The Beginner's Guide to

The FDA PMA Submission Process

Rimsys®

Contents

Introduction

If your organization is planning to market a new medical device in the United States, you first need to determine which regulatory class the device falls under. The vast majority of medical devices regulated by the FDA are either Class I or Class II medical devices, requiring a 510(k) premarket notification or a simple registration if exempt from 510(k) requirements. However, if your device sustains or supports life, is implanted, or presents a "potential unreasonable risk of illness or injury," your device is likely a Class III device which will require Premarket Approval (PMA) from the FDA before it can be marketed in the United States. Novel devices, for which there are no existing substantially equivalent devices, are automatically classified as Class III as well. Novel devices with a lower risk profile, however, may qualify for the De Novo process instead of the PMA. Just 10% of devices regulated by the FDA are Class III devices.

This ebook provides an overview of the PMA process and its requirements, but it is not designed to be the only resource used in compiling a PMA submission. The FDA provides significant documentation on this process, starting with the regulation governing premarket approval that is located in Title 21 Code of Federal Regulations (CFR) Part 814.

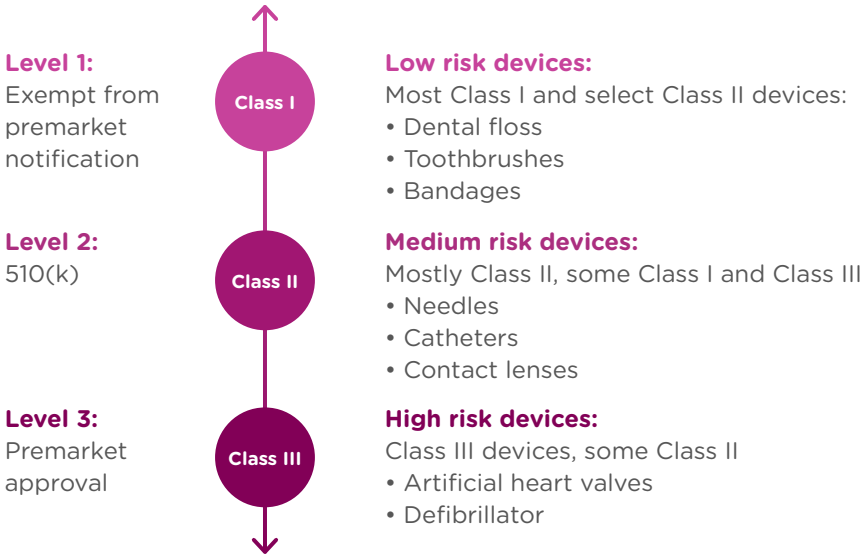
Chapter 1

PMA Basics

FDA: Background and device oversight

Before we explain what a PMA is, let's first talk generally about the Food and Drug Administration (FDA) and device oversight. The FDA is the U.S. governmental agency responsible for overseeing medical devices, drugs, food, and tobacco products. When it comes to medical devices, the FDA's mission is to "protect the public health by ensuring the safety, efficacy, and security of…medical devices." At the same time, the FDA also has an interest in "advancing public health by helping to speed innovations." In other words, the FDA's goal is to make sure devices are safe and effective for public use, while also ensuring that devices have a quick and efficient path to market.

In order to achieve this balance of safety and efficiency, the FDA has three different levels of oversight depending on the risk level of the device: (1) exempt from premarket notification, (2) Premarket Notification, also known as 510(k), and (3) Premarket Approval (PMA).



When is a PMA required?

The PMA process is the most stringent regulatory process for medical device approval under the FDA and applies to almost all Class III devices. To determine whether your device requires a PMA, you must first Classify your device by searching the product classification database. The database will provide you with similar devices; their name, classification, and link to the Code of Federal Regulations (CFR) if applicable.

- If a substantial equivalent is found in the product classification database with a submission type of 510(k), you should submit a 510(k), not a PMA.
- If the product classification database identifies your device as Class III and/or requiring a PMA – you should submit a PMA.
- If your device involves a new concept and does not have a classification regulation in the CFR, the database will list only the device type name and product code. In this case, the three-letter product code can be used to search the PMA database and the 510(k).
- If your device cannot be found in the product classification database because it is a new type of device, it is classified as a Class III device and requires a PMA by default.* However, if your novel device has the lower risk profile of a Class I or Class II device, it may be eligible for the De Novo process.

***Class III devices support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential and unreasonable risk of illness or injury.**

PMA vs 510(k)

Not only are PMA and 510(k) processes applicable to different types of devices, they have different purposes.

510(k)

A 510(k) is intended to demonstrate that the device for which approval is being sought is as safe and effective as a currently marketed device that does not require a PMA.

PMA

A PMA is intended to prove that a new device is safe and effective for the end user, and is much more detailed than a 510(k). Device manufacturers are typically required to present human clinical trial data, in addition to laboratory testing data.

The difference in complexity between a PMA and 510(k) also affects the time needed to process the submissions. The FDA typically accepts or rejects a 510(k) submission within 30-90 days, at which point the device is posted to the FDA's 510(k) database. A PMA submission can take up to 180 days to be processed, at which point the FDA can approve or deny the application. The FDA may also issue an "approvable" or "not approvable" letter, which the applicant can choose to respond to, thereby adding time to the submission process.

PMA application methods

There are a number of types of PMA application methods. While most devices which require a PMA will follow the traditional process, be sure to verify that you are using the correct application process to maximize your chances for success and avoid unnecessary delays:

Traditional PMA

The most common method for attaining FDA clearance for Class III devices, the traditional PMA is the appropriate option for most devices that have completed clinical testing.

Modular PMA

The modular PMA is the appropriate application method for devices that have not yet completed clinical testing. Applicants complete individual "modules," with final confirmation granted once all sections are completed. For additional information on specific requirements of a modular PMA, read the FDA's Premarket Approval Application Modular Review.

Product Development Protocol

Use the Product Development Protocol (PDP) with medical devices that are based on well-established technology. The PDP process for gaining market approval merges the clinical evaluation and development of information, and involves an agreement between the manufacturer and the FDA. The process provides the advantage of early predictability for the manufacturer and allows early interaction that can identify FDA concerns as soon as possible in the development process. Because the PDP identifies the agreed upon design and development details, a completed PDP is considered to have an approved PMA. For additional information, read more about the FDA's PMA Application Methods.

Humanitarian Device Exemption

A Humanitarian Use Device (HUD) is specifically defined as a device intended to benefit patients that are affected by a disease or condition that affects less than 8,000 individuals in the U.S. per year. The Humanitarian Device Exemption (HDE) approval process is designed to encourage clinical activity around rare conditions, and does have certain restrictions, including:

- After receiving HDE approval, a HUD is eligible to be sold for profit only if the device is intended to address a disease or condition that occurs primarily in pediatric patients, or occurs in pediatric patients in small numbers.

- If an HDE is approved to be sold for profit, the FDA will determine an annual distribution number (ADN). Any devices sold beyond the ADN limit are required to be sold for no profit.

For more information see the FDA's explanation of the Humanitarian Device Exemption.

CBER submissions

There are two centers within the FDA responsible for evaluating medical devices. While the majority of devices will go through the Center for Devices and Radiological Health (CDRH), some will be managed by The Center for Biologics Evaluation and Research (CBER). CBER regulates medical devices related to blood and cellular products, including blood collection and processing procedures as well as cellular therapies. This ebook focuses on submissions made through the CDRH, but you can view CBER Regulatory Submissions – Electronic and Paper for more information on the CBER process.

Chapter 2

FDA Interactions

The FDA encourages pre-submission collaboration meetings and communication as early in the product development process as possible. It is in the best interest of organizations seeking approval of a medical device to have an open dialogue with the FDA, enabling the FDA to advise before and during the submission process, provide direction on IDE applications, and identify any potential concerns that may affect approval of the device. This is especially important for devices with novel technology.

The FDA Modernization Act (FDAMA) introduced the "Q-Submission Program" and formalized the process around pre-submission meetings. The Q-submission program refers to the system used to track the collection of interactions described below. FDA reviewers are encouraged to work interactively with submitters during the Q-sub process, which is an important opportunity for submitters to share information with the FDA and to receive input outside of formal submissions. Note that the Q-Submission guidance replaced the "pre-IDE" program.

