Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff

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This document supersedes the draft Guidance on Quality System Regulation Information for Various PreMarket Submissions released for comment on August 3, 1999



U.S. Department Of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Office of the Director
Division of Enforcement III
Office of Compliance

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Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852.

When submitting comments, please refer to Docket No. 99D-2212. 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 Kimberly A. Trautman at (301) 594-4659 or by email kat@cdrh.fda.gov.

Additional Copies

Additional copies are available from the Internet at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070899.pdf
You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance or send a fax request to 301-847-8149 to receive a hard copy. Please use the document number (1140) to identify the guidance you are requesting.

Quality System Information for Certain Premarket Application Reviews

Scope: Use this guidance for PMA; PMA Supplement; PDP; HDE; and Modular Review Submissions.

This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

Introduction

Medical device premarket applications submitted under section 515(c)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 360(e)(c)(1)(C)], are required to include a number of information components, as set forth in 21 Code of Federal Regulations (CFR) Sec. 814.20. One component covers the current good manufacturing practice requirements included in the Quality System (QS) regulation. A Premarket Approval Application (PMA) is required to include a complete description of the methods, facilities, and controls, in sufficient detail so that FDA can make a knowledgeable assessment of the quality control used in producing the medical device (21 U.S.C. 515(c)(1)(C)).

This guidance has been prepared by the Center for Devices and Radiological Health (CDRH), in coordination with the Center for Biologics Evaluation and Research (CBER), to assist medical device manufacturers in preparing and maintaining the QS information required in premarket submissions[1].

This guidance replaces "Guidance for Preparation of PMA Manufacturing Information," found in FDA 91-4245 and FDA 92-4165. This updated guidance includes information that is consistent with the QS regulation that became final on October 7, 1996. ("Medical

[1] PMA amendments or supplements should include design and/or manufacturing information that differs from what has already been submitted in the original PMA or in a prior amendment or supplement for the device.

Devices; Current Good Manufacturing Practice (CGMP) Final Rule; Quality System Regulation" (61 FR 52602--52662) [2].

CDRH's Office of Compliance (OC) will review the QS information submitted in your premarket submission at the same time the Office of Device Evaluation (ODE) reviews the other portions of your application. The appropriate Offices in CBER will review the QS information submitted in CBER regulated premarket submissions. This QS information guidance is meant to help applicants in providing the necessary information in a clear format for efficient review and timely decisions.

This guidance document requests that you provide copies of written procedures or lists of items related to the QS regulation. In most cases, these procedures or lists are explicitly required under provisions of the QS regulation. In the case where the information is not explicitly required under statute or regulation (e.g., production flow diagram, list of any standards used, process validation master plan), we believe the information is the type you are likely to create and maintain as part of your Quality System. Your submission of such information as part of the application process may reduce or eliminate the need for us to request additional information to determine your compliance with the QS regulation under 21 CFR 820. In addition, we believe your submission of this information can help us focus the preapproval inspection process and limit the amount of time our field staff will need to spend in your facility.

A manufacturer who chooses to meet application requirements for the QS information in an alternative way may wish to consult with the appropriate office within the Center prior to the submission. The FDA staff can help identify areas that might raise particular concerns for Center reviewers or investigators.

Note: During a pre-approval inspection, FDA may assess any of the requirements of the Quality System regulation, not just the ones referenced below.

The Least Burdensome Approach

In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on CDRH's web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html.

A. General Information

[2] The Quality System regulation (Title 21 Code of Federal Regulations Part 820) text and preamble is located at www.fda.gov/cdrh/humfac/frqsr.html.

1. Format

The "Cover Letter" and the general information described below in "What to Send" may be submitted only once if all the QS information is submitted at the same time. If the design control information and the manufacturing information are submitted separately, as allowed in programs such as the PMA modular review process and the Product Development Protocol (PDP) process, this general information should be submitted with both submissions. This will allow the reviewers ready access to this basic information with each submission under review and avoid possible delays in trying to reference this information for each submission.

If you are participating in a modular review, FDA suggests, for simplicity, that the design control information and manufacturing information be submitted in module(s) that are separate from other information. (This may be one or two modules). Any manufacturing process information needed by FDA for ODE's safety and effectiveness review should be submitted in those modules to be reviewed by ODE.

Each copy of a premarket submission should include a separate volume or volumes that cover QS information. The volume(s) should have numbered pages, to facilitate our review and any discussions with you.

