

# Guidance for Industry

## **Guidances for the Medical Device Industry on PMA Shell Development and Modular Review**

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**U.S. Department of Health and Human Services  
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Center for Devices and Radiological Health**

**Office of Device Evaluation**

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# Preface

## Public Comment

Until [date 90 days from release date], comments and suggestions regarding this document should be submitted to Docket No. [fill in number], Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 12420 Parklawn Drive (HFA-305), Room 1-23, Rockville, MD 20857. Such comments will be considered when determining whether to amend the current guidance.

After [date 90 days from release date], comments and suggestions may be submitted at any time for Agency consideration to: Office of Device Evaluation, HFZ-400, 9200 Corporate Boulevard, Rockville, MD 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Ms. Ashley Boulware at 301-594-2053 or Ms. Kathy Poneleit at 301-594-2186.

## Additional Copies

World Wide Web/CDRH/[specific web page] home page at [http://www.fda.gov/cdrh/\[specific address\]](http://www.fda.gov/cdrh/[specific address]) or CDRH Facts on Demand at 1-800-899-0381 or 301-827-0111, specify number [fill in number] when prompted for the document shelf number.

06/29/98

## **Premarket Approval Application Content Shell**

### **What It Is and What It Does**

#### The "PMA Shell"

A PMA can be viewed as a compilation of sections and "modules" that together become a complete application. The "PMA Shell" is an outline of those Sections that will be necessary to complete the PMA. It will include all modules needed to support filing and approval of a specific medical device. The term "module" will be used to identify a set of elements, tests, information, etc., addressing a selected aspect of the device subject to a PMA. A module may begin as the simple identification of the issue to be addressed and later developed into a detailed listing of the specific test results to be submitted as one report. What is needed for each module will be decided by agreement between FDA and the module submitter. Discussion and agreement on the shell are needed because modules will be accepted and reviewed individually as sections of a PMA and should therefore include information and analyses with same level of detail as would be included in the PMA. When the PMA is submitted it will consist of the collection of the modules already submitted along with any other information needed to complete the PMA. Ideally, the shell should be constructed during the early stages of the investigational process but it may be established at any time before submission of the PMA.

Once a shell is established and the modular review process has been agreed to, a completed module may be submitted for review in a PMA Modular Submission (see PMA Implementation Procedures for a Modular Approach to PMA Review). As the information required for each module is reviewed and found acceptable by FDA staff, the shell is filled with these completed modules. At any meeting preceding the actual submission of the PMA, the module submitter and FDA can survey the shell to determine which modules have not been submitted and accepted. If the module submitter makes any design or technical changes to the device after the modules have been submitted, the module submitter should identify those changes and their effect in communications with FDA and submit supplement(s) to any relevant module. These supplement(s) should be identified with a description of the design and/or technical change(s), its effect, and identify the module information which has been changed.

When the reviewing division has determined that a module is complete and acceptable, a meeting with the ODE director or designee, an appropriate member of the Program Operations Staff (POS), and appropriate division staff should be held prior to issuing a status letter. Once closed (that is declared acceptable), a module will usually only be reopened for further review when the division director and ODE Director conclude there is strong rationale to do so.

## Modules

Modules will contain various types of information ranging from pictorial representations of the device to clinical study data. The content and format for each element of a module will be specific to the information being conveyed. For example, the device description section and module may include engineering drawings and a description of each functional component or ingredient of the device. Module elements covering device testing (e.g., bench or clinical) may include: a description of the device or component tested and how it compares to the final device design proposed for marketing; the rationale or purpose of the testing; protocols describing the conduct of the test; test reports containing raw data (if required), a summary of the results (e.g., tabular format), and analyses of the results; and conclusions drawn from the testing.

Since modules may be submitted at various times throughout the development and review process, it is essential that each module also contain an easily identifiable “executive” summary describing the content of the submission and conclusions drawn from the data. These summaries will serve the dual purposes of providing an overview summary of the submitted module and, when assembled at the time of the PMA submission, will form the draft Summary of Safety and Effectiveness Data (SSED) for the device. The module submitter should keep in mind that the information provided in the modules should follow the content requirements listed in 21 CFR 814.20, as applicable.

Deficiencies identified during review of a module will be communicated to the module submitter. FDA may work interactively with the modular submitter to resolve some deficiencies. Written correspondence regarding the status of the module will be in the form of a deficiency or acceptance letter. This letter will generally issue within 90 days of receipt of the module or a response to a module deficiency letter. When the review team finds that the issues in a module are resolved, a memo regarding the acceptance of the module will be added to the file and a status letter to the module submitter will be issued declaring the module to be closed. These review memos can be compiled at a later date to serve as the complete review documentation and memorandum for the PMA. A running list of open and closed modules will be maintained.