There are a number of pre-submission meeting types that can be requested. Some of these are Q-Sub meetings that follow the Q-sub process, while others are assigned a Q number for tracking purposes, but follow processes detailed in separate guidance documents. While early communication with the FDA can be extremely important in ensuring a smooth submission process, all pre-submission meetings are voluntary on the part of the submitter.

Q-Sub Meetings

Pre-Submission (Pre-Sub)

A pre-sub provides the opportunity for an organization to obtain FDA feedback before submitting a premarket submission (including PMA), accessory classification request, or CLIA waiver. Pre-sub requests are made in writing and the FDA provides a formal written response, followed by an optional meeting if requested by the submitter.

Submission Issue Request (SIR)

An SIR is submitted in response to issues found in a marketing submission. This includes items called out in, among others, PMA "not approvable" letters. An SIR is intended to facilitate a quick resolution or clarification of issues identified by the agency associated with a marketing submission. Note that submitters are expected to provide a formal response to notifications by the FDA, whether an SIR is requested or not. An SIR request is NOT an appropriate response to a final decision by the agency.

Study Risk Determination

A study risk determination is a request for the FDA to issue a determination as to whether a planned clinical study can be categorized as a significant risk (SR), non-significant risk (NSR), or is exempt from IDE regulations.

Informational Meeting

An informational meeting is a request to share information with the FDA without the expectation of receiving any feedback from the agency. An informational meeting can be used to keep the FDA informed as to ongoing device development, particularly when there may be multiple submissions planned. They are used to document interactions between the FDA and the submitter that do not fall under other types of Q-submissions.

Early collaboration: Determination meeting

A determination meeting is designed to provide a PMA or PDP applicant with the FDA's determination of the type of valid scientific evidence required to demonstrate that the device is effective for its intended use. A determination meeting will result in a decision as to whether clinical studies will be needed to establish effectiveness, and will allow the agency and the applicant to jointly determine the least burdensome way of demonstrating the effectiveness of the device. The FDA will deliver a written determination within 30 days of the meeting, which is binding on the agency.

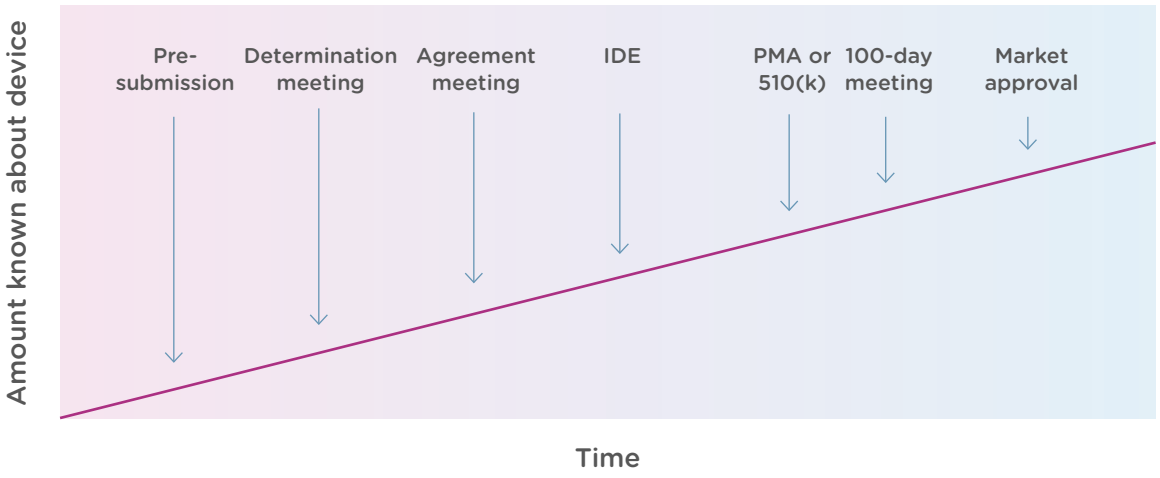
Early collaboration: Agreement meeting

An agreement meeting is used to reach an agreement between the agency and the submitter on key parameters of the investigational plan to be used to demonstrate safety or effectiveness of a device. Unlike a determination meeting, an agreement meeting is open to anyone investigating the safety or effectiveness of a Class III device or any implantable device; meaning that an agreement meeting can be used by submitters of a 510(k) where applicable. As with a determination meeting, results of an agreement meeting are to be provided in writing by the agency and are binding.

For additional information on Determination and Agreement meetings, see "Early Collaboration Meetings Under the FDA Modernization Act: Final Guidance for Industry and for CDRH Staff"

PMA day 100 meeting

The purpose of a PMA day 100 meeting is to discuss the status of a pending PMA submission, and it must be held within 100 days of the submission. A day 100 meeting can be requested with the original PMA submission, or as an amendment to the submission. At least 10 days prior to the meeting, the FDA is required to inform the applicant in writing of any deficiencies and what information will be required to correct the deficiencies. Meeting minutes will be included in the administrative record, and the agency will continue to communicate with the submitter regarding the status of the application at a minimum of every 4 weeks.



Additional pre-submission meetings:

- Breakthrough designation request
- Safer Technologies Program (STeP) entrance request
- Accessory classification request

Chapter 3

Contents of a Traditional PMA Submission

Details on each section of a PMA submission can be found on the FDA website – PMA Application Contents page.

Trade secret or confidential information must be included in all copies of the PMA. Identify in at least one copy all information that is believed to be a trade secret or confidential information.

Cover letter

The cover letter should include:

- Identification of the type of PMA submission (original, supplement, or amendment) and any relevant reference numbers to related submissions or documents needed for FDA tracking purposes.
- Clear identification of the applicant's authorized representative and contact information. Note that most FDA correspondence will come via email.
- Indication for use (for original PMA).
- Indication of whether the submission includes an environmental assessment.

A dated and signed cover letter should be included in the first volume of every copy of the PMA submission.

See Appendix A for an example of a cover letter.

Cover sheet – form 3514

The PMA Submission Cover Sheet (Form FDA 3514) is not required, and will not affect the FDA's decision or process around your submission. However, the cover sheet allows for more efficient processing of your submission by providing all administrative data in a consistent and recognizable format. Form 3514 was specifically developed to reduce common administrative data deficiencies in PMA submissions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CDRH PREMARKET REVIEW SUBMISSION COVER SHEET

Form Approved: OMB No. 0910-0120
Expiration Date: June 30, 2023
See PRA Statement on last page.

Date of Submission	User Fee Payment ID Number	FDA Submission Document Number *(If known)*

SECTION A — TYPE OF SUBMISSION

PMA & PDP
- ☐ Original
- ☐ Modular Submission
- ☐ Amendment
- ☐ Report (annual or PAS)
- ☐ Report Amendment
- ☐ Other:
  - ☐ Premarket Report (reprocessed SUD)
  - ☐ Licensing Agreement

PMA/PDP Supplement
- ☐ 180 day - PAS protocol or labeling change, location change, trade name change
- ☐ 180 day - Design or labeling change
- ☐ Special CBE
- ☐ Panel Track
- ☐ 30-day Notice
- ☐ Real-time Review
- ☐ Amendment to PMA/PDP Supplement

510(k)
- ☐ Original Submission:
  - ☐ Traditional
  - ☐ Special
  - ☐ Abbreviated
  - ☐ 3rd Party Traditional
  - ☐ 3rd Party Special
  - ☐ 3rd Party Abbreviated
  - ☐ Dual Track (Dual 510(k) and CLIA Waiver by Application)
- ☐ Amendment
- ☐ Supplement

CLIA

CLIA Categorization Record (CR)
- ☐ Original
- ☐ Amendment

CLIA Waiver by Application (CW)
- ☐ Original
- ☐ Amendment
- ☐ Supplement

Q-Submission
- ☐ Pre-Submission
- ☐ Informational Meeting
- ☐ Submission Issue Meeting
- ☐ Day 100 Meeting
- ☐ Agreement Meeting
- ☐ Determination Meeting
- ☐ Study Risk Determination
- ☐ Other *(Specify below)*

IDE
- ☐ Original IDE:
  - ☐ Amendment to Original IDE
- ☐ Supplement:
  - ☐ Amendment to Supplement
- ☐ Report:
  - ☐ Amendment to Report

