# Received an RTA Deficiency List or AI Letter? Now What?

## Dealing with Unexpected Issues/Questions during the Submission Review Process

Navigating Submission Challenges to reduce time & risk

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REGULATORY COMPLIANCE ASSOCIATES® INC.

WELLNESS FOR BUSINESS®

# Speakers

## Panelists:

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Moderator:
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# Learning Objectives

**Managing Unexpected FDA Issues/Questions during the Submission Review Process**

Learn how to effectively:

1. Minimize risk of receiving Refuse to Accept (RTA) Deficiencies and/or Additional Information (AI) Letters
2. Address deficiencies noted on the RTA
3. Leverage recent FDA Guidance and Trends
4. Interact with the FDA via Submission Issue Meetings
5. Gain insights on engaging cross-functional support from Engineering, Quality, and New Product Development Teams for the submission
6. Incorporate lessons learned from challenging case studies on managing the submission process through unexpected and challenging paths

## Types of FDA Submissions

# DEVICE SUBMISSION(S)

# 510(K) Submission Requirements

- Medical Device User Fee Cover Sheet (Form FDA 3601)
- CDRH Premarket Review Submission Cover Sheet
- 510(k) Cover Letter
- Indications for Use Statement
- 510(k) Summary or 510(k) Statement
- Truthful and Accuracy Statement
- Class III Summary and Certification
- Financial Certification or Disclosure Statement
- Declarations of Conformity and Summary Reports
- Executive Summary
- Device Description
- Substantial Equivalence Discussion
- Proposed Labeling
- Sterilization and Shelf Life
- Biocompatibility
- Software
- Electromagnetic Compatibility and Electrical Safety
- Performance Testing – Bench
- Performance Testing – Animal
- Performance Testing – Clinical
- Other

# Premarket Approval (PMA) Requirements

- Applicant Name and Address
- Table of Contents
- Summary Section
- Indications for Use
- Device Description
- Alternative Practices and Procedures
- Marketing History
- Summary of Studies
- Conclusions drawn from the Studies
- Complete Description of:
  - the device, including pictorial representations;
  - each of the functional components or ingredients of the device if the device consists of more than one physical component or ingredient;
  - the properties of the device relevant to the diagnosis, treatment, prevention, cure, or mitigation of a disease or condition;
  - the principles of operation of the device; and
- Methods, facilities, and controls used in the manufacture, processing, packing, storage, and where appropriate, installation of the device.
- Performance Standard or Voluntary Standard
- Technical Sections containing Data and Information including:
  - Results of Nonclinical Laboratory Studies
  - Results of Clinical Investigations involving Human Subjects
- A Bibliography of all published reports that concern the safety or effectiveness of the device.
- One or more samples of the device and its components, if requested by FDA.
- Proposed Labeling for the device.
- Environmental Assessment (EA) or Environmental Impact Statements (EIS)
- A Financial Certification or Disclosure Statement or both as required by 21 CFR 54.
- Such other information as FDA may request.
- Other Information (reference to Master File)
- Omissions
- Updates
- Color Additive

# De Novo Requirements

- Cover Letter-“De Novo Request”
- Administrative Information
  - Applicant Name, Contact information, and Address
- Table of Contents
- Regulatory History
- Device Information and Summary
- Change Summary (if applicable)
- Classification Summary
- Classification Recommendation
- Proposed Special Controls for Class II Devices Only
- Supporting Protocols and/or Data
- Summary of Benefits
- Summary of Known and Potential Risks to Health
- Risk and Mitigation Information
- Benefit-Risk Considerations
- Device Labeling