The elements of a PMA are grouped under the following 12 section headings. Each section may consist of one or more modules. The content of each module is dependent upon the specific device and will be determined by discussions between the FDA review team and the module submitter.

04/17/98

## Premarket Approval Application Content Shell

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### **I. General Information**

Device Generic Name:

Device Trade Name:

Module submitter's Name and Address:

Right of Reference to Other Files (e.g. Master Files):

Correspondents to the file:

Manufacturing sites name and address:

### **II. Table of Contents (to be updated with each submission in designated format)**

For multi-volume submissions, provide a complete table of contents for the submission, with volume reference, at the beginning of each volume. The entire submission should have sequentially numbered pages.

### **III. Summary of Safety and Effectiveness Data**

See Summary of Safety and Effectiveness Data template.  
(include electronic ODE compatible copy on disk)

#### **IV. Device Description**

The device, including graphic pictorial engineering drawing representations.  
Each of the functional components or ingredients and their purpose.  
The properties of the device relevant to the indication for use.  
The principle of operation of the device.  
Draft labeling (e.g. indication, contraindications, warnings, precautions) and draft operators manual, if applicable.

#### **V. The Manufacturing Information**

This section should be in accordance with the Quality Systems Regulation [see 21 CFR Part 820 for information to complete this section.]

#### **VI. Certification of conformance, reference to, and status of compliance with any performance standards**

#### **VII. Non-clinical Laboratory Studies**

##### Product Testing

- Bench Testing
- Chemistry
- Electrical Safety
- Battery testing
- Electromagnetic compatibility
- Engineering
- Firmware
- Hazard analysis
- MRI compatibility
- Predicted reliability and durability
- Software
- Stress
- Wear

##### Biological Testing

- Biocompatibility
- Immunology
- Microbiology
- Toxicology

##### Useful Life

- Reuse
- Shelf Life
- Sterilization

Analytical (for IVDs).

Animal Testing of the finished device.

Other laboratory or animal testing as appropriate.

A statement indicating if each study was conducted in compliance with Part 58 (Good Laboratory Practices) or a statement of the reasons for the non-compliance Environmental assessment or claim of categorical exclusion.

## **VIII. Clinical Studies**

A description of the intended use (if the measured end point is not a clinically significant result or event to the non-medical public, a statement of why it should be regarded as evidence of effectiveness).

Justification for a single investigator, if applicable.

Description and copy of the clinical protocols (reference IDE/IDE Supplement where these have been submitted to the Agency and approved).

Number of investigators and number of subjects for each

Subject inclusion/exclusion criteria

Description of study population and study period

Study endpoints

Safety and effectiveness data

Description of the study protocol used.

Indicate if any subjects were not part of an IDE (e.g. foreign or non-significant risk study).

Explanation of applicability of foreign clinical data to the US population.

Subject demographics including a single table listing all subjects and important subject information, as requested by the review division.

A subject accountability tree is suggested , as requested by the review division.

Tabulate and describe the adverse events.

Statistical analysis (suggest it be provided on disk, e.g. Excel, SAS) of safety.

Statistical analysis (suggest it be provided on disk, e.g. Excel, SAS) of benefit/effectiveness/treatment success.

Conclusions drawn from the study.

## **IX. Bibliography/References**

## **X. Device Labeling (see labeling guidance document)**

Indications

Contraindications

Warnings  
Precautions  
Adverse events  
Device description  
Usage instructions  
Troubleshooting  
Patient information  
References

**XI. Operations and Instruction Manual**

**XII. Post-marketing Plan Commitments for Studies, if applicable**

## **Standard Operating Procedures for Modular PMA Review**

### Modular Review

A premarket approval application (PMA) can be viewed as a compilation of sections or “modules” that together are intended to be a complete application as defined in 21 CFR 814. The “PMA Shell” is an outline of those sections that will be necessary to support filing and approval of a specific PMA. The term “module” will be used to identify a set of elements, tests, information, etc. addressing a selected topic needed to support the content requirements of a PMA. Submission of modules for review is intended to allow the potential PMA applicant to bring closure to one or more modules prior to submission of the completed PMA. When appropriate, modular review may also be used for certain PMA supplements where significant clinical data will be developed, e.g., panel-track supplement or for a Humanitarian Device Exemption (HDE).

