing of…”
  - “The FDA granted marketing of…”
  - “The FDA permitted marketing of…”
- Use active voice and “marketing”, i.e. “The FDA authorized marketing of our test on such date/for such indications…” versus “FDA-granted test,” “FDA-authorized test,” “FDA-permitted test”

Tips and Insight from FDA

1. **Use the pre-submission process** to get feedback on your clinical study design.
2. Use pre-submissions to **understand what FDA's concerns are** regarding the risks of your device and the critical pitfalls that should be accounted for.
3. **Be transparent** about how you envision this device being used and how it would benefit patients. Help us understand your "story."
4. **Adopt FDA's conventions** for writing risk/mitigation tables and special controls. Generalize for devices in your proposed regulation. **Remember FDA makes the final decision**.
5. The medical device review paradigm (**whether eSTAR or eCopy**) assumes that the original submission makes the complete "case" for your device.
6. Ensure that you **understand FDA's underlying concerns** in any deficiency we send you.
7. Be aware that **things can change** as FDA completes its understanding of your device.

De Novo Resources

- De Novo Final Rule in the Federal Register
- De Novo Classification Requests (includes guidance links at the bottom of the webpage)

Peter J. Yang, PhD, RAC
De Novo Program Lead
FDA/CDRH/OPEQ/Office of Regulatory Programs
Peter.Yang@fda.hhs.gov


FDA
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ADMINISTRATION

510(k) and De Novo Case Studies

Quynh Hoang
Senior Regulatory Consultant
FDA & Life Sciences Team
Government Matters Practice

Disclaimer

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

Outline

1. Recap
2. Case Studies
    a. 510(k) or De Novo Pathway
    b. Modifications to 510(k)-Cleared or De Novo-granted Devices
    c. Promotional Practices

Recap

510(k) or De Novo Pathway Recap

Compared against a legally marketed (non-PMA) device, the new device has:

1. Same intended use? [Yes: go to 2; No: go to 4]
2. Same technological characteristics? [Yes: 510(k); No: go to 3]
3. Different technological characteristics that do not raise a new question of safety or effectiveness? [Yes: 510(k); No: go to 4]

4. Technological characteristics for the proposed intended use are well understood (i.e., bench/animal/clinical testing can be defined to assure device safety and performance?) [Yes: De Novo; No: go to 5]

5. Likely a PMA device.

Modifications and 510(k) Recap

For each change,

1. Refer to the device-specific guidance, if available;
2. Determine the areas impacted by change (e.g., labeling, technology, software, etc.);
3. Prepare a Regulatory Assessment that covers each impacted area using the considerations and associated flowcharts in FDA's guidance documents, "Deciding When to Submit a 510(k) for … Change(s)":
    - Assess potentially changing the cleared intended use;
    - Assess whether new tests were needed for the change in technology;
    - Consider potential for new risks;
    - Consider test results;
    - Consider unintended consequences; and,
    - Cumulative effects of changes since most recent clearance.
4. Document to the internal record (letter-to-file) **OR** File a new 510(k).

Fundamental Advertising & Promotion Principles Recap

- All promotional communications (whether advertising or promotional labeling) must:
  - Be consistent with and not contrary to the FDA-cleared indications for use (*i.e.*, consistent with label);
  - Disclose warnings and risk information (fair balance);
  - Be adequately substantiated; and
  - Be truthful and not misleading
    - Ex: 510(k) is "cleared" – not "approved" or "FDA-registered"

510(k) and De Novo Case Studies

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5. Likely a PMA device.

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    - Ex: 510(k) is "cleared" – not "approved" or "FDA-registered"

510(k) or De Novo

510(k) or De Novo

- Plastic eye patch and glasses are 510(k)-Exempt devices for treating amblyopia (lazy eye).
- Luminopia would like to market its Virtual Reality game system for treating amblyopia.

coastaleye.com

pharmaphorum.com

Question:

Should Luminopia plan to submit a

(a) 510(k), or

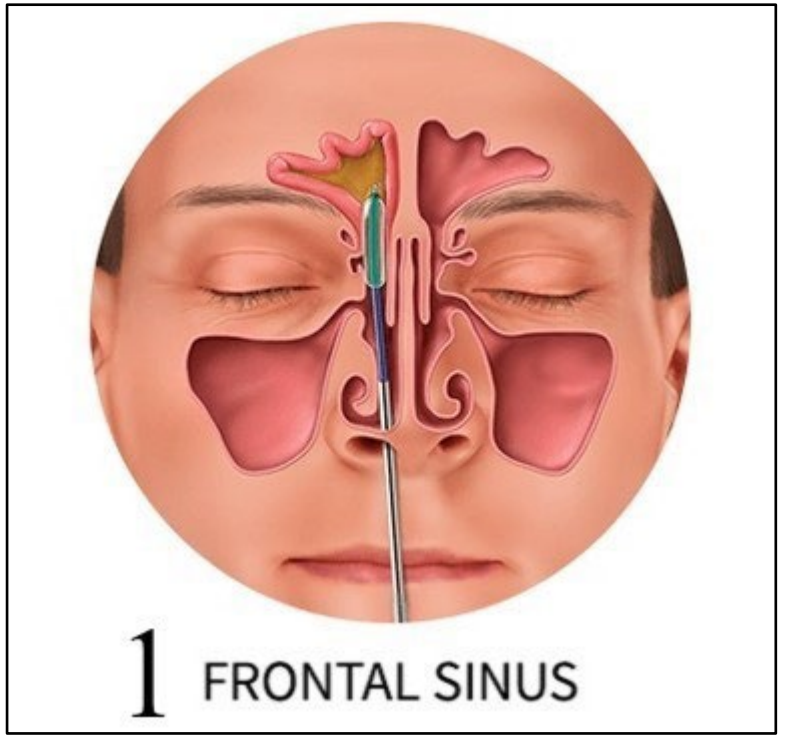
(b) De Novo?

510(k) or De Novo

- ENTco received clearance for its NasoDilation System, as shown.

- Cleared Indications :

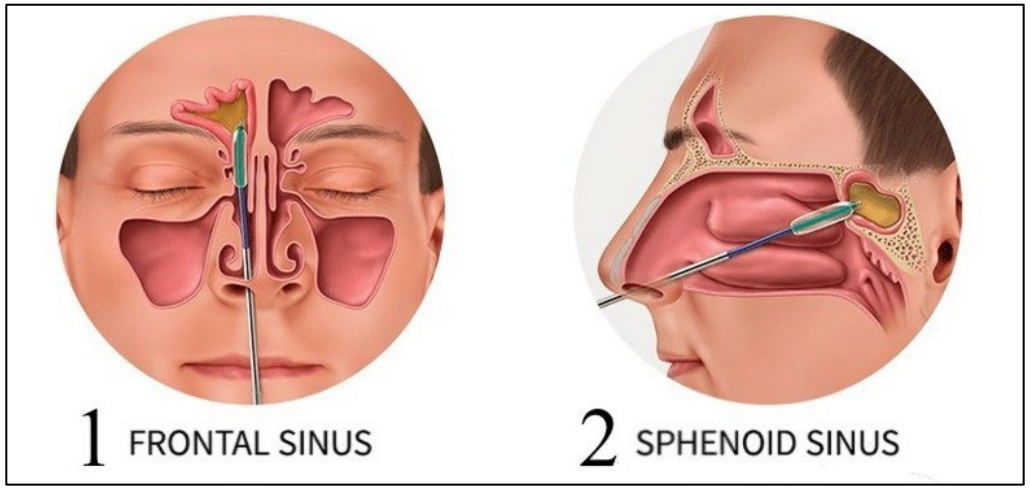
  The NasoDilation System is intended to provide a means to access the frontal sinus space and to dilate the frontal recess, frontal sinus ostia and spaces within the frontal sinus cavity for diagnostic and therapeutic procedures.



medgadget.com

510(k) or De Novo

- ENTco received clearance for its NasoDilation System for #1. Frontal Sinus.
- ENTco would like to market the same technology for #2. Sphenoid Sinus.



medgadget.com

Question:

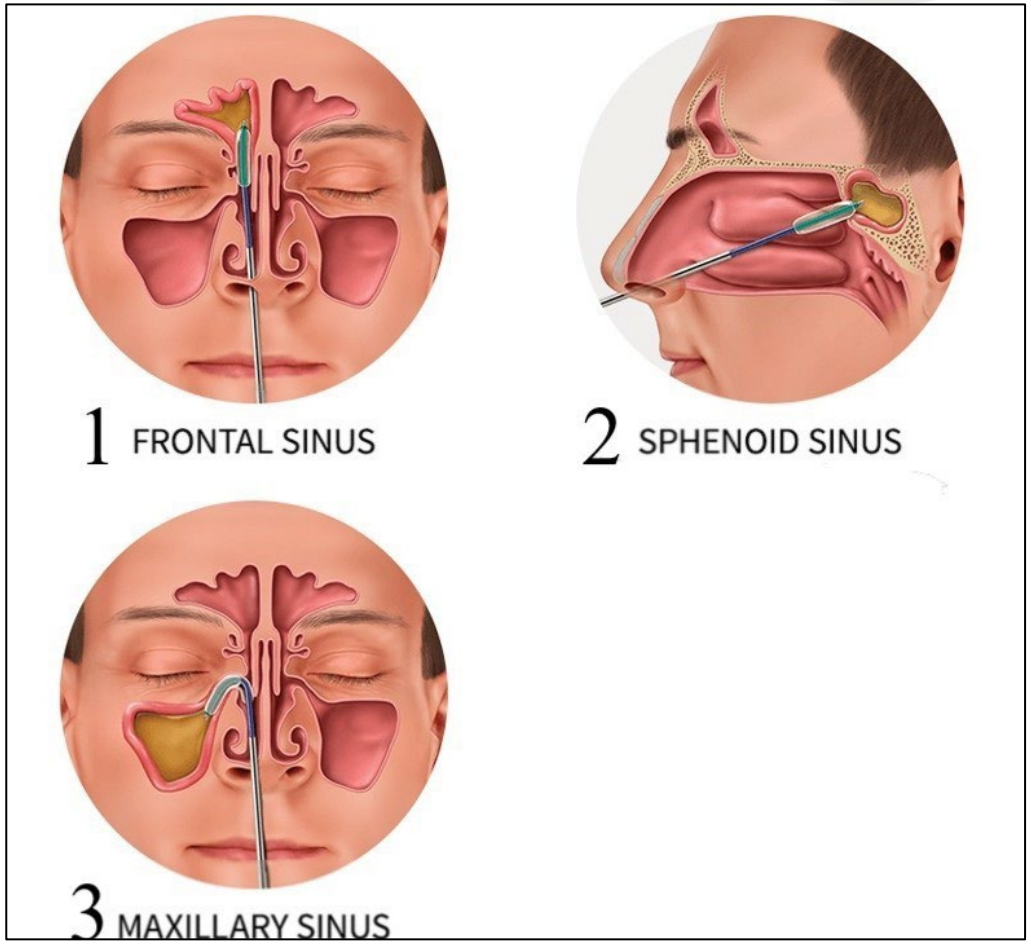
Should ENTco plan to submit a

(a) 510(k), or

(b) De Novo?

510(k) or De Novo

- ENTco received clearances for its NasoDilation System for #1. Frontal Sinus and #2. Sphenoid Sinus.
- ENTco would like to market a similar technology for #3. Maxillary Sinus



entellusmedical.com

Question:

Should ENTco plan to submit a

(a) 510(k), or

(b) De Novo?

510(k) or De Novo

- ENTco received clearances for its NasoDilation System for #1. Frontal Sinus, #2. Sphenoid Sinus, and #3. Maxillary Sinus.

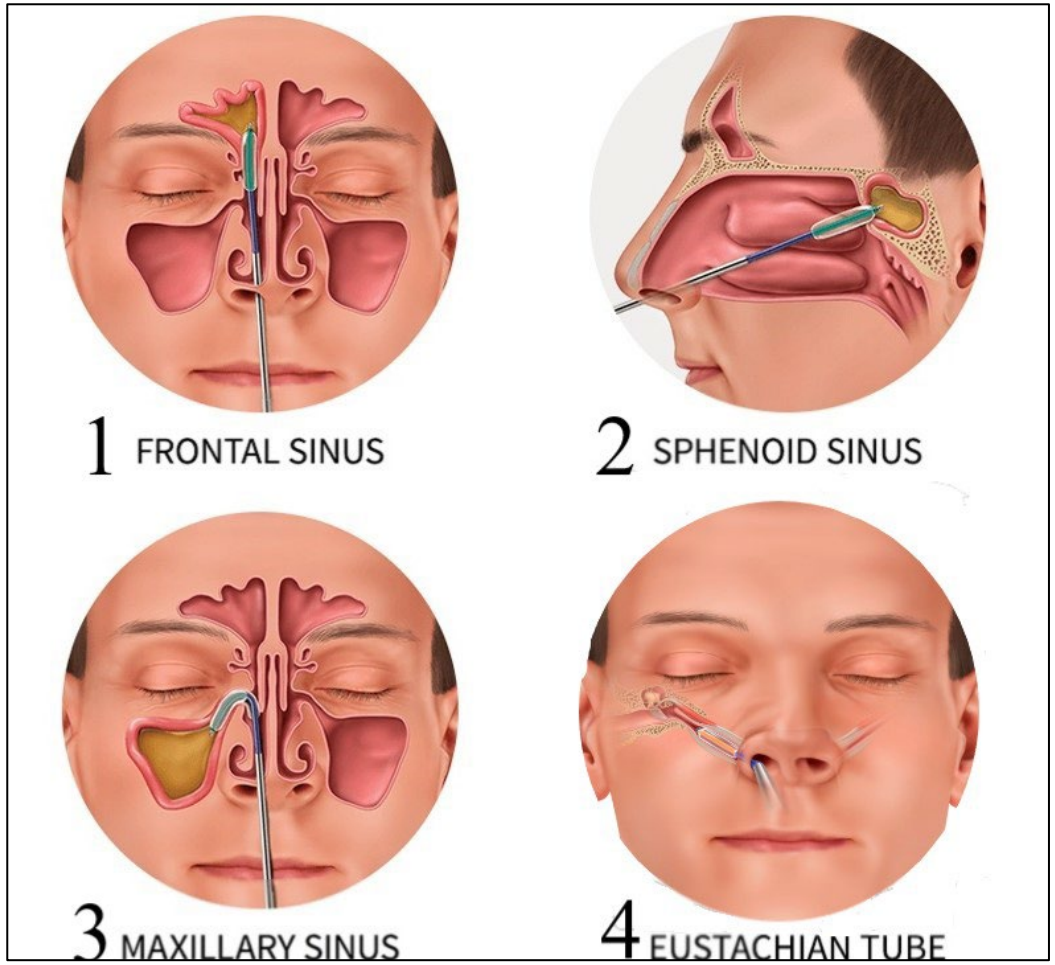
- ENTco would like to market a similar technology for Eustachian Tube dilation.