# LEVERAGING FDA GUIDANCE AND TRENDS

# Leveraging FDA Guidance and Trends

- ***Guidance on Evaluation and Reporting of Age, Race, and Ethnicity Data in Medical Device Clinical Studies*** **– Issued 9/11/2017**
- ***Guidance on Use of Real World Evidence to Support Regulatory Decision Making for Medical Devices*** **– Issued 8/31/2017**
- ***Guidance on FY 2018 Medical Device User Fees*** **– Issued 8/29/2017**
- ***FY 2018 Medical Device User Fee Small Business Qualification and Certification - Guidance for Industry, Food and Drug Administration Staff and Foreign Governments*** **– Issued 8/29/2017**
- ***Medical Device Accessories-Describing Accessories and Classification Pathway for New Accessory Types*** **- Issued 12/30/2016**
- ***Applying Human Factors and Usability Engineering to Medical Devices*** **- Issued 02/03/2016**
- ***Use of International Standard 10993-1, Biological Evaluation of Medical Devices-Part 1: Evaluation and Testing within a Risk Management Process*** **- Issued 06/16/2016**

# Leveraging FDA Guidance and Trends continued

- ***Guidance for Industry and Food and Drug Administration Staff - Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications*** **– Issued 8/24/2016**
- ***Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile - Guidance for Industry and Food and Drug Administration Staff*** **– Issued 1/21/2016**
- ***Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling - Guidance for Industry and Food and Drug Administration Staff*** **– Issued 3/17/2015**
- ***Mobile Medical Applications - Guidance for Industry and Food and Drug Administration Staff*** **– Issued 2/9/2014**
- ***Content of Premarket Submissions for Management of Cybersecurity in Medical Devices - Guidance for Industry and Food and Drug Administration Staff*** **- Issued 10/2/2014**

# Biocompatibility Case Study

**Biocompatibility Data in a 510(k) Submission:**

- Sterile disposable device had undergone a material change to one component of the device
- Biocompatibility data was submitted on the new component only
- FDA would not accept, required complete battery of testing repeated on sterile, finished device
- Resulted in a four month delay while testing was repeated
- Generally very difficult to justify not testing finished device due to potential impact of manufacturing processes

# EARLY COLLABORATION / PRE-SUBMISSION MEETINGS

# Early Collaboration / Pre-Submission (Pre-Sub) Meetings

- Early and frequent communication with the FDA about the planned Marketing Application(s) is highly recommended to ensure a smooth regulatory pathway to product launch. The Agency Centers (CDRH / CBER / CDER) provide extensive guidance on Early Collaboration and/or Milestone Meetings throughout the development process and prior to the submission of Investigational / Marketing Applications
- Pre-Submission Meetings with FDA are critical opportunities to obtain valuable feedback from the Agency on their expectations related to the proposed testing and other supporting data/information required for the Marketing Application(s)

| FDA Meeting Types | |
|---|---|
| Q Submissions | Formal Early Collaboration Meeting |
| Pre-Submissions | Submission Issue Meetings |
| Informational Meetings | Day 100 Meetings for PMA |
| Study Risk Determination | |
| | |

# UNEXPECTED ISSUES/ QUESTIONS DURING THE SUBMISSION REVIEW PROCESS

# Unexpected Issues/Questions during the Submission Review Process

- eCOPY Loading Failure
- Refuse to Accept (RTA) Holds
- Request for Additional Information (AI) Letters

# Unexpected Issues/Questions during the Submission Review Process Cont.

**Common eCopy Issues:**

- Failure to comply with FDA's eCopy Guidance
  - Size restrictions of pdf files, invalid naming conventions of documents and/or folders where the documents are pulled from, hyperlinks, scans of source documents
- Failure to use FDA's eSubmitter Software Tool…but beware!
- Review Clock will not begin until a valid eCopy is received

**eCopy Case Study:**

A "valid" eCopy was prepared using FDA's eSubmitter Software Tool, and the tool confirmed that the "valid" eCopy was created. However, the FDA issued a series of eCopy Hold Letters and recalls of the issued eCopy Hold Letters indicating the eCopy was valid/not valid.