HDE
- ☐ Original Submission
- ☐ Amendment to Original
- ☐ Report
- ☐ Report Amendment
- ☐ HDE Supplement:
  - ☐ 75-day Supplement
  - ☐ 30-day Notice
  - ☐ Special CBE
  - ☐ Amendment to Supplement

Class II Exemption Petition
- ☐ Original Submission
- ☐ Additional Information

Emergency Use Authorization
- ☐ Original
- ☐ Supplement
- ☐ Amendment
- ☐ Report

De Novo
- ☐ Original:
  - ☐ Direct
  - ☐ Post-NSE
- ☐ Amendment
- ☐ Supplement

Pre-Emergency Use Authorization
- ☐ Original
- ☐ Supplement
- ☐ Amendment

Other Submission
- ☐ 513(g)
- ☐ Appeal
- ☐ Other *(Briefly describe submission below)*

Expanded Access to Devices
- ☐ Compassionate Use Request **NOT associated with an IDE**
- ☐ Follow-up Report for Compassionate Use **NOT associated with an IDE**
- ☐ Emergency Use Follow-up Report **NOT associated with an IDE**

SECTION B — APPLICANT / SPONSOR

Company/Institution Name		Establishment Registration Number/FEI *(if known)*
Street Address		City
State/Province	ZIP/Postal Code	Country
Contact Name		Contact Title
Division Name *(if applicable)*		Phone Number *(including area code)*
Fax Number *(including area code)*		Contact Email Address

FORM FDA 3514 (8/20) Page 1 of 7 PSC Publishing Services (301) 443-6740 EF

Table of contents

A table of contents is required that lists the volume and page number for each item included in the submission.

Summary

It is important to include a summary section that provides enough detail so that the reader can gain an overall understanding of the application and the information it includes. The FDA requires that the summary section include the following information:

Indications for use

Include a general description of the disease or condition that the device will be used to treat, along with the definition of the patient population for which the device is intended.

Device description

Include any generic and proprietary names for the device, along with descriptions of the device's functions, scientific concepts, and physical and performance characteristics. An overview of the manufacturing process can also be included if it is important to an overall understanding of the device

Alternative practices and procedures

If similar, alternative Class III devices are available to address the same indications of use, describe each alternative. Include only devices that are currently commercially available.

Marketing history

Include a brief description of both U.S. and international marketing history, if applicable. Include at least a list of each country in which the device has been marketed, along with the date it was introduced into each market. Be sure to also include any information concerning product withdrawals in any market.

Summary of studies

Include a summary of all results of nonclinical and clinical studies, along with an abstract of any additional data or relevant technical information. Each study summary should include:

- Discussion of subject selection and exclusion criteria.
- Study population demographics.
- Study period.
- Safety and effectiveness data.
- Adverse reactions and complications.
- Patient discontinuation.
- Device failures and replacements.
- Tabulations of data from all individual subject reporting forms and copies of forms for each subject who died during a clinical investigation or did not complete the investigation.
- Results of statistical analyses of the clinical investigations.
- Contraindications and precautions for use of the device.
- Any other relevant information from the study.

Be sure to identify any investigation conducted under an IDE.

Conclusions drawn from studies

Demonstrate how the data in the application represents valid scientific evidence according to the definitions in 21 CFR 860.7. Be sure to include a discussion of any adverse effects of the device, and any additional studies that you are proposing following the approval of the *PMA.*

The regulation states that your summary section "should objectively link the medical claim(s) for the device to the hypotheses tested and conclusions drawn from the findings of all studies and investigations." The goal is to create a summary section that can be used as the basis for the FDA's Summary of Safety and Effectiveness Data.

Detailed descriptions

A PMA submission should include complete, detailed descriptions of the following:

- The device and each of its functional components, including pictorial representations.
- The properties of the device that are relevant to its function.
- Principles of operation for the device.
- The methods, facilities, and controls used in producing, storing, and installing the device (if applicable). Use this section to fully describe your quality controls and related processes. *Note that you can temporarily omit complete manufacturing information if it is not yet available per 21 CFR 814.20(d).*

Performance and voluntary standards

Manufacturers are encouraged to use FDA-recognized consensus standards in premarket submissions. While conformance to these standards is voluntary (unless a standard is 'incorporated by reference' into regulation) they are typically used and will facilitate the review process. An application should demonstrate how the device meets any applicable standards, and explain any variation from the standard.

For more information on consensus standards, see the FDA's Standards and Conformity Assessment Program. You can also search the Recognized Consensus Standards database.

Performance standards typically are more applicable to a 510(k) submission, but may apply in certain circumstances to a PMA. Performance standards are defined under Part 514 of the FD&C Act or the Radiation Control for Health and Safety Act of 1968 (RCHSA).

Technical sections

Technical sections contain significant detail and data concerning both clinical and non-clinical investigations and should provide sufficient information to allow the FDA to make a decision on the application.

Nonclinical laboratory studies

This section should contain information concerning investigations involving human subjects, including, but not limited to: animal tests. Be sure to include a statement that each study was conducted in compliance with Good Laboratory Practice for Nonclinical Laboratory Studies (21 CFR 58). Otherwise, you will need to provide a statement as to why a study was not compliant with the regulation.

Clinical investigations

This section should include information concerning investigations involving human subjects. Information should include, but not be limited to:

- Clinical protocols.
- Number of investigators and subjects per investigator.
- Discussion of subject selection and exclusion criteria.

- Study population demographics.
- Study period.
- Safety and effectiveness data.
- Adverse reactions and patient discontinuation data.
- Patient complaints.
- Device failures and replacements.
- Data from all individual subject reporting forms (including copies of forms for any subject who died or did not complete the study).
- Contraindications for device use.

Additional analyses and discussion of any potential biases during the study should also be included if applicable.

You must also include statements regarding the adherence to the following (or a statement of noncompliance if applicable):

- Institutional Review Board regulations under 21 CFR 56 (or was not subject to the regulation per 21 CFR 56.104 or 21 CFR 56.105).
- Informed Consent regulation, 21 CFR 50.
- Investigational Device Exemptions regulation, 21 CFR 812.

Justification for a PMA supported by data from a single investigator

If your PMA is supported by data from a single investigator, you must justify that this is sufficient to demonstrate the safety and effectiveness of the device.

Bibliography of all published reports

Any published report not already referenced that concerns the safety or effectiveness of the device needs to be included here. Consider providing copies and summaries of all key articles, along with discussions of how they relate to the evaluation of the device. It is important to understand that the application is required to include reference to any applicable article or study, if known to the applicant.

Product samples

Include one or more samples of the device and its components. Alternatively, you can provide a location where the FDA may examine and test the device (if impractical to provide samples).

Labeling

Include copies of all proposed labeling, including installation instructions, literature, marketing materials, or anything else that constitutes labeling under 21 CFR Part 801.

Environmental assessment

An environmental assessment is required under 21 CFR 814.20(b)(11), unless the PMA qualifies for an exclusion under § 25.30 or § 25.34. Most devices that are of the same type and for the same use as a previously approved device are excluded from this requirement.

Financial certification or disclosure statement

A financial certification and/or a disclosure statement for each clinical investigator who participated in your study must be submitted. The purpose of this disclosure is to share any arrangements or financial interests that exist between the clinical investigator and the device manufacturer, and to certify that those financial interests do not compromise the validity of the clinical study results. Include a financial certification or disclosure statement, or both, as required by 21 CFR 54:

- Certification: Financial Interests and Arrangements of Clinical Investigators (Form FDA 3454)
- Disclosure: Financial Interests and Arrangements of Clinical Investigators (Form FDA 3455)

For more information, you can access the FDA guidance document regarding financial disclosure requirements.

Additional information

Include additional information as requested by the FDA.

Other references

Reference any applicable information already on file with the FDA. Information that has been submitted by a person other than the PMA applicant will not be considered, unless it is referenced here with signed authorization by the person who submitted the original information.

Omissions

If any information is omitted because the applicant believes it is not applicable to the device, a statement identifying and explaining the omission must be provided here in a separate section and referenced in the table of contents.

Color additives

A color additive used in the device is subject to Part 721 and must be listed for this use by the FDA. If the color additive has not previously been listed for such use, a color additive petition may be submitted to the Center for Food Safety and Applied Nutrition (per 21 CFR 71) or to the CDRH as part of the PMA. See "Color Additives for Medical Devices" for more information.

