U.S. FOOD & DRUG ADMINISTRATION

Navigating the 510(k) Program

2022 FDA IVD Submissions Workshop

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Learning Objectives

- MDUFA IV REQUIREMENTS
- THE 510(k) REVIEW PROCESS
- SUB-PROGRAMS/POLICIES
- ON-GOING PILOTS
- HOW TO INTERACT WITH FDA DURING AND AFTER THE REVIEW PROCESS

MDUFA IV REQUIREMENTS

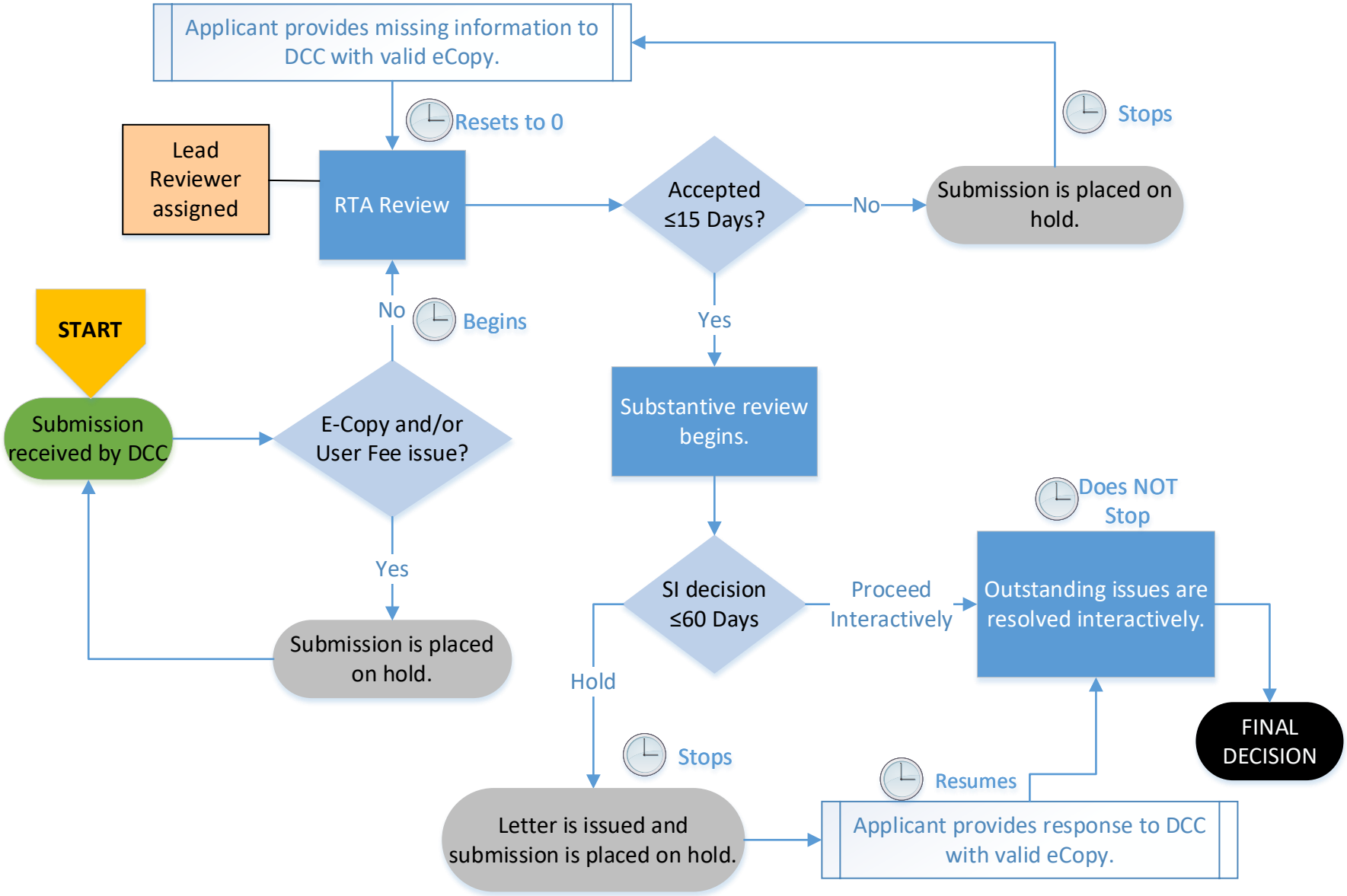
MDUFA IV Review Milestones

MDUFA V Commitment Letter in review/clearance process

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

THE 510(k) REVIEW PROCESS

Review Process Overview



510(k) Administrative Review

FDA completes the **Refuse to Accept (RTA)** checklist prior to beginning the substantive review of the 510(k)

The RTA checklist is a **tool** to identify:

