Premarket Notifications 510(k) and De Novo Requests

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Agenda

1 The 510(k) Paradigm and Submission

2 De Novo Requests

The 510(k) Paradigm and Submission

Overview

- The 510(k) Program was established over 45 years ago as part of the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act (FDCA) in 1976.
- Devices were much different in 1976…

Image source: JSTOR "Commemorating the 40th Anniversary of the 1976 Medical Device Amendments"

What is a 510(k)?

- Section 510(k) of the FDCA – notification of intent to market a medical device
- Classification process for devices
- FDA makes a determination regarding substantial equivalence
- “clearance” not “approval”

510(k) Notices are Required for:

- Small number of Class I devices (specifically called out in the regulations)
- 510(k) exempt devices where the new device exceeds the limitations of the exemption
  - The 8XX.9 limitation.
- Most Class II devices
- Preamendment Class III devices (marketed post-1976) for which PMAs are not currently required; very limited
  - FDA effort ongoing to classify these products
- Unclassified devices (with a product code) for which PMAs are not currently required;
  - FDA effort ongoing to classify these products

Criteria for 510(k) Clearance

- New (subject) device must be **“substantially equivalent”** with respect to both **Intended Use** and **Technological Characteristics**
  - Comparison is to a legally marketed “predicate” device
- **Intended Use:**
  - New device must have the same intended use and similar indications for use
- **Technological Characteristics**
  - New device must have similar technological characteristics
  - Any differences must not raise different questions of safety or effectiveness compared to the predicate

What Can Be Used as a Predicate Device?

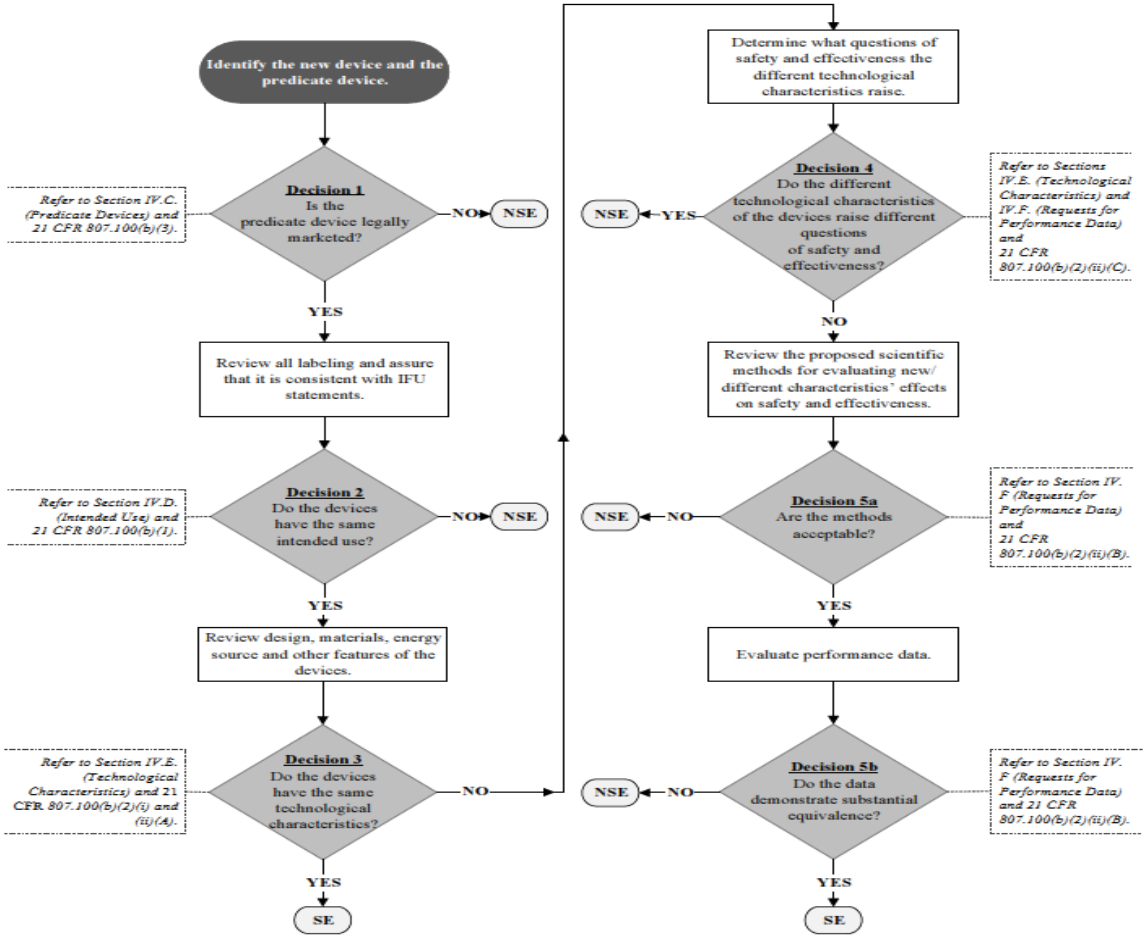
- Legally marketed class I or II device, whether exempt or 510(k)-cleared
- Class III device for which FDA has not yet called for PMA applications
- Pre-amendments devices, with proper documentation of commercial use before 1976
- Predicate that was cleared via *de novo* route
- NOT class III devices with PMA approval, no matter how many have been approved (unless down-classified)
- NOT a device inappropriately introduced to the market by a competitor without necessary FDA clearance/approval