Updates

Periodic updates are required when new information is learned from ongoing or completed studies that may affect the evaluation of the safety or effectiveness of a device. Three copies of each updated report must be submitted and must reference the PMA number assigned by the FDA. Each such update is considered to be an amendment to the original PMA, and as such will not cause any extension to the review timeframe. These amendments must be submitted 3 months after receipt of the PMA approvable letter, and at any other time as requested by the FDA.

It is an accepted practice to include all PMA sections, even those which do not apply to your PMA submission. Note in the submission that the section is not applicable to avoid any confusion over whether the section was omitted by mistake or for other reasons.

Chapter 4

PMA Supplements & Amendments

PMA supplements

A PMA supplement is a required submission supporting a change that affects the safety or effectiveness of a device for which there is an approved PMA. Some of the changes which may require a PMA supplement include:

- New indications of use.
- Labeling changes.
- The use of a different manufacturing, processing, or packaging facility.
- Changes to manufacturing methods or quality control procedures.
- Changes in packaging.
- Changes in sterilization procedures.
- Changes to performance or design specifications, any component or ingredient, principles of operation, or physical layout of the device.
- Extension of the device's expiration date based on new data.

There are multiple types of PMA supplements, as defined in 21 CFR 814.39:

PMA Panel-Track Supplement – 814.39(c)

Used to request significant changes in the design or performance of the device, or for new indication of use. This supplement type requires substantial clinical data to support the requested change and does require a full PMA review.

PMA Supplement (180 days) – 814.39(a)

Used for changes that affect the safety and effectiveness of the device, including significant changes in components, materials, design, specification, software, color additives, or labeling. This supplement type does not usually require additional clinical data. An in-depth review or, in some cases, a full PMA review is required.

Real-Time Supplement – FD&C Act 737(4)(D)

Used for minor changes to the device and for which the FDA has granted a request for a meeting to jointly review and determine the status of the supplement. For additional information, see Real-Time Premarket Approval Application (PMA) Supplements.

Special PMA Supplement – Changes being Effected – 814.39(d)

Used for any change that enhances the safety of the device, including labeling and manufacturing changes. Changes under this type of supplement may be implemented before receiving FDA approval.

30-day Notice and 135 PMA Supplement – 814.39(f)

Used for modifications to manufacturing procedures or methods that affect the safety and effectiveness of the device. Changes that qualify for the 30-day notice supplement can be implemented within 30 days of submitting the supplement to the FDA, unless otherwise notified by the FDA before the 30 days elapses. For additional information, see 30-Day Notices and 135-Day PMA Supplements for Manufacturing Method or Process Changes, Guidance for Industry and CDRH.

PMA Manufacturing Site Change Supplement – 814.39(a)(3)

Used for changes in manufacturing, processing, or packaging facilities in cases where the change affects the safety and effectiveness of the device or the new site was not approved in the original PMA.

The supplement must demonstrate compliance with quality system regulations (21 CFR 820) and a preapproval inspection may be necessary.

For more information, see Manufacturing Site Change Supplements: Content and Submission.

Annual (periodic) Report or 30-day Supplement – 814.39(e)

The FDA may allow some changes to be reported in an annual report instead of a PMA supplement submission. The FDA will notify an applicant with an approved PMA of any changes for which a supplement is not required. These changes may be implemented before they are reported in the periodic report.

PMA amendments

A PMA amendment is used to revise or provide additional information for a pending PMA or PMA supplement. PMA amendments may either be requested by the FDA, when additional information is required to complete a review, or may be initiated by the applicant when additional information becomes available.

Major PMA amendments containing significant new data or new analyses may extend the review period by up to 180 days.

Chapter 5

PMA Quality Management System (QMS)

The FDA requires that manufacturers of Class II, Class III, and some Class I medical devices have a documented quality management system (QMS) in place. The QMS is a set of controlled processes and procedures relative to a medical device's design, manufacturer, risk management, complaint handling, clinical data, distribution, labeling, and more. A QMS ensures that a marketed medical device meets its intended purposes efficiently and effectively.

In almost all cases, an FDA inspection of the QMS will be required, and changes to the QMS will impact a PMA submission.

The FDA defines both design controls and manufacturing controls, along with inspection requirements, for a PMA submission.

Design controls

As defined in 21CFR Part 820 (the "QS" regulation or "QSR"), design controls ensure that a device, as designed, will perform as intended when produced for commercial distribution. A full description of design controls must be provided in a PMA submission to demonstrate that they comply with the QS regulation.

Design controls dictate the establishment and maintenance of procedures that control the design of a device for the purpose of ensuring that design requirements are met. This includes:

- A full description of design and development activities, including implementation responsibilities.
- Identification and description of any interfaces with groups that provide input into the design and development process.
- A complete risk analysis.
- Identification of design inputs and requirements.
- Development of design outputs and specifications.
- Verification that design output meets design input.
- Implementation of regular design reviews.
- Validation that the design meets user requirements and intended uses.
- Validation of any software used in the device.
- Description of the process used for transferring device design to production specifications.
- Documentation of processes that ensure any design changes are controlled, during the design process and after the product is marketed.
- Documentation of design control activities in the design history file.

You can find additional guidance on the design control requirements under the Quality System regulation in the following documents:

Applying Human Factors and Usability Engineering to Medical Devices

Design Control Guidance for Manufacturers

Manufacturing controls

A PMA submission must include a full description of methods, facilities, and controls used for:

- Manufacturing
- Processing
- Packaging
- Storage
- Installation (where applicable)

It is important to include all facilities that provide even a portion of the manufacturing process, such as sterilization or packaging. Contract facilities may provide the device manufacturer with sufficient information to include their processes directly in the PMA submission, or they must submit such information separately to the FDA in the form of a Device Master File.

Additional guidance for the preparation of quality system design and manufacturing information for a PMA submission can be found in the Quality System Information for Certain Premarket Application Reviews.

QS inspections

Pre-approval inspections

The Office of Product and Quality (OPEQ) will review the quality system design and manufacturing information in a PMA submission. If OPEQ determines that the quality system has been described in enough detail that they can make a determination as to whether the manufacturer meets QS requirements, a pre-approval inspection will be initiated.

The inspection will include an assessment of the organization's capability to design and manufacture the device as described in the PMA, and will confirm that the quality system is in compliance with 21 CFR 820.

Guidance on PMA inspections can be found in:

- PMA Compliance Program #P91-3 (blue book memo)
- Inspections of Medical Device Manufacturers, C.P. 7382.845

Post-approval inspections

Within 8 to 12 months of a PMA approval, a post-approval inspection will be conducted. The focus of post-approval inspections is on changes that may have been made to the device design, manufacturing process, or quality systems.

Chapter 6

Review Process and Timeline

The PMA review process consists of four steps:

Administrative review

As defined under 21 CFR 814.42, the first step in the review process includes an administrative and limited scientific review designed to allow the FDA to determine whether the PMA includes all required information and is suitable for filing. If the FDA refuses to file the PMA, the applicant will be notified of the reasons for refusal, and will be advised on what additional information or changes must be made to allow the application to be filed.

Reasons for refusal to file:

- The application is incomplete - it does not contain all information required under sections 515(c)(1) of the FD&C act.
- The PMA does not contain every item required under Section 814.20, or justification for those items omitted (or justification is inadequate).
- There is a pending 510(k) with respect to the same device and a determination has not been made that a PMA is required.
- The application contains a false statement of material fact.
- The financial certification or financial disclosure statement was not included.

If the FDA refuses to file a PMA, the applicant can use the following process for reconsideration:

- Submit request for informal conference with the Office of Health Technology (OHT) Director within 10 days of receiving refusal notice.
- The OHT Director will hold an informal conference within 10 days of receiving the request.
- The OHT Director will make a decision within 5 days after the conference.
- If the OHT Director upholds the decision not to file, a request for reconsideration can be filed within 30 days to the Director of the Office of Product and Evaluation Quality (OPEQ).
- The OPEQ Director will provide a written decision within 60 days of the request for reconsideration. This is considered the final administrative action regarding the review.
- The applicant also has the option of requesting a meeting to review the decision not to file the application instead of the informal conference. The FDA will grant either a request for an informal conference or for a review meeting, not both.