1. Key items that may be important to consider regarding the regulation of the subject device and necessary to begin the substantive review

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

Final Guidance published September 13, 2019

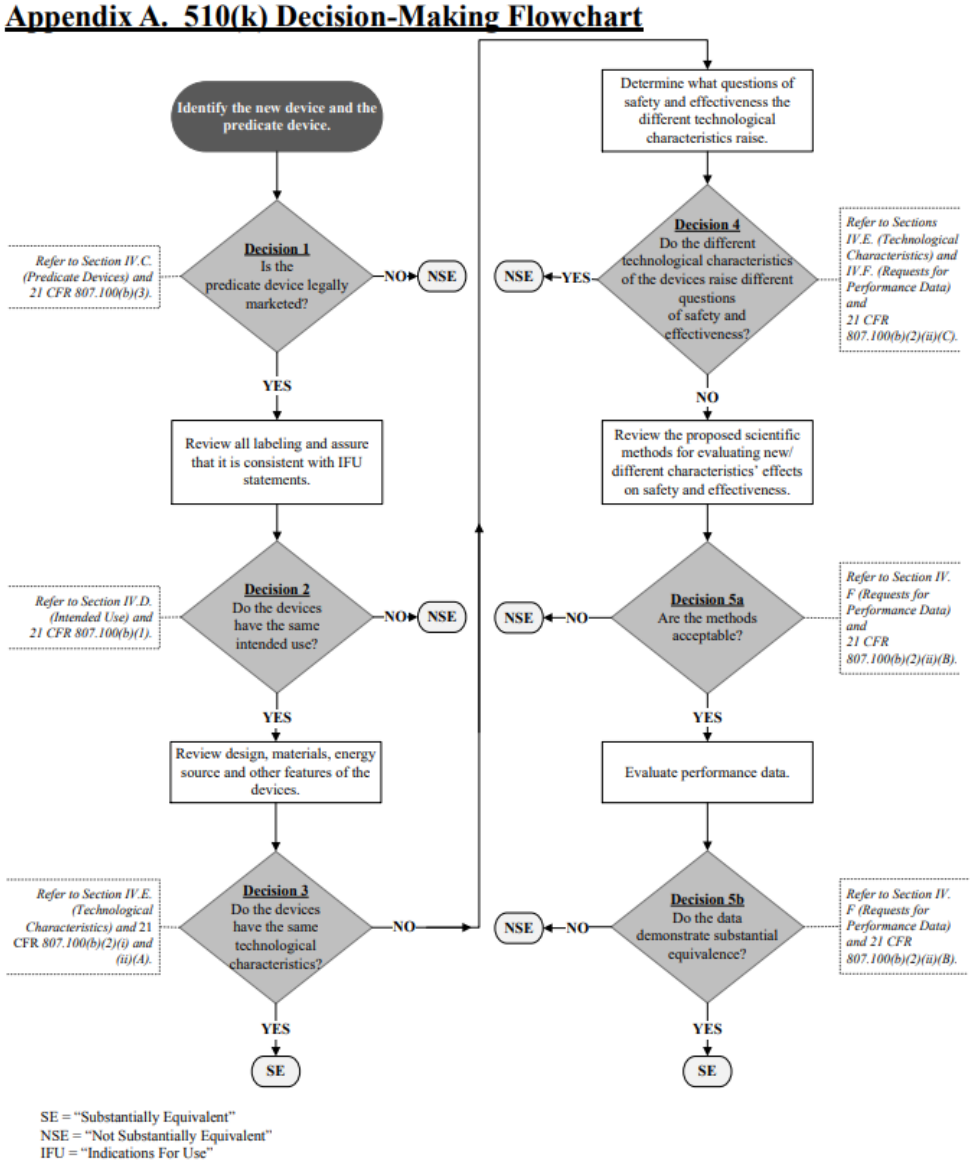
The 510(k) Review

FDA Reviewers use a 510(k) review memo template to enhance review consistency, regardless of device type

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** (e.g., Biocompatibility, Sterility, EMC, bench tests)
- **Discussion of Substantial Equivalence**

510(k) Decision Making Flowchart



- 510(k) Program: Evaluating Substantial Equivalence guidance
  - Flowchart identifies the 6 key decision questions to determine SE
  - Questions must be addressed in order
  - Flowchart is not a standalone tool; use in conjunction with the guidance
  - Utilize device specific and x-cutting guidance to ID relevant submission content

The 510(k) Review: Intended Use/Indication 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 designated indication(s)?
- Are the instructions for use adequate, comprehensive, and clearly written?
- Are the use of symbols properly addressed?
- Are any precautions, warnings or contraindications (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. Demonstrate equivalence to predicate.

- 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 FDA receives. The requirements may differ depending on device type.