When multiple facilities are involved in the design, assembly, or processing of the device, you should submit applicable QS information for each facility in separate volumes that clearly identify the facility to which it applies.

2. Cover Letter

With each submission of QS information, you should include a cover letter that has the following information to help FDA manage your premarket application and related documents more efficiently:

- Identification elements:
  - Full name and street address (no P.O. Box number),
  - Telephone number (with area code),
  - FDA Facility Establishment Identifier (FEI) or registration number,
  - Relationship of (each) manufacturing facility to applicant.
- Contact person (and alternates) and their telephone number(s).
- The date the facility site(s) will be ready for inspection.

The location and affiliation information will help CDRH/CBER determine the appropriate facilities to be inspected under the preapproval process.

3. What to Send

The initial volume for each facility should include the following information:

- A copy of your cover letter, as described above in item 2;
- A description of the device, including pictures, and where possible, the proprietary name, common name, model number(s), product code, and intended use;
- A description of how the device works; and,
- The documentation described in subpart B of this guidance document.

Note: If you are resubmitting information, you should verify that the information does not include any changes that would require a PMA amendment. (See 21 CFR §814.37.)

B. Content

You can facilitate our review by formatting your submission in the order presented below. Provide the most up to date information as it applies to the device under review and to each facility identified in the application. Address all items for each original application. Address all pertinent items for each supplement.

I. Design Control Information_____

Design Controls, General, 820.30(a)

1. You should provide an explanation of where in your design and development process the device became subject to your design control program.

Design and Development Planning, 820.30(b)

2. You should provide the design and development plan(s), or a summary of the plan(s), for the device under review.

   - Your design and development plan(s) or summary should describe or reference, and assign responsibility for the implementation of, the following elements:

     - Design Inputs
     - Design Outputs
     - Design Review
     - Design Verification
     - Design Validation
     - Design Transfer
     - Design Changes
     - Design History File

   - Your design and development plan(s) or summary should identify and describe the interfaces with different groups or activities that provide or result in input to the design and development process.

   - Your design and development plan(s) or your summary should describe the procedures for review, update, and approval of the plan(s) as design and development evolve.

   Design and development plans typically include information such as:
   - the chronology of the development strategy (e.g., Gantt Chart)
   - outline of the timing strategy (i.e., initiation, completion, and analysis)
   - specification and justification of data needed prior to moving onto subsequent studies or activities referenced in the plan

- specific deliverables for each stage
- criteria for initiation, completion, and design review
- critical milestones that must be completed before starting subsequent tasks
- risk management activities

Note: The initial risk analysis must be completed by the conclusion of design validation. 21 CFR 820.30 (g). FDA acknowledges that risk analysis and other risk management activities occur throughout the design process. Firms should clearly explain how they will incorporate these risk management activities in the design and development plans.[3]

Design Input, 820.30(c)

3. You should provide a copy of the procedure(s) used for the identification and control of design input for the device under review.

   - Your procedure(s) should describe the process or mechanism for addressing incomplete, ambiguous, or conflicting requirements.

   - Your procedure(s) should explain how design inputs are documented, reviewed, and approved.

   Examples of potentially relevant aspects for design input consideration:
   - intended use
   - user / patient / clinical (interfaces or needs)
   - performance characteristics
   - safety requirements
   - safety and performance parameters (including standards)
   - toxicity
   - bio-compatibility
   - electromagnetic interference (EMI)
   - compatibility with accessories / auxiliary devices
   - compatibility with the environment of intended use
   - human factors
   - clinical reports
   - physical / chemical characteristics
   - labeling and packaging
   - statutory and regulatory requirements
   - past design history files
   - manufacturing capability

[3] Food and Drug Administration, "Design Controls: Inspectional Objectives" Guide to Inspections of Quality Systems: Quality Inspection System Technique - QSIT, August 1999, pp. 32-45.

This is not an exhaustive list of commonly considered design inputs. Your firm's quality assurance, clinical, and engineering experts should also consider emerging risks that may not have been fully addressed.

Potential risks, even at the early stages of device development, should be identified. Managing risks as the device design evolves is important because changes in design can create new risks.

Design Output, 820.30(d)

4. You should provide a copy of the procedure(s) used to define and document design output in terms that allow an adequate and measurable evaluation of conformance to design input requirements for the device under review. Provide a list of the design outputs you consider essential for the proper functioning of the device for the device under review.

   - Your procedure(s) should contain or refer to design output acceptance criteria.