## Acceptance Review Guidelines for FDA Submissions

# REFUSE TO ACCEPT (RTA) POLICY AND CHECKLIST

# Refuse to Accept (RTA) Policy & Checklist

**FDA's Refuse to Accept (RTA) Policy and Checklist** is intended to provide the FDA and Industry a means to objectively assess whether a Submission meets the minimum requirements for acceptability, and whether it may move on to the Substantive Review Phase.

- Submission is reviewed against specific acceptance criteria via the Refuse to Accept (RTA) Checklist
- Within the first **(15)** calendar days of receipt of the submission, the FDA must notify the Submitter whether or not the submission is administratively complete. Deficiencies will be cited that must be addressed by the Submitter before the Substantive Review may begin.

# Refuse to Accept (RTA) Policy & Checklist Cont.

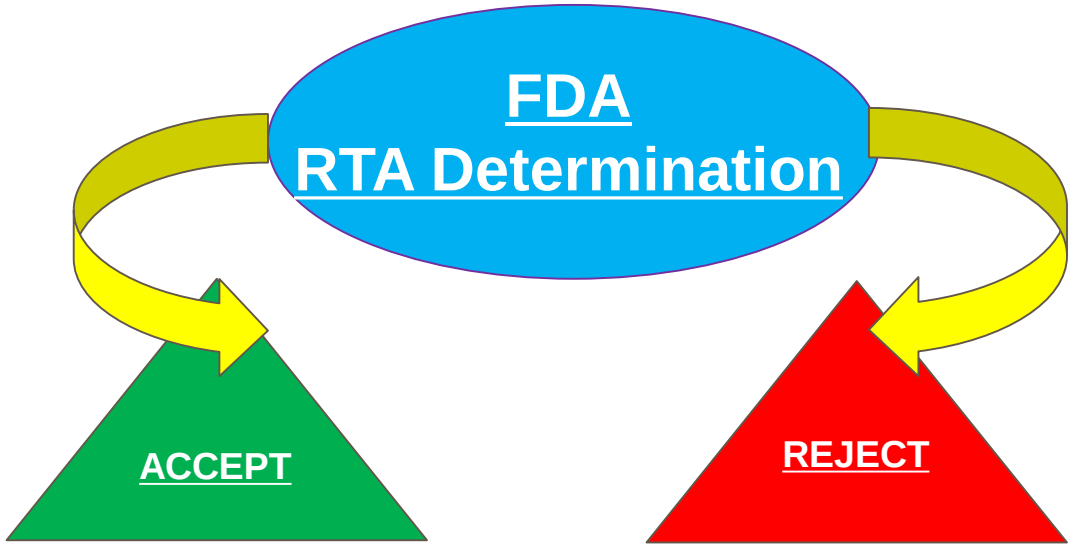
| Acceptance Review | Substantive Review |
|---|---|
| Confirms the completeness of the Submission against pre-defined acceptance criteria (RTA Checklist) | Assesses the quality of the Submission including the Supporting Information |
| Performed for Traditional, Special, Abbreviated 510(k)s, original PMAs, and Panel Track PMA Supplements | FDA Substantive Review begins once the Acceptance Review has been completed and the FDA has “accepted” or confirmed that the submission meets the pre-defined acceptance criteria as defined in the RTA checklist. |
| FDA Acceptance Review occurs within the first (15) fifteen calendar days of receipt of the submission. | |

# Refuse to Accept (RTA) – Common Issues/Deficiencies

**Common Issues noted by the FDA on the RTA Checklist include:**

- Indications for Use language is not consistent throughout the entire submission and its supporting documentation
- Device Description does not include information required per applicable device-specific guidance
- Engineering Drawings, labels, and other supporting documentation is missing (Shelf Life, Biocompatibility, Sterilization, Software)
- Detailed descriptions of accessories and/or components of the device are not provided
- Inadequate or missing explanations describing how/why the bench, animal, and clinical testing specifically supports substantial equivalence and/or safety and effectiveness
- Missing Test Protocols and/or Final Test Reports

# FDA Determinations on RTA




- RTA Checklist Criteria Met
- Substantive Review Begins
- No Effect on Review Clock
- Notification of Acceptance