For more information, see the PMA Acceptance and Filing Review Policy.

Substantive review

An in-depth review of the PMA begins after it is accepted for filing, and must be completed within 180 days from the date of filing. An amendment to the PMA containing significant data which may impact the decision can extend the review period up to 180 days.

During the review period, the FDA will notify the applicant of any additional information needed to complete the review through major and minor deficiency letters. In addition, the applicant has the opportunity to request a meeting with the FDA within 100 days of the filing of the PMA to review the status of the application. This request can be submitted with the PMA or as an amendment to the PMA, and must be submitted within 70 days of the original submission.

Guidance on PMA Interactive Procedures for Day-100 Meetings and Subsequent Deficiencies – for Use by CDRH and Industry; Final

Panel review

First-of-a-kind and some newer types of devices are likely to be referred to an FDA advisory committee for review. The advisory committee is required to hold the FDA will communicate with the committee and with the applicant to address any questions or requests for additional information that arise. During the review process, the advisory committee is required to hold a public meeting to review the PMA.

Once the FDA determines they have enough information to evaluate the safety and effectiveness of a particular device type, they will not continue to refer that type of device for additional review by an advisory committee.

For additional information, see Procedures for Meetings of the Medical Devices Advisory Committee – Guidance for Industry and Food and Drug Administration Staff.

Final review and decision

The FDA will render one of the following decisions on a PMA within 180 days of the application:

Approval Order

The FDA approves the application on the condition that final printed labeling be submitted to the FDA prior to marketing. The FDA will publicly announce the decision and the summary of safety and effectiveness data (SSED) via the PMA Approvals lists on their website.

Approvable Letter

The FDA issues an approvable letter when they determine the application substantially meets the requirements of the FD&C Act, but the FDA believes that it can approve the application only if specific additional information is submitted or specific conditions are agreed to by the applicant (conditional approval). An applicant has three choices upon receipt of an approvable letter:

- Amend the PMA as requested.
- Consider the approvable letter a denial, and request an administrative review.
- Withdraw the PMA.

Non Approvable Letter

The FDA issues a non approvable letter when they determine that the application cannot be approved for one or more reasons cited in 814.45(a) or if there is insufficient information to make a determination. The letter will describe the deficiencies and, when practical, what steps are necessary to make the PMA approvable. In response to a non approvable letter, the applicant has the same options as an approvable letter. However any amendment in response to a non approvable letter is considered a major amendment.

Denial of Approval

The FDA will deny approval of a PMA for any of the following reasons:

- Conditions set forth in 515(d)(2)(A-E) of the FD&C act apply.
- The PMA contains a false statement of material fact.
- The device's proposed labeling does not comply with the requirements in Part 801, Labeling, or Part 809, In Vitro Diagnostic Products for Human Use.
- The applicant does not permit an authorized FDA employee to inspect applicable facilities and controls, or to verify all pertinent records.
- An essential nonclinical investigation or clinical investigation was not conducted in compliance with applicable regulations and standards.

The FDA can also withdraw approval of a PMA if post-approval orders have not been met, or it is determined that applicable requirements are not being met.

PMA timeline

Early collaboration meetings	FDA response within 30 days of meeting
PMA Submission	
PMA Filing	Within 45 days of PMA receipt by FDA
"Day 100"Meeting	Needs to be requested within 70 days of submission filing
FDA Action (approved / denied)	Within 180 days of PMA filing
If approvable or non-approvable letter is received	Response required by applicant within 180 days of finding

PMA costs

The Medical Device User Fee Amendment (MDUFA) for FY2022 defines fees associated with FDA submissions.

All organizations must first pay the **Annual Establishment Registration Fee of $5,672**, for which there are no waivers or reductions. Additional fees for FY2022 (October, 2021 through September, 2022) are listed below.

Application Type	Standard Fee	Small Business Fee*
510(k)	$12,745	$3,186
513(g)	$5,061	$2,530
PMA,PDP,PMR,BLA	$374,858	$93,714
De Novo Classification Request	$112,457	$28,114
Panel-track Supplement	$281,143	$70,286
180-Day Supplement	$56,229	$14,057
Real-Time Supplement	$26,240	$6,560
BLA Efficacy Supplement	$374,858	$93,714
30-Day Notice	$5,998	$2,999
Annual Fee for Periodic Reporting on a Class III device (PMAs,PDPs, and PMRs)	$13,120	$3,280

** For businesses certified by the CDRH as a small business*

Appendices

Appendix A: Cover Letter Example

(from FDA's PMA documentation)

Original PMA Cover Letter

[Date]

Document Control Center - WO66-G609

Center for Devices and Radiological Health

Food and Drug Administration

10903 New Hampshire Avenue

Silver Spring, MD 20993-0002

SUBJECT: Original PMA for [device trade name and model number if applicable]

To Whom It May Concern:

[Applicant's name] is submitting this original premarket approval application for the [device trade name], [device generic name] intended for use in [indication for use].

Clinical studies of the above device were initiated on [date] and [were/were not] conducted under an approved investigational device exemption [give IDE number if a significant risk device]. [If applicable, include the FDA reference number for any premarket notification, reclassification petition, or color additive petition submitted for this device].

[Include a paragraph providing the name and address of each facility involved in the manufacture of the device and indicate whether the facility is prepared for an FDA inspection. If not prepared, provide an expected date when the facility will be ready for inspection. If a waiver of the QS information is requested, provide an anticipated date that the information will be provided.]

If another document is incorporated by reference, e.g., a master file, please include the original letter of authorization as an attachment to this cover letter.

The existence of this PMA and the data and other information that it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905, 21 USC 331(j), 5 USC 552, and other applicable laws is hereby claimed. [Tip: confidentiality claims cannot be made unless the applicant has complied with the applicable requirements.

If there are questions regarding this submission, [name] may be contacted at [give telephone number including area code].

Sincerely yours,

[signature]

[Name and title of applicant's representative]

Amendment to Original PMA

SUBJECT: Amendment to [original PMA or PMA supplement reference number] for [device trade name]

Unsolicited submission of additional information

[Applicant's name] is submitting this amendment to its [premarket approval application] [original PMA reference number] for the [device trade name] to provide [identify the additional information being provided].

Appendix B: Financial Certification and Disclosure Forms

Certification: Financial Interests and Arrangements of Clinical Investigators (Form FDA 3454)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2022

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
FIRM/ORGANIZATION	
SIGNATURE	DATE *(mm/dd/yyyy)*

This section applies only to the requirements of the Paperwork Reduction Act of 1995.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Do NOT send your completed form to the PRA Staff email address below.

Department of Health and Human Services
Food and Drug Administration
Office of Operations
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

FORM FDA 3454 (4/21)

PSC Publishing Services (301) 443-6740 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2022

TO BE COMPLETED BY APPLICANT

The following information concerning _____ , who participated
Name of clinical investigator

as a clinical investigator in the submitted study _____
Name of

_____ is submitted in accordance with 21 CFR part 54. The
clinical study

named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable check boxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
FIRM/ORGANIZATION	
SIGNATURE	Date *(mm/dd/yyyy)*

This section applies only to the requirements of the Paperwork Reduction Act of 1995.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 5 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Do NOT send your completed form to the PRA Staff email address below.