What Does Substantial Equivalence Mean?

- FDA's Guidance "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]" (July 28, 2014) - Outlines explanation of difference between indications for use and intended use, as well as how to assess when technological differences raise different questions of safety or effectiveness.

- *The term "substantially equivalent" is not intended to be so narrow as to refer only to devices that are identical to marketed devices nor so broad as to refer to devices which are intended to be used for the same purposes as marketed products. The Committee believes that the term should be construed narrowly where necessary to assure the safety and effectiveness of a device but not so narrowly where differences between a new device and a marketed device do not relate to safety and effectiveness.* (House Report No. 853, 94thCongress, 2d Session 36-37 (1976))

510(k) Flowchart



Decision 1

Is the predicate device legally marketed?

- Predicates can be
  - Preamendment devices marketed prior to May 1976
  - Any device that has been cleared via 510(k) notification
  - Any device that has been granted via de novo petition
  - Any class I exempt device
- Predicates cannot be
  - Devices that are marketed in Europe
  - Any device that has been approved via a PMA or HDE
- Keep in mind a marketed device may differ from what FDA cleared

Decision 2

Do the devices have the same intended use?

- **“Intended use”** means the general purpose of the device or its function.
- **“Indications for use”** describes the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended.
    - FDA will “Review all labeling and assure that it is consistent with IFU statements.”
- Intended use also encompasses
    - How the device will be used
    - Therapeutic effect

Indications for Use Must Be Similar

- Any differences in indications for use must not introduce a new intended use or raise different questions of safety or effectiveness
- When has FDA found a change to indications to be a change to intended use?
  - Tissue adhesive: A new general surgery device is used in a **body cavity**, while the predicate device is used only to treat **external injuries**.
    - A comparison to the predicate device may not be adequate to address the risk of infection posed by internal use of the device.
  - Surgical laser: New indications for a surgical ablation device to treat **atrial fibrillation**, while predicate cleared for **ablation of cardiac tissue**
    - To treat atrial fibrillation requires extensive ablation to create linear lines of conduction block in a maze-like pattern that eliminates fibrillatory conduction in the atria.
    - The risks of iatrogenic heart block and collateral cardiac or extra-cardiac damage are either raised or increased when such a complex and extensive lesion set is created.

Decision 3

Do the devices have the same technological characteristics?

- FDA will review design, materials, energy source and other features of the devices.
- Technological features include
  - Size and shape
  - Material
  - Power input/output
- Same technological characteristics occurs only when devices are identical
  - If devices are identical then SE determination is made

Decision 4

Do the different technological characteristics of the devices raise different questions of safety and effectiveness?

- A "different question of safety or effectiveness" is a question not applicable to the predicate device, and poses a significant safety or effectiveness concern for the new device.
- Example
  - **Predicate:** A mechanical device used for embryo dissection
  - **New Device:** An electrical device used for embryo dissection
  - **Why:** changes the way the device operates and raises different safety concerns
    - the heating aspect can affect the embryo.
    - Because these types of questions do not necessary to take into account the predicate device, the new device would be found NSE.

Decision 5a

Are the scientific methods acceptable?

- FDA reviews the proposed scientific methods for evaluating new/ different characteristics' effects on safety and effectiveness
- Determine if the right tests were done
- If not, FDA will request them and if they are not supplied determine the device is not substantially equivalent (NSE)

Decision 5b

Do the data demonstrate substantial equivalence?