Question:

Should ENTco plan to submit a

(a) 510(k), or

(b) De Novo?



entellusmedical.com and drgomd.com

Modifications To 510(k)-Cleared or De Novo-Granted Devices

510(k) Modifications Exercise

- BrainsRWe received clearance for its BrEEG System, as shown.
- Cleared Indications :

  The BrEEG System is an electroencephalograph intended to be used to acquire, display, store and archive electrophysiological signals.

  It is intended to be used by trained medical professionals in clinical environments such as hospital rooms, epilepsy monitoring units, etc.

  It can be used with patients of all ages but is not designed for fetal use.

510(k) Modifications Exercise

Post-clearance, BrainsRWe plans to market electrode caps with the number of electrodes as ordered by the physician.

510(k) Cleared Electrode Caps

Question:

Should BrainsRWe release the new electrode caps after

(a) testing and letter-to-file, or

(b) a new 510(k) clearance?

510(k) Modifications Exercise

Post-clearance, BrainsRWe plans to claim that the cleared BrEEG System can be used at home by patients under the supervision of medical professionals.

Cleared indications:

The BrEEG System is an electroencephalograph intended to be used to acquire, display, store and archive electrophysiological signals.

It is intended to be used by trained medical professionals in clinical environments such as hospital rooms, epilepsy monitoring units, etc.

It can be used with patients of all ages but is not designed for fetal use.

Question:

Should BrainsRWe make the new claim after

(a) testing and letter-to-file, or

(b) a new 510(k) clearance?

510(k) Modifications Exercise

Post-clearance, BrainsRWe plans to claim that the cleared BrEEG System can be used at home by patients under the supervision of medical professionals.

WHAT IF the Cleared indications were:

The BrEEG System is an electroencephalograph intended to be used to acquire, display, store and archive electrophysiological signals.

~~*It is intended to be used by trained medical professionals in clinical environments such as hospital rooms, epilepsy monitoring units, etc.*~~

It can be used with patients of all ages but is not designed for fetal use.

Question:

Should BrainsRWe make the new claim after

(a) testing and letter-to-file, or

(b) a new 510(k) clearance?

510(k) Modifications Exercise

Post-clearance, BrainsRWe plans to miniaturize the BrEEG System to make it portable.

Cleared indication and device:

The BrEEG System is an electroencephalograph intended to be used to acquire, display, store and archive electrophysiological signals.

It is intended to be used by trained medical professionals in clinical environments such as hospital rooms, epilepsy monitoring units, etc.

It can be used with patients of all ages but is not designed for fetal use.

Question:

Should BrainsRWe release the portable BrEEG System after

(a) testing and letter-to-file, or

(b) a new 510(k) clearance?

510(k) Modifications Exercise

Post-clearance, BrainsRWe plans to push out software upgrades to provide more options on how the EEG signals are to be displayed and printed.