Department of Health and Human Services
Food and Drug Administration
Office of Operations
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

FORM FDA 3455 (4/21)

PSC Publishing Services (301) 443-6740 EF

Appendix C: Checklist for Acceptance and Filing of PMAs

* from Acceptance and Filing Reviews for Premarket Approval Applications

Contains Nonbinding Recommendations

Appendix A. Checklists for Acceptance and Filing of PMAs

Checklist for Acceptance Review for PMAs

(should be completed within 15 days of DCC receipt)

PMA Number: _____ **Date Received:** _____
Device: _____ **Procode:** _____
Company Name/ Address: _____
Contact Name/Phone Numbers: _____
Lead Reviewer Name: _____

Preliminary Questions		
Answers in the shaded blocks indicate consultation with an identified Center advisor is needed. (Boxes checked in this section represent FDAs preliminary assessment of these questions at the time of administrative review.)	**Yes**	**No**
1. Is the product a device (per 201(h) of the FD&C Act) or a combination product with a device constituent part subject to review under PMA? If it appears not to be a device or such a combination product, or you are unsure, consult with the CDRH Product Jurisdiction Officer or CBER Product Jurisdiction Officer to determine the appropriate action and inform your division management. *Provide summary of Product Jurisdiction Officer's determination.* If the product does not appear to be a device or such a combination product, mark "No."		
2. If the product is a device or a combination product with a device constituent part, is it subject to review by the Center in which the application was received? If you believe the application is not with the appropriate Center or you are unsure, consult with the CDRH Product Jurisdiction Officer or CBER Product Jurisdiction Officer to determine the appropriate action and inform your division management. *Provide a summary of the Product Jurisdiction Officer's determination.* If application should not be reviewed by your Center, mark "No."		
3. If a Request for Designation (RFD) was submitted for the device or combination product with a device constituent part and assigned to your center, identify the RFD # and confirm the following: • Is the device or combination product the same (e.g., design, formulation) as that presented in the RFD submission? • Are the indications for use for the device or combination product identified in the PMA the same as those identified in the RFD submission? If you believe the product or the indications presented in the PMA have changed from the RFD, or you are unsure, consult with the CDRH Product Jurisdiction Officer or appropriate CBER Product Jurisdiction Officer to determine the appropriate action and inform your division management. *Provide summary of Product Jurisdiction Officer's determination.* If the answer to either question above is no, mark "No."		
Is the application for a combination product that contains as a constituent part a drug that has the same active moiety as an approved drug with exclusivity as described in 21 USC 503(g)(5)(C)(ii)-(v) (section 503(g)(5)(C)(ii)-(v) of the FD&C Act)?If "Yes," then contact the CDRH Product Jurisdiction Officer or CBER Product Jurisdiction Officer, provide a summary of the discussion with them, and indicate their recommendation/action.		
4. Is class III/PMA review required for the device? NOTE: If you believe an application is for a new type of device for which we have never received a marketing application and is thus class III/PMA, you should (1) document why the device would be found NSE and (2) obtain concurrence from the CDRH/OPEQ/ORP/Division 1 or appropriate CBER staff prior to the accepting the original PMA. *Attach a copy of the 510(k) Staff's concurrence.*		
5. Is there a pending 510(k) for the same device with the same indications for use? The regulations allow FDA to refuse to file a PMA if a 510(k) for the same device is pending (21 CFR 814.42(e)(3)).		
6. Is the applicant the subject of an Application Integrity Policy (AIP)? If "Yes", consult with the CDRH Office of Product Evaluation and Quality/Office of Clinical Evidence and Analysis/Division of Clinical Science and Quality (OPEQ/OCEA/DCEA1) or CBER Office of Compliance and Biologics Quality/Division of Inspections and Surveillance/Bioresearch Monitoring Branch (OCBQ/DIS/BMB) to determine the appropriate action. Check on web at https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/application-integrity-policy/application-integrity-policy-		

If the answer to 1 or 2 appears to be "No," then stop review of the PMA and contact the CDRH Product Jurisdiction Officer or CBER Product Jurisdiction Officer.
If the answer to 3 appears to be "No," then stop the review and contact the CDRH Product Jurisdiction Officer or CBER Product Jurisdiction Officer.
If the answer to 4 is "Yes," then contact the CDRH Product Jurisdiction Officer or CBER Product Jurisdiction Officer, provide a summary of the discussion with them, and indicate their recommendation/action.
If the answer to 5 is "No", the PMA lead reviewer should consult division management and other Center resources to determine the appropriate action.
If the answer to 6 is "Yes," then stop review of the PMA, contact the CDRH/OPEQ/ORP/Division 1, or appropriate CBER staff.
If the answer to 7 is "Yes," then contact CDRH Office of Product Evaluation and Quality/Office of Clinical Evidence and Analysis/Division of Clinical Science and Quality (OPEQ/OCEA/DCEA1) or CBER/OCBQ/DIS/BMB, provide a summary of the discussion with the BIMO Staff, and indicate BIMO's recommendation/action.

Appendix D: Inventory of Organizational and Administrative Elements

* from Acceptance and Filing Reviews for Premarket Approval Applications

Contains Nonbinding Recommendations

Inventory of Organizational and Administrative Elements (21 CFR 814.20 unless otherwise indicated)								
Check "Yes" if item is present, "N/A" if it is not needed and "Not Present" if it is not included but needed.								
	• Any "Not Present" answer will result in a "Refuse to Accept" decision. • Each element on the checklist should be addressed within the application. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present ("Yes"). An assessment of the rationale will be considered during the review of the application.						**Present**		**Not Present (No)**
							Yes	**N/A**	
A.	PMA Content								
	1.	Are all required sections in English or accompanied with an English translation?					☐		☐
	2.	Is there a table of contents?					☐		☐
	3.	Is a bibliography provided?					☐	☐	☐
		a.	Have copies of key articles been provided and are English translations included, if appropriate? Check "N/A" if applicant includes a statement that upon searching they found no literature related to their device				☐	☐	☐
	4.	If a device sample has been requested by FDA, has it been provided or if impractical to submit, has the applicant offered alternatives to allow FDA staff to view or access the device?					☐	☐	☐
	5.	Is there a summary of the contents of the PMA?					☐		☐
	6.	Device Characteristics							
		a.	Is a description of device included?				☐		☐
			i.	Pictorial representations?			☐		☐
			ii.	Materials specifications?			☐		☐
				•	If there is a color additive present: • has the color additive been identified by common name and chemical name, and • has the amount of each color additive in the formulation by weight percent of the colored component and total amount (e.g., µg, ppm) in the device been provided?		☐	☐	☐

Inventory of Organizational and Administrative Elements (21 CFR 814.20 unless otherwise indicated)						
Check "Yes" if item is present, "N/A" if it is not needed and "Not Present" if it is not included but needed.						
	• Any "Not Present" answer will result in a "Refuse to Accept" decision. • Each element on the checklist should be addressed within the application. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present ("Yes"). An assessment of the rationale will be considered during the review of the application.			**Present**		**Not Present (No)**
				Yes	**N/A**	
		b.	Is a description of the principles of operation of the device (including components) and properties relevant to clinical function present?	☐		☐
	7.	Is the Device Manufacturing Section included? (see the guidance entitled "Quality System Information for Certain Premarket Application Reviews," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quality-system-information-certain-premarket-application-reviews. For original PMA or a panel-track supplement with a new manufacturing site or substantially different manufacturing procedures.		☐	☐	☐
		a.	Has a description of the methods, facilities, and controls used in the manufacture, processing, packing, storage, and installation of the device been provided?	☐		☐
	8.	Are summaries of the nonclinical laboratory studies and full test reports* provided? Note: the applicant can reference data located in other submissions. Check "Yes" if nonclinical data is not provided in the current submission, but found in another submission. State where the data were provided (e.g., modular submission, licensing PMA). *Full test report includes objective of the test, description of test methods and procedures, study endpoint(s), pre-defined pass/fail criteria, results summary, discussion of conclusions)		☐	☐	☐
		a.	Sterilization	☐	☐	☐
		b.	Biological/Microbiological	☐	☐	☐
		c.	Immunological	☐	☐	☐
		d.	Toxicological/Biocompatibility	☐	☐	☐
		e.	Engineering (stress, wear, etc.)	☐	☐	☐
		f.	Chemistry/Analytical (typically for IVDs)	☐	☐	☐

Inventory of Organizational and Administrative Elements (21 CFR 814.20 unless otherwise indicated)							
Check "Yes" if item is present, "N/A" if it is not needed and "Not Present" if it is not included but needed.							
	• Any "Not Present" answer will result in a "Refuse to Accept" decision. • Each element on the checklist should be addressed within the application. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present ("Yes"). An assessment of the rationale will be considered during the review of the application.				**Present**		**Not Present (No)**
					Yes	**N/A**	
		g.	Shelf Life		☐	☐	☐
		h.	Animal Studies		☐	☐	☐
		i.	Other Essential Laboratory Testing		☐	☐	☐
	9.	Is a summary of the clinical investigation(s) and results provided?			☐		☐
		a.	Are the final versions of the clinical protocols included? (If performed under IDE, these should be the final FDA-approved versions of the clinical protocols, incorporating any Notices of Changes.)		☐		☐
		b.	Is a description of study population demographics provided?		☐		☐
		c.	Is a description of adverse events (e.g., adverse reactions, complaints, discontinuations, failures, replacements) given?		☐		☐
		d.	Have report forms for patients who died or who did not complete the investigation been provided (i.e., to resolve potential bias)? Check "N/A" only if no patients died or were discontinued.		☐	☐	☐
	10.	Are statistical analyses of the clinical investigations provided?			☐		☐
		a.	Are the results of all analyses identified in the protocol provided?		☐		☐
	11.	Has appropriate draft labeling been submitted?					
		a.	Physician Labeling		☐		☐
			i.	Are indications for use included?	☐		☐
			ii.	Are contraindications, warnings, and precautions included?	☐		☐
			iii.	Are instructions for use included?	☐		☐
		b.	Patient Labeling Check "N/A" only if CDRH has indicated that patient labeling is not necessary.		☐	☐	☐