FDA envisions at least four different scenarios for the application of modular review. In the first, a potential PMA applicant may submit a number of nonclinical modules and submit the remainder of the required information in the PMA. In a second scenario, an applicant may submit all of the nonclinical information in modules, submitting only the clinical information and final draft labeling in the PMA. A third option is to submit only the manufacturing information in a module. The remainder of the nonclinical and clinical information is submitted in the PMA. Finally, in a fourth scenario, an applicant may submit all of the nonclinical and clinical testing in modules, and submit the PMA when the manufacturing information will be complete within 90 days and when the manufacturing site is prepared to manufacture the device and undergo inspection. There may be additional scenarios, depending on the applicant and the specific device. This process is intended to be flexible, allowing applicants to submit information as the product is developed.

Procedures for the proposal and submission of a PMA Shell and modules to FDA are described below.

### Points to Consider for the Module Submitter:

1. FDA and a potential PMA applicant will generally develop a complete PMA shell during an early collaboration or comparable meeting(s) at the beginning of the device development (e.g., prior to or during the IDE process). In cases where an IDE will not be submitted, such as during in vitro diagnostic device development, it is suggested that the shell be developed prior to initiation of the clinical studies or other studies intended to demonstrate safety and effectiveness. For devices that are beyond the initial stages of the development process, a shell may be established at any time before submission of the PMA. However, the earlier FDA and the applicant agree on the types of data necessary

for each module to support safety and effectiveness of the product, the more efficient the development and review processes will be. Additionally, the benefit of modular review is its staged approach; the submission of modules over time and more closely in time to the development of the data will result in the most efficient review. The shell should consider all of the information that would be necessary to be included in the PMA when developing the content of each module, similar to a PDP proposal; however, unlike a detailed PDP submission, the shell does not necessarily include detailed protocols or success criteria for each component module.

2. The potential PMA applicant should develop the shell for their product, including identification of the proposed modules, and submit it to CDRH for review. Applicants should contact division staff for submission instructions. Within 30 days of receipt, FDA will complete its review of the proposed shell/modules and provide comments either in writing or in a meeting with the applicant (by telephone, video, or face-to-face). If the shell is discussed during a meeting, the division representative responsible for taking meeting minutes will summarize the agreements/deficiencies at the end of the meeting. After the meeting, FDA will send written confirmation of any agreements or deficiencies within 30 days. This communication may be a cover letter with the meeting minutes attached. FDA and the applicant should work to reach an agreement on what information will be considered as complete for stand-alone modules. The sum of these modules will constitute the shell for that particular product.
3. When agreement has been reached on the shell and modules, the shell should be formally submitted to the Document Mail Center (DMC) at the address below:

Document Mail Center (HFZ-401)  
Office of Device Evaluation  
Center for Devices and Radiological Health  
9200 Corporate Boulevard  
Rockville, MD 20850

Upon receipt, the submission will be assigned a shell number such as “MXX0001,” where “M” identifies that the product is undergoing modular review; “XX” identifies the year of the initial submission; and “0001,” with the year, indicates the number assigned to the product. The title and content of each module should be entered and a number assigned such as “/M001, /M002, etc.” (if not previously numbered by the applicant). Modules will keep the assigned module numbers, even if they are not submitted in numerical order. An acknowledgment letter will be issued that states that the PMA Shell and modules have been agreed upon and provides the shell and module numbers assigned for that product.

Applicants may submit a written request to make a change in the shell at any time, subject to the concurrence of the division staff. Typical changes may include adding a module, splitting one module into two modules, combining two modules or even postponing the submission of a module until the submission of the PMA. In the event that

a module is postponed, the module will be closed out. Should the applicant later decide to submit the postponed module, a new module number will be assigned. An acknowledgment letter reflecting the updated shell will be sent to the applicant.