Cleared indication:

The BrEEG System is an electroencephalograph intended to be used to acquire, display, store and archive electrophysiological signals.

It is intended to be used by trained medical professionals in clinical environments such as hospital rooms, epilepsy monitoring units, etc.

It can be used with patients of all ages, but is not designed for fetal use.

Question:

Should BrainsRWe release the new software after

(a) testing and letter-to-file, or

(b) a new 510(k) clearance?

510(k) Modifications Exercise

Post-clearance, BrainsRWe plans to push out software to enable the BrEEG System to point out epileptic episodes in the previously recorded data.

Cleared indication:

The BrEEG System is an electroencephalograph intended to be used to acquire, display, store and archive electrophysiological signals.

It is intended to be used by trained medical professionals in clinical environments such as hospital rooms, epilepsy monitoring units, etc.

It can be used with patients of all ages, but is not designed for fetal use.

Question:

Should BrainsRWe release the new software after

(a) testing and letter-to-file, or

(b) a new 510(k) clearance?

Promotional Practices For 510(k) Devices

Promotional Practices Exercise

Somnem Technologies newest product is a 510(k)-cleared device called *NoSnorz.*

Indication: *The NoSnorz is an intraoral device intended to reduce or alleviate snoring and mild to moderate obstructive sleep apnea.*

Contraindications: *NoSnorz* is contraindicated in patients with severe respiratory disorders or advanced periodontal disease.

Warnings: *NoSnorz* should not be used when the patient experience jaw pain or mouth injury.

Precautions: Patients who had dental implants within the last 6 months should be further assessed as the intraoral device may move the implant.

Cleared Labeling:

NoSnorz Patient-Directed Marketing Proposal

Indication: *The NoSnorz is an intraoral device intended to reduce or alleviate snoring and mild to moderate obstructive sleep apnea.*

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Claim on Webpage for Patients:

1. **Consistent with Labeling?**
2. **Fair Balance?**
3. **Adequately Substantiated?**
4. **Truthful and Not Misleading?**

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3. **Adequately Substantiated?**
4. **Truthful and Not Misleading?**

Patient Testimonial on Social Media:

"I have been using *NoSnorz* for the last six months and I have never slept better in my life! I can sleep through the night, all night long – and so can my wife now that she's no longer woken by my snoring."

NoSnorz Physician-Directed Marketing Proposal

Indication: *The NoSnorz is an intraoral device intended to reduce or alleviate snoring and mild to moderate obstructive sleep apnea.*

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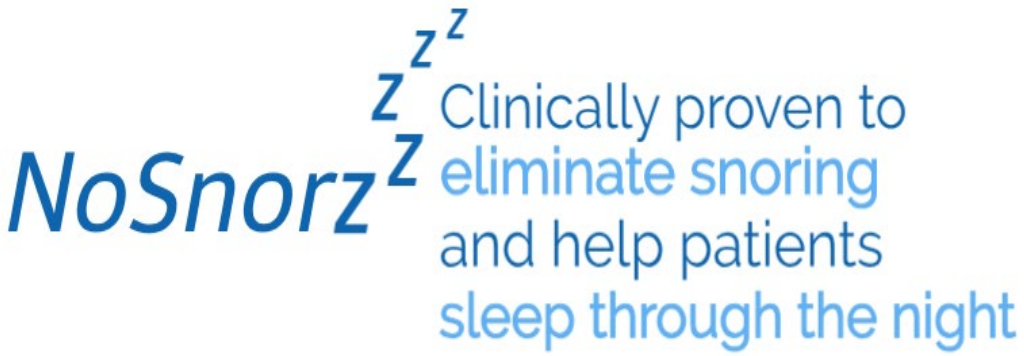
1. **Consistent with Labeling?**
2. **Fair Balance?**
3. **Adequately Substantiated?**
4. **Truthful and Not Misleading?**

Claim in Physician Brochure:



NoSnorz Physician-Directed Marketing Proposal

Indication: *The NoSnorz is an intraoral device intended to reduce or alleviate snoring and mild to moderate obstructive sleep apnea.*

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Precautions: Patients who had dental implants within the last 6 months should be further assessed as the intraoral device may move the implant.

1. **Consistent with Labeling?**
2. **Fair Balance?**
3. **Adequately Substantiated?**
4. **Truthful and Not Misleading?**

Sales reps to distribute copies of medical journal articles discussing NoSnorz for:

- patients with severe chronic sleep apnea.
- temporomandibular joint (TMJ) disorder.

Acknowledgment- Promotion & Advertising Slides

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