Inventory of Organizational and Administrative Elements (21 CFR 814.20 unless otherwise indicated)							
Check "Yes" if item is present, "N/A" if it is not needed and "Not Present" if it is not included but needed.							
	• Any "Not Present" answer will result in a "Refuse to Accept" decision. • Each element on the checklist should be addressed within the application. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present ("Yes"). An assessment of the rationale will be considered during the review of the application.				**Present**		**Not Present (No)**
					Yes	**N/A**	
		c.	Technical/Operators Manual		☐	☐	☐
	12.	Statements/Certifications/Declarations of Conformity					
		a.	Does the application utilize voluntary consensus standard(s) (See section 514(c) of the FD&C Act). *This includes both FDA-recognized and non-recognized consensus standards. Select "N/A" if the submission does not utilize voluntary consensus standards.*		☐	☐	
			i.	If the application cites FDA-recognized voluntary consensus standard(s), does the application include: a Declaration of Conformity (DOC) as outlined in FDA's guidance "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/appropriate-use-voluntary-consensus-standards-premarket-submissions-medical-devices**OR** if citing general use of a standard, the basis of such use is included along with the underlying information or data that supports how the standard was used?	☐	☐	☐
			ii.	If the application cites non-FDA-recognized voluntary consensus standard(s), does the application include the basis of use along with the underlying information or data that supports how the standard was used?	☐	☐	☐
		b.	Has the applicant provided documentation to establish that it has followed the recommendations in applicable FDA guidance/ guidelines or otherwise met applicable statutory or regulatory criteria? Check "N/A" only if no guidance/guidelines are used.		☐	☐	☐

Inventory of Organizational and Administrative Elements (21 CFR 814.20 unless otherwise indicated)							
Check "Yes" if item is present, "N/A" if it is not needed and "Not Present" if it is not included but needed.							
	• Any "Not Present" answer will result in a "Refuse to Accept" decision. • Each element on the checklist should be addressed within the application. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present ("Yes"). An assessment of the rationale will be considered during the review of the application.				**Present**		**Not Present (No)**
					Yes	**N/A**	
		c.		Investigator Financial Disclosure For additional information refer to the guidance document "Financial Disclosure by Clinical Investigators," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/financial-disclosure-clinical-investigators. As required by 21 CFR Part 54, has the applicant submitted either: 1. A signed and dated Certification Form (3454) or 2. A signed and dated Disclosure Form (3455) Note: the signature should be from a responsible corporate official or representative of the applicant.	☐ ☐	☐ ☐	☐ ☐
			i.	For a Certification Form (3454): Is the required list of all investigators and subinvestigators attached to the Form?	☐	☐	☐
			ii.	If box 3 is checked, does the Form include an attachment with the reason(s) why financial disclosure information could not be obtained?	☐	☐	☐
			iii.	For a Disclosure Form (3455): Does the application provide details of the financial arrangements and interests of the investigator(s) or subinvestigator(s), along with a description of any steps taken to minimize potential bias?	☐	☐	☐
		d.		Environmental Assessment under 21 CFR 25.20(n) ((d)(i) or (ii)	☐		☐
			i.	If claiming a categorical exclusion, information to justify the exclusion, OR	☐	☐	☐
			ii.	An environmental assessment (ONLY required for devices that present new environmental concerns)	☐	☐	☐

Inventory of Organizational and Administrative Elements (21 CFR 814.20 unless otherwise indicated)							
Check "Yes" if item is present, "N/A" if it is not needed and "Not Present" if it is not included but needed.							
	• Any "Not Present" answer will result in a "Refuse to Accept" decision. • Each element on the checklist should be addressed within the application. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present ("Yes"). An assessment of the rationale will be considered during the review of the application.				**Present**		**Not Present (No)**
					Yes	**N/A**	
		e.	Did the application include a completed FORM FDA 3674, *Certification with Requirements of ClinicalTrials.gov Data Bank*? (42 U.S.C. 282(j)(5)(B)) Note: Enter the NCT number(s) in CTS or other regulatory tracking database		☐		☐
			Data from FORM FDA 3674 (mark "Yes" for the applicable one):				
			i.	No clinical trials referenced in submission.	☐	☐	
			ii.	Requirements are not applicable to referenced clinical trials.	☐	☐	
			iii.	Requirements are applicable and have been met.	☐	☐	
		f.	Statements of Compliance for Clinical Investigations Select "N/A" if the application does not contain any clinical data from investigations (as defined in 21 CFR 812.3(h)) to demonstrate reasonable assurance of safety and effectiveness. For multicenter clinical investigations involving both United States (US) and outside the United States (OUS) sites, part (i) should be addressed for the US sites and part (ii) should be addressed for the OUS sites. 21 CFR 812.28 applies to all OUS clinical investigations that enroll the first subject on or after February 21, 2019. Please refer to the guidance document entitled "*Acceptance of Clinical Data to Support Medical Device Applications and Submissions - Frequently Asked Questions*," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-clinical-data-support-medical-device-applications-and-submissions-frequently-asked, for more information.		☐	☐	

Inventory of Organizational and Administrative Elements (21 CFR 814.20 unless otherwise indicated)							
Check "Yes" if item is present, "N/A" if it is not needed and "Not Present" if it is not included but needed.							
	• Any "Not Present" answer will result in a "Refuse to Accept" decision. • Each element on the checklist should be addressed within the application. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present ("Yes"). An assessment of the rationale will be considered during the review of the application.				**Present**		**Not Present (No)**
					Yes	**N/A**	
			i.	For all clinical investigations conducted in the US, the application includes one of the following for each investigation (*check all that apply*): ☐ A statement of compliance with 21 CFR parts 50, 56, and 812. ☐ A brief statement of the reason for noncompliance with 21 CFR parts 50, 56, and 812. *Select "N/A" if the clinical investigations were conducted solely OUS.*		☐	☐
			ii.	For all clinical investigations conducted OUS, the application includes one of the following for each investigation (*check all that apply*): ☐ A statement that the clinical investigations were conducted in accordance with good clinical practice (GCP) as described in 21 CFR 812.28(a)(1). ☐ A brief statement of the reason for not conducting the investigation in accordance with GCP and a description of steps taken to ensure that the data and results are credible and accurate and that the rights, safety, and well-being of subjects have been adequately protected. ☐ A waiver request in accordance with 21 CFR 812.28(c). *Select "N/A" if the clinical investigations were conducted solely inside the US.*		☐	☐
	13.	Pediatric Use - Per 515A(a)(2) of the FD&C Act, did the application include:					
		a.	A description of any pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose, or cure, or statement that no pediatric subpopulation exists for the disease or condition for which the device is intended. This statement does not mean the device is indicated for treating pediatric patients.		☐		☐