- FDA will evaluate performance data.
- Data can have an absolute performance goal
  - SAL of 10^{-6}
  - Survive 5 Mc at 10 kN
- Data can have relative performance goals
  - Not worse than predicate device

Predicate Considerations

- No Split Predicates
  - FDA not able to accept SE arguments where one predicate has the same intended use but technological characteristics that raises different questions while the other predicate has a different intended use but raises the same S&E questions
- Multiple predicates can only be used when each predicate passes decisions 1 – 4 on the chart
  - i.e. each predicate must have the same intended use and similar S&E questions
  - It is possible to use predicate A for bench test A, and predicate B for bench test B
  - FDA prefers the selection of a single predicate
    - Requests designation of primary and additional predicates when multiple are used
    - Branch dependent

Reference Device

- Not a predicate
- If a manufacturer successfully navigates through Decision Point 4 on the Flowchart using a single predicate device, other legally marketed devices, which FDA calls “reference devices,” may be used to support scientific methodology or standard reference values at Decision Point 5a or b.

Types of 510(k) Submissions

- 3 types of 510(k) submissions
  - Traditional
  - Special
  - Abbreviated

Traditional 510(k)

- Most commonly used
- No limitations on selection of predicate
- Provide complete test reports of supporting data
- Submission timeline
  - Refuse to accept (RTA) by day 15
  - Substantial interaction by day 60
  - Single 180 day hold freezes FDA clock
  - Final determination by day 90
  - Total day goal of 128 days FY 2023 (MDUFA V)

Special 510(k)

- Provides a shorter review time
  - Refuse to accept (RTA) by 15 days
  - Substantial interaction by 30 days
  - Final determination by 30 days after response, with a single 180 day hold
- To qualify must:
  - Be modifying your own predicate
  - Not changing the indications for use
  - Not changing the fundamental technology of the device
  - FDA must not need to see complete test reports
- Content differs somewhat from Traditional 510(k)

Abbreviated 510(k)

- Same timeline as traditional 510(k)
- Can be used if
  - There is a device specific guidance document
  - Special controls for the device were established
  - CDRH has recognized the relevant consensus standards
- Allows the submission of summary report and declaration of conformity to standards in lieu of providing complete test reports
- Draft guidance to expand program to include demonstrating equivalence to FDA accepted acceptance criteria
- Manufacturers have the option to use a third party to assess conformance with the recognized standard

Review Process

Content of a 510(k)

- FDA regulations detail the specific information that each 510(k) submission must contain, including:
  - Proposed labeling
  - A statement regarding the similarities and differences between the device and others of comparable type
  - Supporting data
  - Any additional information regarding the device requested by FDA that is necessary for FDA to make a finding as to whether or not the device is substantially equivalent to a device in commercial distribution

Review Process

Refuse to Accept Policy for 510(k)s

- To focus FDA's review resources on complete 510(k) submissions and provide for a more efficient review process, FDA adopted a Refuse to Accept (RTA) policy for 510(k)s.
- The policy includes an early review against specific acceptance criteria.
- The submitter is informed within the first 15 calendar days after receipt of a submission if the submission is complete, and, if not, FDA identifies the missing elements.
- The 510(k) submitter may respond to an RTA notification by providing the missing information. A new submission and new user fee are not required.
- If a response to the RTA notification is not received within 180 days of the date of the notification, FDA will consider the 510(k) to be withdrawn.

- Reference FDA guidance Refuse to Accept Policy for 510(k)s (Sept. 13, 2019)

Review Process

Additional Information (AI) Request

- FDA requests AI when a 510(k) submission lacks the information necessary for the agency to continue or complete its review and to determine whether the device is SE or NSE.
- An AI request places the 510(k) review on hold. An AI request is an interim action that stops the review clock and marks the end of an FDA review cycle. The review clock resumes upon the receipt of a complete response to the AI request in the appropriate Document Control Center.
- Under the regulations, if the AI is not submitted within 30 days following the date of the request, FDA will consider the premarket notification to be withdrawn. However, FDA automatically grants an extension of a maximum of 180 days from the date of the AI request.