   - Your procedure(s) should explain the mechanism used to ensure that you identify those design outputs that are essential for the proper functioning of the device.

   Your identification of essential design outputs will help us determine the adequacy of your design verification and design validation.

Design Review, 820.30(e)

5. You should provide a copy of the procedure(s) that define and control the design reviews for the device.

   - Your procedure(s) should explain how formal design reviews are planned and how you ensure that formal design reviews are conducted at appropriate stages of the design and development process for the device under review.

   - Your procedure(s) should describe how you ensure that:

     - Design reviews are comprehensive and systematic;
     - All of the functions and people involved with the stage under design review are included in the design review;
     - An independent individual participates in all formal design reviews (this individual may be an employee who does not have direct responsibility for the design stage being reviewed); and,

- Any specialists that are needed participate in formal design reviews.

- Your procedure(s) should define the method of recording design reviews for the design history file and should include:

  - Identification of the design
  - Date
  - Individual(s) performing the review
  - Action items

Design Verification, 820.30(f)

6. You should provide a copy of the procedure(s) used to verify the device design for the device under review.

   - Your procedure(s) should describe the process that confirms the design outputs meet the design input requirements and the mechanism for resolving any discrepancies.

   - Your procedure(s) should define the method of recording design verification activities for the design history file and should include:

     - Verification results
     - Identification of the design
     - Verification methods
     - Date(s) of verifications
     - Individual(s) performing the verifications

Design Validation, 820.30(g)

7. You should provide a copy of the procedure(s) used to validate the device design for the device under review.

   - Your procedure(s) should define the method of recording design validation for the design history file and should include:

     - Validation results
     - Identification of the design
     - Validation methods
     - Date(s) of validation
     - Individual(s) performing the validation

   - If validation activities were performed on devices that were not made using production methods or equipment that you expect to use during full scale manufacturing, summarize the process or

scientific method you used to prove equivalence. We need to evaluate the equivalence of the manufacturing or devices used to validate the design to ensure the validation data can be applied to devices that you plan to make under normal production methods.

- You should summarize how the clinical evaluations of the device ensure the device meets user needs and the intended uses.

- If the device is automated with computer software, you should explain how you have (or will) complete your software validation, and include any system integration testing.

- As stated earlier in the design and development planning section, risk management issues will be addressed throughout the design control process. You should describe how and when risk analysis was or will be performed. Your design validation procedure(s) should describe how you will document, use, and update your risk management program. For additional guidance on risk analysis and risk management activities, see the QS regulation preamble comment #83. [61 FR 52620-52621; see footnote 2.]

Design Transfer, 820.30(h)

8. You should provide a copy of the procedure(s) used to transfer the design output to manufacturing for the device under review.

    - Your procedure(s) should explain how you will conduct the final review and approval of design and development activities in order to transfer the design to manufacturing.

    - Your procedure(s) should describe what design documents comprise the device master record.

Design Changes, 820.30(i)

9. You should provide a copy of the procedure(s) for controlling design change.

    - Your procedure(s) should describe when and how you use change control within the original design process and after the original design has been transferred to manufacturing. Your change control procedures should ensure that change control is implemented after you initially approve any design inputs.

    - Your procedure(s) should describe when you use verification for certain design changes instead of using validation. You should

clearly define and document the reason for choosing verification rather than validation of a design change.

- Your procedure(s) should explain how you ensure that changes are validated or verified, reviewed, and approved before the design change is implemented.

- Your procedure(s) should describe how changes in the manufacturing process will be managed.

Design History File, 820.30(j)

10. You should provide a copy of the procedure(s) for maintaining the contents of the Design History File (DHF) for the device under review.

    If more than one device shares a common design history file, explain how you identify each device within the group having common design elements.

II. Manufacturing Information _____

Quality System Procedures, 820.20(e)

1. You should provide a copy of your basic quality system procedure(s).

    - Your basic quality system procedure(s) should include:

        - Quality audit or internal audit procedure(s)
        - Management review procedure(s)
        - Outline of the structure of the quality system documentation

    The development of a quality manual that includes the referenced elements below would satisfy the requirement in 820.20(e) for an outline of the documentation used in the quality system:

    - Title and scope of application
    - Table of contents
    - Definitions (if needed)
    - Outline of the structure of the quality manual or quality system documentation
    - Quality policy and objectives
    - Organizational structure and responsibilities or authority
    - References to basic quality system procedures
    - Guide or appendix for supportive data (if needed)

Production Flow

2. You should provide a production flow diagram that identifies the steps involved in the manufacture of the device under review. This information helps to show the important aspects of your production process.