- RTA Checklist Criteria Not Met
- Substantive Review Does Not Begin
- Review Clock Stops
- Notification with RTA Deficiencies
- Submitter must respond w/in 180 Days
- Review Clock Resets to Day (0) once missing criteria is provided

# CDRH RTA Statistics (from MDUFA III Performance Report 5/17/2017)

| | 2013 | 2014 | 2015 | 2016 | 2017 (as of 3/31) |
|---|---|---|---|---|---|
| 510(k)'s Submitted | 2,954 | 3,677 | 3,640 | 3,553 | 1,862 |
| RTA rejected 1st Cycle | 1,715 | 1,731 | 1,323 | 1,063 | 517 |
| Rate | 58.1% | 47.1% | 36.5% | 30.1% | 29.6% |

# RTA Case Study

- Acceptance Review is now conducted by the assigned Lead Reviewer
- Firm received very detailed commentary back on the RTA Checklist
- Requested additional performance testing, questioned appropriateness of biocompatibility testing and predicate
- Becoming more common to receive a more substantive review during RTA screening
- Differing views on this trend –
  - PRO: Requesting AI in the RTA screening gives you time “off the clock” to complete it, assuming you would receive the request in an AI letter
  - CON: If you receive request in AI letter, potential you could convince FDA that additional data isn’t necessary under Least Burdensome requirements

## FDA Actions on the Submission

# POSSIBLE FDA ACTIONS TAKEN ON THE SUBMISSION

# FDA Actions on the Submission

The FDA may take any of the following actions on a Submission after it conducts its review:

- Issue an Order Declaring a Device SE
- Issue an Order Declaring a Device NSE
- Request Additional Information (AI)
- Advise the Submitter that the 510(k) is Not Required
  - Not-a-Device Decision
  - Exempt from 510(k) Decision
- Issue a Notice of Withdrawal if Sponsor doesn't submit a response within FDA's designated timeframe

## Types of FDA Determination(s) for a 510(k) Submission

# SUBSTANTIALLY EQUIVALENT (SE)

# Substantial Equivalence (SE) Determination

**Determination of Substantial Equivalence (SE) for a 510(k) Submission**

To find a device substantially equivalent under section 513(i) of the FD&C Act, FDA must find that the Subject Device has the:

(1) Same intended use as the predicate device, and either,

(2) Same technological characteristics as the predicate device, or has different technological characteristics, as defined at section 513(i)(1)(B), and

(3) Submission contains information, including appropriate clinical or scientific data if necessary, that demonstrates the device is as safe and effective as the predicate and does not raise different questions of safety and effectiveness than the predicate.

## Types of FDA Determination(s) for a 510(k) Submission

# NOT SUBSTANTIALLY EQUIVALENT (NSE)

# Not Substantially Equivalent (NSE) Determination – Category 1

**Category 1:** NSE Determination based on FDA's decision that the device is a Class III and cannot be reviewed in a 510(K) submission due to findings such as:

- Lack of a Predicate Device
- New Intended Use
- Different Technical Characteristics that raise different questions about Safety and Effectiveness when the Subject Device is compared to the cited Predicate Device.
- Performance-Based Deficiencies are typically not noted in a Category 1 NSE Determination. Results in Automatically Classifying Device as a Class III that requires Premarket Approval (PMA), or if eligible, a De Novo (DN) before marketing.

# Not Substantially Equivalent (NSE) Determination – Category 2

**Category 2:** NSE Determination based on FDA's decision that the information provided in the 510(k) Submission is insufficient to demonstrate Substantial Equivalence to the Predicate Device.

- Performance-Based Deficiencies related to insufficient and/or lack of Performance Testing are typically noted in a Category 2 NSE Determination.