- Reference: 21 C.F.R. § 807.100; FDA guidance Guidance for Industry and FDA Staff: FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Goals (Oct. 2, 2017)

Review Process

FDA Decision Regarding a 510(k)

- After review of a 510(k) submission, FDA will:
  - Issue an order declaring the device substantially equivalent (SE)
  - Issue an order declaring the device not substantially equivalent (NSE)
  - Request additional information (AI)
  - Advise that a 510(k) is not required
- An applicant may not proceed to market until receiving an order declaring the device SE

- Reference: 21 C.F.R. § 807.100; FDA guidance Guidance for Industry and FDA Staff: FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Goals (Oct. 2, 2017)

Review Process

Options Following NSE Decision

- If FDA determines that a device is NSE, the applicant may:
  - Submit another 510(k) with new data;
  - Submit a PMA;
  - Request a Class I or Class II designation through the de novo review process; or
  - File a reclassification petition.

- Reference: FDA guidance CDRH Appeals Process (Mar. 2, 2022)

Contents of a Traditional 510(k)

- Required forms
  - User fee
  - CDRH coversheet
  - Clinicaltrials.gov
  - Financial disclosure
  - Standards forms
  - Truthful and accuracy statement
  - Indications for Use statement
- 510(k) Summary
- Executive summary
- Device description
- Substantial equivalence argument
- Draft labeling
- Sterilization
- Biocompatibility
- Software
- EMC testing
- Bench testing
- Animal/Clinical testing

Content of a Traditional 510(k)

510(k) Summary or Statement

- Under 21 CFR 907.92 (Summary) or 907.93 (Statement), every 510(k) must contain either a 510(k) Summary or Statement
- Summaries contain a high level description of the information in the 510(k)
- Statements assert that you will provide within 30 days a copy of the submission (excluding trade secret or confidential commercial information) to anyone that requests it
- FDA began to review 510(k) summaries for completeness in 2009
- These are publicly available

Content of a Traditional 510(k)

Executive Summary

- Optional, but strongly recommended
- Should include
  - High level device description,
  - Indications
  - Summary of performance testing
  - Summary of substantial equivalence
    - Key similarities and differences

Content of a Traditional 510(k)

Device Description

- Intended use
  - Indications
  - Patient population
- Technological Characteristics
  - Description of components
  - What they do
  - How they interact
  - Pictures/engineering drawings
- Principles of Operation
  - How the device achieves its intended use

Content of a Traditional 510(k)

Substantial Equivalence

- Describe in narrative form the substantial equivalence argument
  - Do not overlook discussion of any differences
  - Be complete and walk audience through the argument
- Be consistent and specific regarding predicate throughout section and across other sections
- Include a comparison chart

Content of a Traditional 510(k)

Labeling

- Three parts to labeling
  - Package label – placed on the outside of the box
  - Package insert – placed inside the box
  - Surgical technique/ Operator's manual - provides detailed instruction regarding how to use the device
- In 510(k)s FDA only reviews draft labeling, but they will closely review it

Content of a Traditional 510(k)

Sterilization and Shelf Life (if applicable)

- Submission states that the device, and/or accessories, and/or components are: (*one of the below must be checked*)
  - Provided sterile, intended to be single-use
  - Requires processing during its use-life
  - Non-sterile when used (and no processing required)
- If sterile, explain the method and validation
- Also describe packaging and shelf life and explain how the shelf life was validated

Content of a Traditional 510(k)

Biocompatibility

- Provide a list of patient contacting materials and describe the testing that has been done to demonstrate biocompatibility
  - Contact classifications are defined in ISO 10993 and in FDA's GD Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" and used to determine testing requirements
- Color additives have become a big deal. If present, see if they are in the list of color additives that are exempt from certification (21 CFR part 70). If they are not, additional data will be required
- If testing is needed, complete test reports need to be supplied

Content of a Traditional 510(k)

Software Section

- Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices (May 11, 2005)
- Level of Concern – Determines the documentation needed for submission
  - **Major**
    - A failure or latent flaw could result in death or serious injury to the patient or operator, either directly or indirectly, through incorrect or delayed information
  - **Moderate**
    - A failure or latent design flaw could result in minor injury to the patient or operator, either directly or indirectly, through incorrect or delayed information
  - **Minor**
    - Failure or latent design flaws are unlikely to cause any injury to the patient or operator.