- **Sterilization/Shelf Life/Reuse**
  - Does the sterilization method and procedures meet guidance/standards for this type of product?
  - Does shelf-life data support the labeling? If accelerated, is it appropriate for this device/device type?
- **Biocompatibility**
  - Does this section adequately address materials for this device?
  - Does testing data meet horizontal and vertical guidance/ standards?
  - Did testing cover key areas such as cytotoxicity, sensitization, irritation, toxicity, implantation, hemo-compatibility, carcinogenicity, etc. for contact type, materials, and duration?
  - Are there other questions of safety or effectiveness not answered?

The 510(k) Review: Performance Testing

These are examples of the types of performance data FDA receives. The requirements may differ depending on device type.

Software

- Has the company adequately addressed the items below in support of the suggested level of risk:
  - Level of Concern – to be assessed prior to the mitigation of hazards
  - Software description
  - Hazard analysis
  - Software requirements, architecture, and design
  - Traceability matrix and development
  - Verification and validation
  - Versions and revision level history
  - Unresolved anomalies
  - Cybersecurity

The 510(k) Review: Performance Testing

These are examples of the types of performance data FDA receives. The requirements may differ depending on device type.

Electromagnetic Compatibility and Electrical, Mechanical, and Thermal Safety

- Does the testing and/or summary report demonstrate the product meets applicable guidance/standards (IEC, UL, ANSI, AAMI, etc.) for this type of product?
- Are the design, shielding, and grounding appropriate to protect the patient?
- Does the device perform properly during/after exposure to environmental hazards, especially for the environment in which the product will be used?
- Are there questions of safety or effectiveness not answered by the sponsor?

The 510(k) Review: Performance Testing

IVD Devices reviewed by OHT-7 may have additional requirements not necessarily required by other OHTs

- For IVD products, were Clinical and Laboratory Standards Institute (or other appropriate) protocols followed with robust data analysis?

- IVDs have specific performance characteristics, which include:
  - Precision/reproducibility
  - Accuracy
  - Sensitivity
  - Analytical specificity
  - CLIA

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

- Voluntary use
- Dynamic pdf template for assembling submission
  - Outlines the specific content and sections relevant for review
  - Standardizes format and layout to enhance consistency and efficiency
- Modeled after the SMART review template used by review staff
- No RTA review
  - There is a technical hold if it is not filled out correctly

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) Public Law 114-255.
- Least Burdensome Provisions: Concepts and Principles Guidance Document

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

- Predicate is an eligible device type
  - Check webpage for device-specific guidances
- 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 groups and eligible product codes are available on the webpage.

- Applicant submits their 510(k) to the Third Party for initial review
- When complete, the 510(k) is submitted to FDA by the Third Party group
  - All subsequent communication with FDA will be through the Third Party
- FDA supervisory concurrence should be received within 30 days
- No user fees are required to FDA as you are paying the Third Party for the review services

Third Party Review Program Final Guidance

Breakthrough Devices

Breakthrough device requests should be done through a pre-submission.

Priority review does not equate to expedited clearance.

- Program replaced "Expedited Review"
- Less common for 510(k) devices
- Addresses priority review for devices:
  - With potential for clear, clinically meaningful benefit as compared to existing devices
  - That provide revolutionary (not incremental) advances
  - For which there is no approved alternative therapy
  - Should be made available in the best interests of patients
- What happens with Priority Review?
  - The submission goes to the top of the pile each time information is submitted
- Questions: BreakthroughDevicesProgram@fda.hhs.gov

ON-GOING PILOTS

Pilot Program: ASCA

ASCA Webpage

- Voluntary program
- Increases consistency and predictability in assessing conformance with FDA-recognized standards
- Enhances the FDA's confidence in test methods and results
- Decreases 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

510(k) Requests for Additional Information (AI)

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

Two main types of AI Requests

Interactive Requests

- 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.

Hold Letter

- 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.

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 (September 29, 2017):
https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073680.pdf

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.

If you disagree with/require clarification on any item:

Day-10 Call

What it is

- Teleconference within 10 days post issuance of an AI Letter
- Ensure understanding of the deficiencies issued in the letter
- Determine need for a Submission Issue Request (SIR)

What it is not

- Review of additional information provided by the submitter
- Discussion of issues unrelated to the deficiencies in the Letter
- In place of a SIR