## Types of FDA Determination(s) for a PMA Submission

# PMA APPROVAL OR DENIAL ORDER

# PMA Approval or Denial Order

- Within **(180)** calendar days, the FDA will make a determination whether the PMA has been Approved or Denied
- FDA must notify Submitter of determination
- Notice of PMA Approval or Denial is published on the FDA Website
  - Announces the data on which the decision is based; and
  - Provides an opportunity for Interested Persons to Petition the FDA within **(30)** days reconsideration of the decision

## Types of FDA Determination(s) for a De Novo Submission

# DE NOVO REQUEST GRANTED OR DENIED

# De Novo Request Granted or Denied

- Within **(120)** calendar days, the FDA will make a determination whether the De Novo Request has been Granted or Denied
- FDA must notify Submitter of determination
- Notice of De Novo Request Grant or Denial is published on the FDA Website
  - A new classification regulation is established for the new device
  - The new device may serve as a Predicate Device for a 510(k) Submission
  - FDA publishes order in the Federal Register along with the new classification regulation and special controls for Class II devices
  - Decision Summary is posted by the FDA

## Types of FDA Determination(s)

# REQUEST FOR ADDITIONAL INFORMATION (AI)

# FDA Request for Additional Information (AI) Process

**FDA Issues AI**

- FDA issues AI Deficiencies List
- Submission placed "On Hold"

**AI Response**

- Submitter must Respond to AI Deficiencies
- Specified Timeframe

**Impact of AI**

- Deficiencies Adequately Addressed
- Possible Withdrawal of Submission/Resubmit

# FDA Request for Additional Information (AI) – Common AI Deficiency Types

| | |
|---|---|
| Indications for Use | Missing; No Predicate Identified for Indication Sought; Indication Requires a PMA; Inconsistency throughout Submission; Not supported by Data; Missing Important Information (i.e. Model Numbers, Prescription/Over-the-Counter Labeling, etc.) |
| Inadequate Device Description | Discrepancies and/or Inconsistency throughout Submission |

Poor Quality of Submission

- Failure to follow Guidance Documents
- Performance Testing Inadequate or Missing
- Clinical Data Inadequate or Missing
- Predicate Device Comparison Inadequate or Missing
- Software Documentation (if applicable) Inadequate or Missing
- Missing FDA Forms
- Biocompatibility Testing Inadequate or Missing
- Sterilization Information/Validation Inadequate or Missing

# AI Letter Case Study #1

Receiving a second AI letter is rare, but it does happen.

- Firm's response to initial AI letter included additional testing conducted by an outside agency.
- Results of that testing revealed a device component was not meeting its specification. Firm argued it was a minor issue and did not pose a safety or efficacy concern. FDA required data to validate this claim.
- As review clock was nearing the end, FDA issued a second AI letter to allow the firm time to resolve the issue.
- Firm ultimately made a design change to correct the issue. Testing was conducted to validate the design change and submitted.
- 510(k) was successfully cleared.

# AI Letter Case Study #2

Aged Samples Verification Testing

- Bench testing was completed using packaged and sterilized disposables that were not fully aged to stated shelf life
- Agency requested verification testing on aged samples to justify shelf life using “clinically relevant worst case scenario”
- Locating adequate number of aged samples to repeat testing was a challenge.
- Resulted in significant delay in responding while samples were located or aged.
- 510(k) was ultimately cleared.

# AI Letter Case Study #3

IEC 60601 Electrical Safety Testing for Devices

- Electrical safety testing in a submission is frequently sent to a qualified EE Reviewer. Entire test reports are required.
- Firm received a four page AI letter focused solely on IEC testing
  - Design Team should work closely with Test House to establish appropriate test parameters with justifications
  - Always have your IEC test reports thoroughly reviewed internally by an EE prior to submission – there are often errors
  - Pay special attention to the EMC tables in user manuals to assure all values are specified correctly and match test reports
  - Home use environment is considered “uncontrolled” – FDA required testing to 4th Edition of IEC 60601-1-2 which has higher limits for electromagnetic immunity

## FDA Interactions

# TYPES OF COMMUNICATION(S) DURING SUBMISSION REVIEW

## FDA Interactions

# ACCEPTANCE REVIEW COMMUNICATION

# Acceptance Review Communication

**Purpose:** (1) identify the Lead Reviewer or Regulatory Project Manager assigned to the Submission and (2) confirm acceptance of the Submission or notify the Submitter that the Submission was not accepted based upon the review of the submission against objective acceptance criteria.