Software Documentation

SOFTWARE DOCUMENTATION	MINOR CONCERN	MODERATE CONCERN	MAJOR CONCERN
Level of Concern	A statement indicating the Level of Concern and a description of the rationale for that level.		
Software Description	A summary overview of the features and software operating environment.		
Device Hazard Analysis	Tabular description of identified hardware and software hazards, including severity assessment and mitigations.		
Software Requirements Specification (SRS)	Summary of functional requirements	The complete SRS document.	
Architecture Design Chart	No documentation is necessary	Detailed depiction of functional units and software modules. May include state diagrams as well as flow charts.	

Software Documentation

SOFTWARE DOCUMENTATION	MINOR CONCERN	MODERATE CONCERN	MAJOR CONCERN
Software Design Specification (SDS)	No documentation is necessary	Software design specification Document.	
Traceability Analysis	Traceability among requirements, specifications, identified hazards and mitigations, and Verification and Validation testing.		
Software Development Environment Description	No documentation is necessary	Summary of software life cycle Development plan, including a summary of the configuration management and maintenance activities.	Summary of software life cycle development plan. Annotated list of control documents generated during development process. Include the configuration management and maintenance plan documents.

Software Documentation

SOFTWARE DOCUMENTATION	MINOR CONCERN	MODERATE CONCERN	MAJOR CONCERN
Verification and Validation Documentation	Software functional test plan, pass / fail criteria, and results.	Description of V&V activities at the unit, integration, and system level. System level test protocol, including pass/fail criteria, and tests results.	Description of V&V activities at the unit, integration, and system level. Unit, integration and system level test protocols, including pass/fail criteria, test report, summary, and tests results.
Revision Level History	Revision history log, including release version number and date.		
Unresolved Anomalies (Bugs or Defects)	No documentation is necessary	List of remaining software anomalies, annotated with an explanation of the impact on safety or effectiveness, including operator usage and human factors.	

Content of a Traditional 510(k)

Cybersecurity

- Devices that communicate wirelessly have increased cybersecurity concerns
  - Content of Premarket Submissions for Management of Cybersecurity in Medical Devices, October 2, 2014
  - Needs to be part of the hazard analysis and integrated to software documentation
  - Show how limit access to trusted users only and ensure trusted content

Content of a Traditional 510(k)

Electrical Safety and EMC

- Electrical Safety
  - IEC 60601-1 Medical electrical equipment -- part 1: General requirements for basic safety and essential performance
  - FDA now only accepts AAMI / ANSI ES60601-1:2005/(R)2012 and **A1:2012**, C1:2009/(R)2012 and A2:2010/(R)2012 (Edition 3.1)
- Electromagnetic compatibility testing
  - IEC 60601-1-2 Medical electrical equipment - part 1-2: General requirements for basic safety and essential performance - collateral standard: electromagnetic compatibility - requirements and tests
  - FDA still accepts 3rd edition until December 31, 2018
- Wireless devices require coexistence testing
  - Radio Frequency Wireless Technology in Medical Devices August 14, 2013
- Home use devices have additional EMC concerns
  - Design Considerations for Devices Intended for Home Use August 5, 2014

Content of a Traditional 510(k)

Bench/Mechanical Testing

- A summary of the bench testing should be provided in the body of the 510(k)
  - What was tested
  - Worst-case rationale
  - Pre-determined acceptance criteria
  - Summary of methods
  - Summary of test results (tabular)
  - Why this established equivalence
- Complete test reports should be provided in attachments

Content of a Traditional 510(k)

Animal and Clinical Testing

- Under the least burdensome approach, FDA only asks for clinical data when bench and animal testing is not adequate
  - Needed for 10 – 15% of 510(k)s
- Requested when the device has a new technological characteristic that cannot be evaluated in an animal model or on the bench
  - Confirmatory study – smaller, uncontrolled, just demonstrates the new feature works
  - Efficacy study- larger, controlled, typically not statistically powered

Confidential, Proprietary, and Trade Secret Information

- FDA regulations address the confidentiality of information submitted to FDA. (See 21 C.F.R. §807.95 and Part 20)

- 21 C.F.R. §807.95
  - In certain, specified instances, FDA will disclose the existence of a 510(k) submission.
  - In certain, specified instances, FDA will not disclose the existence of a 510(k) submission for a device that is not on the market and where there is the intent to market the device has not been disclosed for 90 days from the receipt of the submission.
  - FDA will make a 510(k) summary available to the public within 30 days of an SE determination. 21 C.F.R. §807.95(d)
  - Data or information submitted in a 510(k) submission are subject to disclosure, unless exempt from disclosure under 21 C.F.R. Part 20.