Inventory of Organizational and Administrative Elements (21 CFR 814.20 unless otherwise indicated)							
Check "Yes" if item is present, "N/A" if it is not needed and "Not Present" if it is not included but needed.							
	• Any "Not Present" answer will result in a "Refuse to Accept" decision. • Each element on the checklist should be addressed within the application. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present ("Yes"). An assessment of the rationale will be considered during the review of the application.				**Present**		**Not Present (No)**
					Yes	**N/A**	
		b.	The number of affected pediatric patients.		☐		☐
	14.	Combination Product Provisions – Per 503(g) of the FD&C Act. Select "N/A" if the product is not a combination product. 21 CFR 3.2(e). The remaining criteria in this section will be omitted from the checklist if "N/A" is selected. If you are unsure if the product is a combination product, consult with the CDRH Product Jurisdiction Officer or CBER Product Jurisdiction Officer.				☐	
		a.	Application identifies the product as a combination product.		☐		☐
		b.	The combination product contains as a constituent part an approved drug as defined in section 503(g)(5)(B) of the FD&C Act. Select "N/A" if the combination product does not contain as a constituent part an approved drug. Please also select "N/A" if a right of reference or use for the drug constituent part(s) is included with the application. If "N/A" is selected, part a below is omitted from the checklist.		☐	☐	
			i.	The application includes appropriate patent statement or certification and a statement that the applicant will give notice, as applicable. See 503(g)(5)(A)&(C).	☐		☐
B.	Issues Identified by FDA Prior to PMA Application - history of the applicant with this device						
	1.	Does the applicant list prior submissions or state that there were no prior submissions? (may be located in CDRH Coversheet Form 3514, Section F) If the applicant lists prior submissions, address the applicable questions below:			☐		☐
		a.	510(k) #_____		☐	☐	

Inventory of Organizational and Administrative Elements (21 CFR 814.20 unless otherwise indicated)							
Check "Yes" if item is present, "N/A" if it is not needed and "Not Present" if it is not included but needed.							
	• Any "Not Present" answer will result in a "Refuse to Accept" decision. • Each element on the checklist should be addressed within the application. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present ("Yes"). An assessment of the rationale will be considered during the review of the application.				**Present**		**Not Present (No)**
					Yes	**N/A**	
			i.	If this device has been the subject of an NSE decision, does the PMA address any issues relating to safety or effectiveness?	☐	☐	☐
		b.	IDE #_____		☐	☐	
			i.	Have the data presented in the PMA taken into account any safety or effectiveness concerns (e.g., "future considerations") previously communicated through IDE correspondence?	☐	☐	☐
		c.	PMA #_____		☐	☐	
			i.	If a previously submitted PMA for this device been withdrawn, does the current PMA address any issues related to safety or effectiveness raised during review of the prior PMA?	☐	☐	☐
		d.	Modular PMA #_____		☐	☐	
			i.	If "Yes", how many modules submitted? _____ How many modules were closed? _____			
			ii.	If there are modules that are on hold, does the PMA address outstanding deficiencies?	☐	☐	☐
	2.	Does the applicant list Q-Submission(s) regarding the device or this application in which FDA feedback regarding data or information related to safety and/or effectiveness in the PMA was provided by email or during a meeting (in person or by phone), or state that there were no prior Q-Submission interactions with the FDA regarding this application? If the applicant lists Q-Submissions, address the applicable questions below:			☐		☐

Inventory of Organizational and Administrative Elements (21 CFR 814.20 unless otherwise indicated)						
Check "Yes" if item is present, "N/A" if it is not needed and "Not Present" if it is not included but needed.						
	• Any "Not Present" answer will result in a "Refuse to Accept" decision. • Each element on the checklist should be addressed within the application. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present ("Yes"). An assessment of the rationale will be considered during the review of the application.			**Present**		**Not Present (No)**
				Yes	**N/A**	
		a.	Q-Submission #_____ Meeting date(s), if applicable_____			
		b.	Copy of minutes from each meeting or other written feedback?	☐	☐	☐
		c.	Were all staff concerns or action items previously presented to the applicant in the Q-Submission minutes or feedback addressed in the PMA or has the applicant provided a detailed scientific or clinical justification for an alternative approach?	☐	☐	☐

Appendix E: Additional Resources and Links

FDA PMA Documentation

https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-approval-pma

Form 3514: Premarket Review Submission Cover Sheet

https://www.reginfo.gov/public/do/DownloadDocument?objectID=3006101

SSED Template: Summary of Safety and Effectiveness Data

https://www.fda.gov/media/113810/download

PMA Review Checklist

https://www.fda.gov/media/83408/download

Glossary

510(k) – Section 510(k) of the Food, Drug and Cosmetic Act requires device manufacturers who must register, to notify FDA of their intent to market a medical device at least 90 days in advance. This is known as Premarket Notification – also called PMN or 510(k).

Act – Federal Food, Drug, and Cosmetic Act (sections 201-902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 321-392).

Agency – U.S. Food and Drug Administration.

CFR – Code of Federal Regulations.

Class I Devices – Low-risk devices. Examples include bandages, handheld surgical instruments, and nonelectric wheelchairs.

Class II Devices – Devices that have a moderate to high risk to the patient and/or user. Most medical devices are considered Class II devices.

Class III Devices – Devices that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.

De Novo Process – an alternate pathway to classify novel medical devices that had automatically been placed in Class III after receiving a "not substantially equivalent" (NSE) determination in response to a premarket notification [510(k)] submission.

FDA – U.S. Food and Drug Administration.

Humanitarian Device Exemption (HDE) – a premarket approval application submitted under 21 CFR 814 Subpart H seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the FD&C Act as authorized by section 520(m)(2) of the Act.

Humanitarian Use Device (HUD) – a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.

IDE – an approved or considered approved Investigational Device Exemption under 21 CFR 812 and section 520(g) of the FD&C Act.

Indications of use – The circumstances or conditions in which the device would be used. For example, the device may be designed to diagnose, treat, prevent, cure, or mitigate. Indications of Use also includes a description of the target patient population.

Master file – a reference source that a person submits to FDA. A master file may contain detailed information on a specific manufacturing facility, process, methodology, or component used in the manufacture, processing, or packaging of a medical device.

PMA – any premarket approval application for a class III medical device, including all information submitted with or incorporated by reference. "PMA" includes a new drug application for a device under section 520(l) of the FD&C Act.

PMA amendment – information an applicant submits to FDA to modify a pending PMA or a pending PMA supplement.

PMA supplement – a supplemental application to an approved PMA for approval of a change or modification in a Class III medical device, including all information submitted with or incorporated by reference.

Person – any individual, partnership, corporation, association, scientific or academic establishment, government agency or organizational unit, or any other legal entity.

Postamendment device – a device that is commercially distributed on or after May 28, 1976, the date the Medical Device Amendments of 1976 were signed into law.

Preamendment device – a device that was commercially distributed before May 28, 1976, the date of the Medical Device Amendments of 1976 were signed into law.

Predicate device – a device that is used to show substantial equivalence to a device in a 510(k) premarket submission. A predicate device must be legally marketed in the U.S. and not be subject to Premarket Approval (PMA.

QS – Quality System, 21 CFR 820.

Reasonable probability – that it is more likely than not that an event will occur.

Serious, adverse health consequences – any significant adverse experience, including those which may be either life-threatening or involve permanent or long term injuries, but excluding injuries that are nonlife-threatening and that are temporary and reasonably reversible.

Statement of material fact – a representation that tends to show that the safety or effectiveness of a device is more probable than it would be in the absence of such a representation. A false affirmation or silence or an omission that would lead a reasonable person to draw a particular conclusion as to the safety or effectiveness of a device also may be a false statement of material fact, even if the statement was not intended by the person making it to be misleading or to have any probative effect.

Substantial equivalence – Substantial equivalence is required for a 510(k) submission, and lack of substantial equivalence triggers either a PMA or De Novo submission. A device is substantially equivalent to a predicate (legally marketed) device if it has the same intended use and technological characteristics as the new device, in addition to demonstrating that the device is as safe and effective as the predicate device.

Trade Name – an established product name under which each device is marketed. The trade names are used in a product's labels and labeling as well as in other promotional materials. Proprietary name is a commercial name created by a naming authority for use in marketing a drug/device product in a particular jurisdiction.

About Rimsys

Rimsys is bringing regulatory order to the medtech industry. The Rimsys Regulatory Information Management (RIM) platform digitizes and automates regulatory activities, freeing teams from inefficient administrative work, and helping them confidently establish and secure global regulatory compliance. Unlike complex spreadsheets, or expensive consultants, Rimsys centralizes all regulatory information, automates submission processes, and monitors relevant expirations, standards, and global regulations. Overburdened regulatory affairs teams struggle to keep pace with the increasingly complex global landscape. Rimsys streamlines all regulatory activities in an integrated platform, helping MedTech companies get to market more quickly and reduce risk of non-compliance, product recalls, and unexpected expirations.

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