**Timing:** The Acceptance Review Communication should occur within **(15)** calendar days of receipt of a 510(k), Original PMAs, or a Panel-Track PMA Supplement and within **(14)** calendar days of receipt of a Pre-Submission.

Please note that the Acceptance Review does not start until FDA has received a valid eCopy and, if applicable, the User Fee has been paid.

**FDA Guidance on Acceptance Review: Refuse to Accept (RTA) Policy**

# Acceptance Review Communication Continued

**Content:** FDA should communicate the outcome of the Acceptance Review to the Applicant by fax, email, or other written communication. This communication represents a review of the Submission for completeness and is not intended to identify deficiencies that may be identified later in the review cycle.

## When the Submission is Accepted

FDA should provide the name of the FDA Lead Reviewer or Regulatory Project Manager and notify the Applicant that the Submission has been accepted. For a 510(k) and Pre-Submission, the Submission is accepted for substantive review. For an Original PMA or Panel-Track PMA Supplement, the Submission is accepted for filing review.

## When the Submission is Not Accepted

FDA should provide the name of the FDA Lead Reviewer or Regulatory Project Manager and notify the Applicant that the Submission has not been accepted and identify those items necessary for the Submission to be considered accepted.

## FDA Interactions

# SUBSTANTIVE INTERACTION

# Substantive Interaction

**Purpose:** Substantive Interaction is one of the following actions:

- FDA notification that they intend to continue working with the Applicant to resolve any outstanding deficiencies via Interactive Review, and the Submission will not be placed on hold; or
- FDA notification placing the Submission on hold and identifying the deficiencies to be addressed in order for Substantive Review to continue.

**Timing:** Substantive Interaction should occur following acceptance of the Submission and after FDA has performed a **complete** review of the Submission and within:

  - **(60) calendar days** of the receipt date of a complete Submission for 510(k)s;
  - **(90) calendar days** of the filing date for Original PMAs and Panel-Track PMA Supplements; and
  - **(90) calendar days** of the receipt date for 180-Day PMA Supplements.

Note that the timeframes for Substantive Interaction include the **(15)** calendar days used for the Acceptance Review. An approval, approvable, or clearance letter issued prior to the Substantive Interaction goal date is considered an on-time Substantive Interaction for the purpose of meeting the MDUFA III goal.

# Substantive Interaction Continued

**Content**: Based on the nature and/or extent of the deficiencies, the submission may or may not be placed on hold.

| When the Submission is Not Placed on Hold | When the Submission is Placed on Hold |
| --- | --- |
| FDA should inform the applicant via email or fax that, based on a complete review of the entire Submission, the Agency does not intend to place the Submission on hold and that any additional deficiencies will be handled through Interactive Review. This type of Substantive Interaction has no start/stop impact on the review clock. | FDA intends to place the Submission on hold in accordance with current practice. Deficiencies identified in the hold notification should be based upon a complete review of the entire Submission, and should include both major and any unresolved minor deficiencies. |

## FDA Interactions

# INTERACTIVE REVIEW

# Interactive Review - Purpose

**Purpose:** To facilitate the efficient and timely review and evaluation by FDA of premarket submissions through increased informal interaction between FDA and applicants, including the exchange of scientific and regulatory information. Objectives include the following:

- Improve the interaction between the FDA Review Staff and the Applicant during the review process;
- Prevent unnecessary delays in the completion of the review, thus reducing the overall time to market;
- Ensure that FDA's concerns are clearly communicated to the Applicant during the review process, as appropriate;
- Minimize the number of review cycles / Minimize the number of review questions conveyed through deficiency letters; and
- Ensure timely responses from Applicants.