Confidential, Proprietary, and Trade Secret Information

- 21 C.F.R. Part 20
  - Part 20 specifies FDA's policies and procedures governing the disclosure of FDA records
    - General policy
    - Procedures and fees
    - Exemptions
    - Limitations on exemptions
    - Availability of specific categories of records

Modifications to a Legally Marketed Device

- By law (21 C.F.R. § 807.81(a)(3)(i)-(ii)), a new 510(k) is needed when there is:
  - A change or modification in the device that could significantly affect the safety or effectiveness of the device (e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process); or
  - A major change or modification in the intended use of the device.
- FDA allows companies to initially make this decision, but has the final say

User Fees for 510(k) Submissions

- Under the authority granted to it by the Medical Device User Fee Act, FDA collects user fees for its review of 510(k)s.
- •The standard user fee for a 510(k) submission in FY2023 is ***$19,870***.
- •The small business fee for a 510(k) submission in FY2023 is ***$4,967***.

Review Times for 510(k) Submissions

- Under the FDCA, the standard review time for a 510(k) is 90 calendar days.
- CDRH performance data shows the following:

Performance Metric	FY 2020	FY 2021	FY 2022
510(k)s Accepted	3,499	3,707	2,122
Non-MDUFA IV Decision	369	230	22
MDUFA IV Decision (SE/NSE)	3,081	2,949	901
MDUFA IV Decision Within 90 FDA Days	2,956	2,667	874
510(k)s Pending MDUFA IV Decision	49	528	1,199
510(k)s Pending MDUFA IV Decision Over 90 FDA Days	26	108	92

Source: 3rd Quarter FY 2022 MDUFA IV Performance Report

De Novo Requests

De Novo Paradigm History

- 1997: Creation of 510(k) de novo downclassification process via The Food and Drug Administration Modernization Act (FDAMA) to resolve need to avoid PMA applications for low risk devices
  - Officially titled “Evaluation of Automatic Class III Designation”
- 2012: Direct de novo pathway created by section 607 of Food and Drug Administration Safety and Innovation Act (FDASIA) due to industry complaints that the “510(k) de novo” process was broken

What is a De Novo Request?

- If company believes device is appropriate for classification into Class I or Class II and determines there is no legally marketed predicate device, may submit a direct de novo request
  - Preceding 510(k) and NSE decision no longer required
- Prior to FDASIA, FDA reclassified devices under section 513(e) of the FDC Act through rulemaking; FDASIA changed to an order process
- See *Guidance for Industry and Food and Drug Administration Staff -- De Novo Classification Process (Evaluation of Automatic Class III Designation)* (October 30, 2017)
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM273903.pdf

When is a De Novo Appropriate?

- Device that does not fall into an existing classification regulation, or has been found NSE due to:
  - Lack of a predicate
  - New intended use, or
  - Different technological characteristics that raise different questions of safety and effectiveness
- In addition:
  - Low to moderate risk
  - Appears to meet statutory standard for classification into Class I or Class II under section 513(a)(1) of FDC Act
    - Special plus general controls (for Class II) or general controls alone (for Class I) would provide reasonable assurance of safety and effectiveness of the downclassified device
  - Known risks and benefits can be explained and risks can be mitigated through general and special controls

When is a De Novo Not Appropriate?

- Devices found NSE only due to lack of performance data
- Devices that have a predicate device and fall within an existing classification regulation
- Devices within an existing Class III regulation (or of the same type as an approved PMA device)
  - In this case, mechanism for classification into Class I or II is reclassification under section 513(e) or (f)(3) of FDC Act

Procedures for De Novo Request

- To pursue *de novo* downclassification, first step is often gaining FDA agreement
  - Companies can submit pre-submission (“pre-sub”)
  - Other options are to pursue an informal discussion, or file a formal 513(g) request
  - Company can submit Direct De Novo request without consulting FDA, but not advisable
- Pre-sub provides opportunity to discuss regulatory pathway and data requirements with FDA
  - Highly encouraged

Procedures for Review of De Novo Request

- Classification review
  - No pre-sub, 510(k) or PMA submission for same device is currently under review
  - No similar device has been determined to be Class III
- Substantive review
  - Check that submission contains all required information
  - Request(s) for additional information
  - 120 day review cycles
- Denial or grant of de novo request
  - Determination whether requirements for Class I or II are met