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

Handling Requests for Additional Information

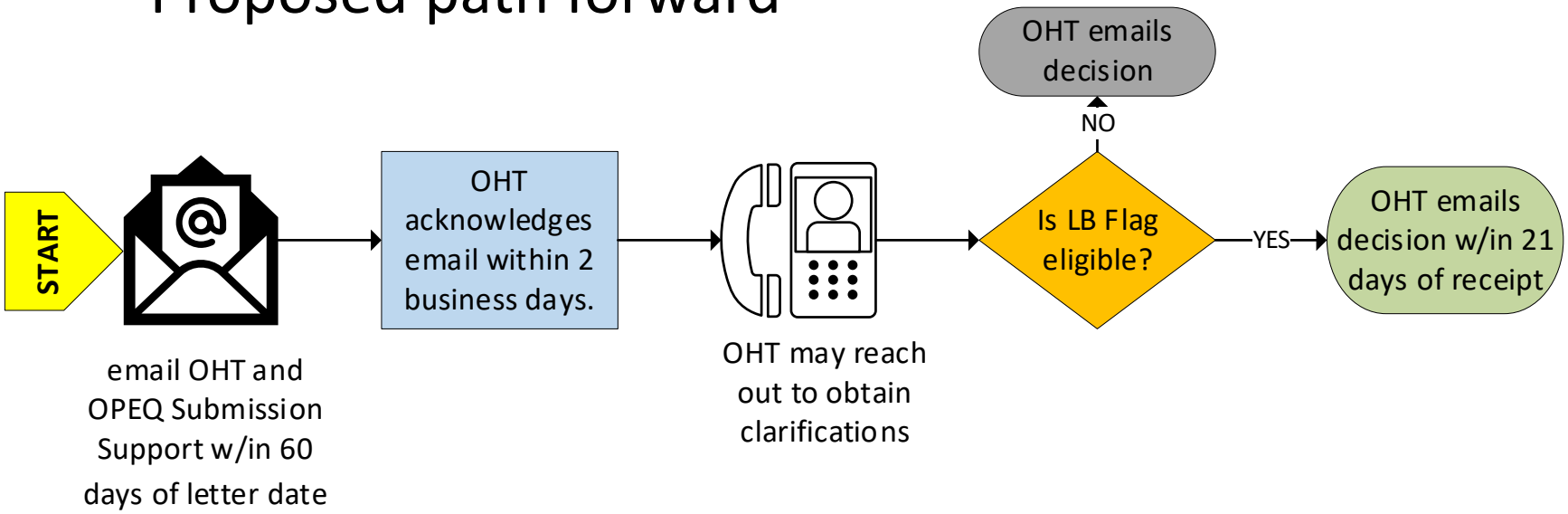
Least Burdensome (LB) Flag

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

Handling Requests for Additional Information

Least Burdensome (LB) Flag con't

- The email should include a 1-2 page summary:
  - Disagreement(s) limited to 2 topic areas
  - Relevant prior communications
  - Proposed path forward

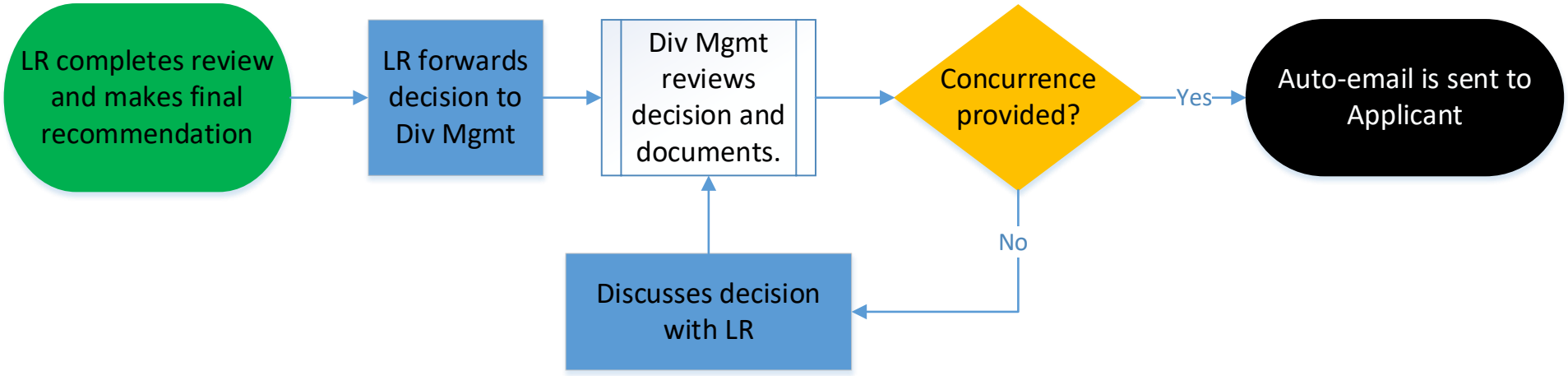


Handling Post-Hold Interactions

The period of time between the response to a hold letter and the final decision is commonly referred to as Interactive Review (IR)

- 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.
- An inadequate or lack of response could lead to an unfavorable decision.

Processing a Final Recommendation



Legend
LR = Lead Reviewer
Div Mgmt = Division Management

Note: Different levels of management are required for different final decisions

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

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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