# Interactive Review – Timing/Expectations

**Timing & Expectations:** There are different expectations for Interactive Review depending on when, during FDA's review of the Submission, the need to communicate occurs.

**(1) Interactive Review After Substantive Interaction for 510(k)s, Original PMAs, Panel-Track PMA Supplements, and 180-Day PMA Supplements**

- FDA intends to engage in Interactive Review after Substantive Interaction.

**(2) Additional Interactive Review**

- FDA encourages the use of Interactive Review at other points in the review process to facilitate the efficient and timely review of medical device submissions. More specifically, at FDA's discretion, Interactive Review can be used:
  - Prior to Substantive Interaction for 510(k)s, Original PMAs, Panel-Track PMA Supplements, and 180-Day PMA Supplements; and
  - As needed for other submission types, such as: *[other PMA Submissions; Pre-Submissions; Third Party Review; De Novo Petition; 513(g) Request; Humanitarian Device Exemption (HDE); Investigational Device Exemption (IDE); Product Development Protocol (PDP)].*

# Interactive Review Process – Effect on FDA Review Clock

**Interactive Review Process Effect on FDA Review Clock:**

- Occurs while the Submission is under Review and it does not affect the Stop/Start Impact on the Review Clock
- FDA determines an acceptable timeframe for the Applicant to provide a response to the deficiencies/ FDA should clearly communicate the due date for responding to the Interactive Review request.
- If the Submission was previously on hold, then any new deficiencies (i.e., deficiencies not raised as part of the hold notification) should be limited to issues raised by the information provided by the Applicant in its response, unless the Reviewer concludes (and received supervisory concurrence) that the initial deficiencies identified do not adequately address important issues materially relevant to a decision of substantial equivalence (510(k)) or safety and effectiveness (PMA).

# Interactive Review – Appropriate for Certain Types of Deficiencies

**Types of Deficiencies Appropriate for Interactive Review:**

- Deficiencies that are more significant than "minor," but could likely be addressed by the Applicant in a time frame that would allow FDA review of the response prior to the MDUFA performance goal for that submission type without placing the submission on hold. Examples may include, but are not limited to:
  - Requests for limited additional short-term laboratory bench or biocompatibility testing
  - Further justification/rationale for the omission of a test
  - Additional statistical analysis of the clinical data not related to the primary safety or effectiveness endpoint

# Interactive Review – Response to Deficiencies

**Response to Deficiencies :**

- If the outstanding deficiencies are not likely to be resolved through Interactive Review (e.g., a device submitted in a 510(k) has a new intended use or different technological characteristics that raise new questions of safety or effectiveness; a new clinical study will be needed for a device submitted in a PMA), FDA may proceed with a MDUFA decision without engaging in Interactive Review (e.g., issuing a Not Substantially Equivalent (NSE) letter for a 510(k) or a Not Approvable (NOAP) letter for a PMA).
- Communications may be via email, fax, and/or phone
- FDA should accept email responses to the information requested via the Interactive Review process and include that information as part of the official administrative file for the submission.
- FDA should not request that the applicant also formally submit these Interactive Review responses to the appropriate Document Control Center (DCC) as part of an official submission.

# Interactive Review – Applicant's Role

**Role of Applicant During Interactive Review Process:** To help ensure that the Interactive Review process is effective, the Applicant should do the following:

- Submit a well organized and administratively and scientifically complete submission consistent with applicable regulations, recommendations in the available guidance documents, and communications with FDA prior to submission;
- Include complete contact information in the cover letter (i.e., name, email, phone number, fax number) in the company cover letter for each submission. FDA also recommends providing alternative contact information in case the lead contact is not available. In addition, foreign applicants should have a U.S. representative available to participate in the Interactive Review process and to provide a means to contact the foreign company as quickly as possible;
- Apply appropriate material or testing standard(s) and submit the necessary declarations or data to support the use of the standard(s); and
- Provide a complete response to all deficiencies communicated via Interactive Review within the FDA-allotted timeframe