Contents of Direct De Novo Request

- Administrative Information
- Regulatory History
- Device Information and Summary
- Change Summary
- Classification Summary
- Classification Recommendation
- Proposed Special Controls (for Class II devices)
- Supporting Protocols and/or Data
- Benefit/Risk Analysis
- Device Labeling

Contents of Direct De Novo Request

Administrative and Introductory Info

- Contact, name, address, phone email
- Administrative forms can be helpful:
  - CDRH Premarket Cover Sheet
  - Data Standards Forms
  - Financial Disclosure Forms
- Cover Letter and Executive Summary are advisable
- Regulatory History
  - Prior submissions
  - Explain how the company has addressed any prior FDA comments

Contents of Direct De Novo Request

Device Information

- Device Description
  - Indications for use
  - Describe technological characteristics, components
  - Describe principles of operation of device
- Change Summary
  - Changes to device, labeling, or test protocols since prior submission(s) (pre-sub or 510(k))

Contents of Direct De Novo Request

Classification Summary and Recommendation

- Describe why device has no predicate, does not fit into existing classification regulation, or is not of type approved in a PMA
- Recommend Class I or II, applicability of 510(k) requirement (exempt or not)
- Describe why general (for Class I) or special plus general (for Class II) controls are adequate to provide reasonable assurance of safety and effectiveness

Contents of Direct De Novo Request

Proposed Special Controls

- If recommending Class II, describe special controls that, along with general controls, provide reasonable assurance of safety and effectiveness
- Drafting a Special Controls Guidance document can be helpful to the agency
  - Varies by Division
- Demonstrate how the device meets these special controls

Contents of Direct De Novo Request

Supporting Data

- Declarations of conformity with standards
- Preclinical data - can include:
  - Sterilization and shelf life
  - Biocompatibility
  - Software
  - EMC/Electrical safety
  - Wireless compatibility
  - Bench testing
  - Animal testing
- For each study, include:
  - Study Purpose/Rationale
  - Methodology
  - Results
  - Analysis of Results
  - Conclusion

Contents of Direct De Novo Request

Supporting Data (con't)

- Clinical data required for most de novo requests
  - Study population
  - Inclusion/exclusion criteria
  - Duration
  - Data collection methodology
  - Observed AEs
  - Results
  - Statistical analysis
  - Conclusions

Contents of Direct De Novo Request

Risk/Benefit Information

- Summary of benefits supporting effectiveness of device
  - Cite to data in request, literature
- Summary of known and potential risks to health, reasons for risk
  - Cite to data supporting safety
- Risk and mitigation information
  - Table listing mitigations for each risk, which mitigations are general and special controls
- Benefit-risk considerations
  - Discussion showing probable benefits to health outweigh any probable injury or illness
  - Fill out worksheet from FDA *Risk-Benefit* guidance

AI Submissions – Special Issues

- FDA released AI/ML Discussion Paper and Action Plan
- "Traditional paradigm of medical device regulation was not designed for adaptive AI/ML technologies, which have the potential to adapt and optimize device performance in real-time to continuously improve healthcare for patients"
- Proposes framework for modifications to AI/ML-based Software. TPLC approach to facilitate rapid cycle of product improvement while maintaining safety/effectiveness

- CDRH included AI/ML guidance ("Marketing Submission Recommendations for A Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions") on 2023 Proposed Guidance List
- Example of Marketed AI Devices (through De Novo):
  - AI based device for detecting diabetic retinopathy,
  - AI based device for alerting providers of a potential stroke in patients

User Fees for De Novo Submissions

- Under the authority granted to it by the Medical Device User Fee Act, FDA collects user fees for its review of De Novos.
- •The standard user fee for a 510(k) submission in FY2023 is ***$132,464***.
- •The small business fee for a 510(k) submission in FY2023 is ***$33,116***.

Review Times for De Novo Submissions

- Under the FDCA, the standard review time for a De Novo is 150 calendar days.
- CDRH performance data shows the following:

Performance Metric	FY 2020	FY 2021	FY 2022
De Novos Accepted	64	55	45
Non-MDUFA IV Decisions	0	0	0
MDUFA IV Decisions	61	29	4
MDUFA IV Decision Within 150 FDA Days	40	20	4
De Novos Pending MDUFA IV Decision	3	26	41
De Novos Pending MDUFA IV Decision Over 150 FDA Days	3	6	1

Source: 3rd Quarter FY 2022 MDUFA IV Performance Report

New Guidance Documents

Thank you!