4. When a potential PMA applicant has completed all of the testing and analyses to be included in an agreed-upon module, the pertinent data and analyses for that module should be submitted. The cover letter should identify the submission as a module and reference the previously assigned shell number and module number. If the pertinent information was previously submitted in an IDE, the module may incorporate by reference a specific IDE and/or IDE supplements (by volume and page number). An executive summary of the testing and analyses to be incorporated in the corresponding section of the Summary of Safety and Effectiveness Data (SSED) should be included as a cover to the submission. The submission should include 3 copies (or more, if requested by the division) of the module and be addressed to the DMC at the address above.
5. A PMA/Shell project manager will usually have been or should be identified by the division. The project manager will be responsible for coordinating review of the proposal for a shell and, upon receipt of a module, consulting reviews, interactive review meetings, and acceptance/deficiency letters. Reviews for Good Manufacturing Practices (GMP) and Bioresearch Monitoring will be coordinated by the PMA Staff.
6. Generally, within 30 days of receipt of a module by the project and/or consulting reviewer, a brief review will be conducted to determine if the module contains the elements agreed upon in the shell. If the contents of the module are not consistent with the shell, the module will be considered incomplete. A letter will issue to the module submitter stating that the module is considered incomplete and review will not proceed. Upon the submission of an amendment that provides the balance of the missing information, the 90-day review period will begin.

The full benefits of modular review to both FDA and the module submitter cannot be realized if module submissions are routinely incomplete. In these cases, FDA may reevaluate its ability to receive and review data for the submitter's device in a modular fashion.

7. Each module should be considered as a section of a PMA and include information and analyses with same level of detail as would be included in the PMA. It is important to note that the information needed to begin a clinical study under IDE may or may not require the same level of documentation as information submitted in a PMA or module. A module is considered complete for review only when the corresponding section of the draft SSED is received.

8. An acceptance or deficiency letter will generally be issued for each module within 90 days of receipt of the module.
  - a. When the review is complete and the reviewing division has determined that a module is acceptable, both division- and office-level concurrence will be obtained before the acceptance letter will be issued to the module submitter. Once closed (that is, declared acceptable), a module will generally not be reopened for further review. Only when the division director and the ODE Director concur that there is a significant safety or effectiveness issue will the module be subject to re-evaluation.
  - b. If the module is deficient and additional information is necessary, a deficiency letter will be issued.

A status report will be sent to the module submitter as an attachment to all acceptance or deficiency letters.

9. When a module submitter responds to a deficiency letter, the submission will be logged in by DMC as an amendment (M980001/M001/A001). The review clock will be adjusted to reflect up to another 90-day review period. Upon completion of the review, an acceptance or deficiency letter should issue following the procedures described above.
10. If a module submitter makes a modification to the device after a module has been declared acceptable, the submitter should contact the appropriate division staff to discuss the modification and any testing needed to support the change. As agreed by the submitter and division staff, data generated to support the change should be submitted separately to each of the affected modules with a revised executive summary. These submissions will be logged in as a supplement (M980001/M001/S001). As described above, a status letter should issue to the module submitter within 90 days of receipt of the supplement.

The module submitter should also consider whether additional information should be submitted to the IDE to support the change. If the information required to support the change is the same for both the IDE and the module, the new module may incorporate the IDE supplement by reference.

11. The manufacturing section may be submitted as a module prior to submission of the PMA. Modules containing manufacturing information will be reviewed jointly by the Office of Compliance (OC) and ODE. A copy of this module will be sent by the PMA Staff to OC for concurrent review.

In accordance with current practice, manufacturing deficiencies identified by the OC reviewer will be communicated to the submitted in separate letters. Once both offices agree that the module is acceptable, ODE will prepare and issue the letter finding the manufacturing module acceptable. A GMP inspection assignment will be considered once the PMA has been received.

12. The last module(s) to be submitted (most commonly the final clinical report, the final draft labeling, and the completed SSED), plus the incorporation of previously submitted modules, will complete the PMA. The final submission should be clearly labeled in the cover letter as an original PMA and should reference by shell and module numbers the modules that have been previously submitted and accepted. The cover letter should identify any modules deficient at the time of PMA submission and describe where each deficiency was addressed within the PMA. Upon receipt of this submission, a PMA number will be assigned and the "PMA clock" will be started. The PMA, including the referenced modules, should meet all of the requirements for PMA submission as described in 21 CFR 814. The PMA review should continue according to existing procedures.

The filing review should be conducted by the existing team augmented with individuals in disciplines applicable to the newly submitted information. The review will take into account the status of modules previously found acceptable and therefore, should focus on the information submitted in the PMA, any responses to modules which were still deficient at the time of PMA submission, and the draft SSED. If a manufacturing section has not been submitted previously as a module and is not included in the PMA, the PMA may still be considered for filing. However, if an amendment containing the complete manufacturing section is not received by Day 90, the PMA will be considered for denial.

13. Once the PMA is submitted, the shell and its associated modules will be considered closed. Any outstanding deficiencies from previously submitted modules still deficient at the time of PMA submission will be addressed within the PMA review and correspondence process.