# Interactive Review – Contacting Lead Reviewer

**When the Applicant should Contact the Lead Reviewer:**

- To reconcile any disagreement with a deficiency cited by the Lead Reviewer or Consulting Reviewer during Interactive Review;
- To inquire whether a revised Interactive Review timeframe may be given to address a deficiency because the initial timeframe cannot be met (this does not pertain to last Interactive Review communication at the end of the review cycle, which the FDA intends to limit to 7 calendar days);
- To discuss procedural questions related to the submission; To correct errors in the data submitted; To clarify information in the submission that the applicant subsequently notices is unclear; and
- To alert FDA that it intends to submit new, unsolicited information or data (depending on its extent, the information/data may necessitate a new submission or be logged in as an amendment to an existing submission).
- Applicants should refrain from using Interactive Review to request status updates as such requests may interfere with FDA's ability to meet applicable timeframes.

## FDA Interactions

# MISSED MDUFA DECISION COMMUNICATION

# Missed MDUFA Decision Communication

**Purpose:** To facilitate a timely resolution to any outstanding issues that have precluded FDA from reaching a MDUFA decision prior to the appropriate MDUFA decision goal.

**Timing:** A Missed MDUFA Decision communication should occur for those submissions that have not reached a MDUFA decision by:

- 100 FDA days for 510(k)s; and
- 20 FDA days after the applicable FDA day goal for Original PMAs and Panel-Track PMA Supplements.

**Content:** The feedback should reflect appropriate management input and approval and should include:

- All outstanding issues with the application preventing FDA from reaching a decision; Action items for FDA and/or the applicant;
- The estimated completion date for the action items identified for each party; and
- Proposed dates for meetings from which the applicant may choose (the applicant may, in turn, propose alternative dates to FDA).
- Outstanding issues should be resolved through Interactive Review whenever possible. If all of the outstanding issues are adequately presented through the written correspondence, FDA and the Applicant can agree that a meeting or teleconference is not necessary.

## Six Step Process

# SUCCESSFULLY MANAGING FDA ISSUES/QUESTIONS

# 6 Step Process for Successfully Managing FDA Issues/Questions

- **Step 1** – Upon receipt of RTA Hold Notice and/or Request for Additional Information (AI), ensure that the FDA's cited deficiencies are clearly understood by your organization and communicated to the appropriate stakeholders.
- **Step 2** - Review the list of FDA Deficiencies with a cross-functional team and categorize each one according to the time and effort required to adequately address the issue(s).
- **Step 3** – Determine what actions may be necessary to address each deficiency (i.e. additional testing, updates to labeling, etc.). Prepare a timeline.
- **Step 4** – Assign responsibilities to members of the cross-functional team.
- **Step 5** – Contact the Lead Reviewer and confirm that you will submit a formal response and/or request clarification on specific issues. Actively engage in communications with the Lead Reviewer if he/she is amenable to doing so.
- **Step 6** – Prepare and submit a formal response to the RTA Deficiency List and/or Request for Additional Information (AI) Letter

# Lessons Learned

- Follow applicable FDA Guidance Documents to ensure that you will meet the FDA's expectations
- Use FDA's eSubmitter Tool and send a screen shot of the confirmation of a successful eCopy version along with the submission
- Use the Refuse to Accept (RTA) Checklist as your guide when preparing the submission
- Engage in early and frequent interactions with the FDA and build a strong working relationship with the FDA Lead Reviewer, including utilizing the Pre-Submission Meeting process when you are unsure of the regulatory pathway
- When responding to FDA inquiries or requests for additional information submit a comprehensive, well-organized response that addresses each specific element, or provide a reasonable rationale as to why certain information is not provided
- Regulatory professionals should seek assistance from internal company and/or external subject matter experts to ensure information provided and/or responses are technically appropriate.

# Questions?

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## Dealing with Unexpected Issues/Questions during the Submission Review Process

Navigating Submission Challenges to reduce time & risk

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