Use of Standards

3. You should provide a list of any standard(s) used in the manufacturing process or for the device itself.

Purchasing Controls, 820.50

4. You should provide a copy of the procedure(s) for purchasing controls. This is especially important if you use a contract design service or contract manufacturer(s) for the device under review. The controls applicable to these suppliers should be specified.

- Your procedure(s) should describe your supplier evaluation process and describe how you will determine type of and extent of control you will exercise over suppliers.
- Your procedure(s) should define how you maintain records of acceptable suppliers and how you address the purchasing data approval process.
- Your procedure(s) should explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.

For additional guidance on the relationship between purchasing controls and receiving acceptance activities, see the QS regulation preamble comment #99. [61 FR 52624; see footnote 2.]

Production and Process Controls, 820.70

5. You should provide a copy of the procedure(s) for environmental and contamination controls, if such conditions could adversely affect your device. (Note: if this involves a large number of procedures, a sample of the most relevant procedures would be sufficient.)

Inspection, Measuring, and Test Equipment, 820.72

6. You should provide a copy of the procedure(s) that explain how inspection, measuring, and test equipment is routinely calibrated, inspected, checked, and

maintained. (Note: if this involves a large number of procedures, a sample of the most relevant procedures would be sufficient.)

Process Validation, 820.75

7. You should provide a copy of your process validation master plan, or a description of which manufacturing processes you will validate, for the device under review. Provide a list of processes for the device under review that you do not plan to validate but will verify by inspection and test.

    - Your process validation master plan or your description should also include any validations of software used as part of the production or quality system. (See 820.70(i))

    - It would also be very helpful to identify in your process validation master plan or description which type of processes you have never validated before. (For example, a different type of sterilization process.) This would allow us to work with you on validation issues as early as possible before the preapproval inspection.

    The QS regulation requires you to validate processes whenever the results of a process cannot be fully verified by subsequent inspection and test methods. If you choose to validate a process that can be fully verified by subsequent inspection and test, these processes are also subject to the validation requirements of 21 CFR § 820.75. For additional guidance, see the Global Harmonization Task Force's Process Validation Guidance http://www.ghtf.org/sg3/inventorysg3/sg3-n99-10.doc. (Note the QS regulation does not permit option E in Figure 1 of the Global Harmonization Task Force's Process Validation Guidance.)

Process Validation, 820.75(a)

8. You should provide a copy of the validation procedure(s) or individual validation plan(s) for each process that will be validated for the device under review. When available, you should provide a copy of any completed validation reports.

    - Your validation procedure(s) or plan(s) should contain or refer to objective and measurable acceptance criteria.

    - Your validation procedure(s) or plan(s) should describe how appropriate statistical methods for data collection and analysis are used.

- Your validation procedure(s) or plan(s) should define the criteria for re-validation.

Your validation plan and procedures(s) should be in place at the time of submission of the manufacturing information. Process validations do not have to be completed at the time of submission. However, process validations must be completed prior to the preapproval inspection and prior to distribution of any finished devices. [820.75(a)].

Receiving Acceptance Activities, 820.80(b)

9. You should provide a copy of the procedure(s) for receiving or incoming acceptance activities. (Note: if this involves a large number of procedures, a sample of the most relevant procedures would be sufficient.)

- Your procedure(s) should address the extent of acceptance activities, based in part on the degree to which the supplier has demonstrated a capability to provide products and services that meet your specifications. You make this determination based on a combination of assessment techniques, such as your inspection and tests, supplier audits, a vendor's quality history with you, and the risk of the product or service as identified in your risk management program.

For additional guidance on the relationship between receiving acceptance activities and other assessment techniques, see the QS regulation preamble comment #106. [61 FR 52625; see footnote 2.]

- Your procedure(s) should define the acceptance/rejection criteria.

- Your procedure(s) should outline the disposition of rejected or nonconforming products, and include how and when nonconforming product are reworked, accepted, regraded, scrapped, or returned.

- Your procedure(s) should ensure documentation of acceptance activities, including:

  - Activity performed, e.g., chemical purity analysis
  - Dates the acceptance activities were performed
  - Results
  - Signature of the individual(s) conducting the acceptance activities
  - Equipment used, where appropriate

For additional guidance on recording of results, see the QS regulation preamble comment #147. [61 FR 52631; see footnote 2.]

Final Acceptance Activities, 820.80(d)

10. You should provide a copy of the procedure(s) for final acceptance activities. (Note: if this involves a large number of procedures, a sample of the most relevant procedures would be sufficient.)

- Your procedure(s) should identify the specific release criteria. For example, sterilization release criteria could be based on biological indicator results, validated parametric release protocols, or other valid scientific methods.

- Your procedure(s) should describe the quarantine or other controls used for finished devices until it is determined that all acceptance criteria are met and recorded properly.

- Your procedure(s) should ensure that finished devices are not released for distribution until:

  - Device Master Record requirements for release are met
  - Review of associated release data and documentation
  - Authorized for release by the signature of a designated person(s)
  - The date final release is authorized is recorded

Nonconforming Products, 820.90

11. You should provide a copy of the procedure(s) for handling nonconforming product. If your Corrective and Preventive Action (CAPA) procedure(s) includes provisions for handling nonconforming product, then please specify where that information is located in your CAPA procedure(s).

- Your procedure(s) should address the:

  - Identification
  - Documentation
  - Evaluation
  - Segregation
  - Disposition of nonconforming product

- Your procedure(s) should ensure that the evaluation process includes a determination of the need for an investigation and notification of the persons responsible for the nonconformance.

- Your procedure(s) should describe how any nonconforming product evaluation and investigation is tied to your CAPA system.

- Your procedure(s) should define the necessary documentation to justify the use of nonconforming product and who will be responsible for the authorizing signature.

Corrective and Preventive Action (CAPA), 820.100

12. You should provide a copy of the procedure(s) for your corrective and preventive action (CAPA) system.

    - Your procedure(s) should explain how your CAPA system is tied to your risk management program.

    For additional discussion on this topic, see the QS regulation preamble comment #159. [61 FR 52633-52634; see footnote 2.]

    - Your procedure(s) should define how your CAPA system will address nonconforming practices as well as nonconforming product.

    For additional discussion on this topic, see the QS regulation preamble comment #162. [61 FR 52634; see footnote 2.]

    - Your procedure(s) should address the analysis of the multiple data inputs from your quality system. Your procedure(s) should make it clear what will be included in this analysis as well as the mechanism for justification when something is not included.

    - Your procedure(s) should define the following to ensure that the corrective and/or preventive action is effective and does not have an adverse effect on the device:

        - Method for determining verification or validation
        - Implementation planning to include recording changes in methods and procedures
        - Method for disseminating information on the quality problem or nonconforming product to those responsible

- Your procedure(s) should define how and what type of CAPA information will be submitted to management for review.

- Your procedure(s) should explain how design changes made under your CAPA program interact with your design change control system and risk management program.

- Your procedure(s) should incorporate the need for reviews within your CAPA system to determine whether a record or report should be established, as required by the Corrections and Removal regulation (21 CFR Part 806) or Medical Device Reporting regulation. (21 CFR Part 803).

Complaint Files, 820.198

13. You should provide a copy of the procedure(s) for handling complaints and Medical Device Reporting (MDR) (21 CFR § 803). If your CAPA procedure(s) includes provisions for handling complaints and MDRs, then please specify where that information is located in your CAPA procedure(s).

    - Your procedure(s) should describe the criteria or decision making process used to determine if a complaint investigation is necessary.

    - Your procedure(s) should include a written justification for the reason that no complaint investigation was made and the name of the person responsible for the decision not to investigate.

    - Your procedure(s) should explain how complaints that are also MDRs, submitted to FDA under 21 CFR Part 803, are clearly identified or kept in a separate part of the complaint file.

    - Your procedure(s) should describe how records of complaint investigations are coordinated with your procedures for handling nonconforming products.

    - Your procedure(s) should ensure and explain the necessary coordination between your complaint handling system and your CAPA system.

    For a general discussion on the intent of the complaint handling requirements, see the QS regulation preamble comment #190. [61 FR 52638-52639]

Servicing, 820.200

14. You should provide a copy of the procedure(s) for servicing, if appropriate, for the device under review.

- Your procedure(s) should explain how information from servicing reports is coordinated with your complaint handling system to ensure that MDRs are filed with FDA when appropriate, and integrated into your CAPA system.

For a discussion on servicing reports with respect to complaint handling and CAPA, see the QS regulation preamble comment #201. [61 FR 52640]