

Guidance on Submitting Quality System Information

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The Food and Drug Administration's final guidance document on the type of quality system information that should be submitted in some types of premarket submissions was published in February 2003. The final guidance replaces previous draft guidance. This article discusses the final guidance document.

The critical element in PMAs

In the United States (US), Class III medical devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury. Premarket approval (PMA) is the Food and Drug Administration's (FDA) process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. It is the most stringent type of device marketing application that FDA requires.

A critical element of a PMA application is a complete description of the methods, facilities and controls used in the manufacture, processing, packing, storage and, where appropriate, installation of the device. In addition, to determine whether a company has the capability to design, manufacture or process the device, the FDA Center for Devices and Radiological Health Office of Compliance (OC) may issue an inspection assignment for a preapproval inspection. These inspections cannot be scheduled until the manufacturer has demonstrated in the PMA submission that the design and manufacturing process meets the requirements of the Quality System (QS) Regulation (21 Code of Federal Regulations (CFR) Part 820) and that the facility is ready for inspection.

On 3 August 1999, FDA published a Federal Register (FR) notice¹ on a draft guidance document that it was making available for comment. The purpose of the document was to assist medical device manufacturers with the

quality system information they should include in PMA applications and product development protocols (PDPs). In addition, the document also described information that should be maintained at the manufacturing facility for premarket notifications, also known as 510(k) submissions. The draft guidance was discussed in a previous article.²

Recommendations questioned

Before discussing the contents of the final guidance, which was published in February 2003, it is useful to consider some of the changes made as a result of comments received on the draft guidance. FDA discusses the actions taken or not taken in response to these comments in the preamble of the FR notice announcing the availability of the final guidance.³

Design control information. Several comments questioned the recommendation that manufacturers have design control information available on request for devices subject to the 510(k) process. These comments pointed out that this documentation could be requested as part of the determination of substantial equivalence that occurs during the review of a 510(k) submission. FDA agreed with the comments and has excluded 510(k) submissions from the scope of the final guidance document.

Process-flow diagrams. Other comments questioned whether the draft guidance document exceeded requirements in the QS Regulation by requesting information →



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such as process-flow diagrams and other documentation not explicitly required under the QS regulation. These comments were rejected by FDA because this type of information is still requested in the final guidance document. FDA states that any information requested that is not explicitly required by regulation is the type that manufacturers are likely to create and maintain as part of the quality system. FDA also states that submission of the information will reduce or eliminate the need for FDA to request additional information during the review and preapproval process. The introduction section of the final guidance document states this rationale.

A choice. FDA also states that compliance with the guidance document is a recommendation and thus not required. This is true of all FDA guidance documents, which always state that an alternative approach may be used if that approach satisfies the requirements of the applicable statute and regulations. However, manufacturers choosing to vary from the recommendations in FDA guidance documents should weigh their decisions carefully, base any decisions on a clear understanding of the requirements, and when in doubt confirm the chosen approach directly with FDA.

More detailed guidance

The final guidance, titled Quality System Information for Certain Premarket Application Reviews,⁴ has been prepared to assist medical device manufacturers in preparing and maintaining QS information required in PMAs, PMA supplements, PDPs, Humanitarian Device Exemption applications and Modular Review submissions. Readers should note that its scope no longer includes the 510(k) submission process. According to FDA officials, the document is meant to concentrate on essential quality system information and not all the procedures required for complying with the QS regulation. In this way, there is some assurance that the basic quality management system has been documented.

The final guidance document supplies more detailed guidance on the format of the QS information to be submitted. For example, it states that each copy of a premarket submission should include a separate volume or volumes that cover QS information. When multiple facilities are involved in the design, assembly or processing of a device, the applicable QS information for each facility should be submitted in separate volumes that clearly identify the relevant facility. The contents of the cover letter are also listed, including a request for the date when each facility will be ready for inspection. The QS information to be submitted is presented in two principal sections, Design Control Information and Manufacturing Information.

Design Control information

The Design Control section requires a procedure or other documentation on the implementation of each of the design control elements listed in the QS regulation. For example, under Design Controls, General, 820.30(a), the

guidance requests an explanation of where in the company's design and development process the device became subject to the design control programme. Under Design and Development Planning, 820.30(b), the guidance requests a copy of the design and development plan(s) or a summary of the plan(s) for the device under review. Additional information that should be provided is also described such as the procedures for the review, update and approval of the plan(s) as design and development evolve.

One of the more interesting aspects of the guidance document is the inclusion of references to the preamble of the Final Rule published in the FR on 7 October 1996.⁴ For example, under Design Validation, 820.30(g), the guidance requests submission of the design validation procedure(s) and states that the procedure(s) should describe how the risk management programme will be documented, used and updated. For additional guidance on risk analysis and risk management activities, the guidance recommends a review of a comment provided in the QS regulation preamble comment #83, 61 FR 52620-52621. The FDA response to comment #83 includes advice on conducting risk analysis, including the need to identify possible hazards in normal and fault conditions and on calculating risks associated with the hazards and other advice. More importantly, reference is made to the European and international standards related to medical device risk analysis.

Manufacturing information

The guidance on the QS information related to manufacturing has been significantly expanded in comparison with the information requested in the draft guidance document. In this section, procedures or documents are requested for the implementation of selected QS regulatory provisions: Quality system procedures 820.20(e); Purchasing controls 820.50; Production and Process Controls 820.70; Inspection, Measuring, and Test Equipment 820.72; Process Validation 820.75; Process Validation 820.75(a); Receiving Acceptance Activities 820.80(b); Final Acceptance Activities 820.80(d); Nonconforming Products 820.90; Corrective and Preventive Action (CAPA) 820.100; Complaint Files 820.198; and Servicing 820.200.

The QS information requested under Quality System Procedures includes a request for a copy of the basic QS procedures including internal audit procedures, management review procedures and an outline of the structure of the QS documentation. In this section, the guidance states that the development of a quality manual that includes the referenced items listed such as title and scope and other elements would satisfy the requirements in 820.20(e) for an outline of the documentation used in the quality system.

This section also requests a production flow diagram that identifies the steps involved in the manufacture of the device under review. The guidance states that this information helps to show the important aspects of the produc-



tion process. A list of any standards used in the manufacturing process or for the device itself is also requested. The guidance on the information to be submitted for several of the regulatory provisions includes references to the QS regulation preamble, including the sections on purchasing controls, receiving acceptance activities, CAPA, complaint files and servicing.

Three useful reasons

Why should the type of information requested, including the reference to the QS regulation preamble, be of interest to readers?

Documenting key elements. The guidance helps to ensure that companies have documented the major elements of the quality management system as required by the QS regulation. This helps companies with limited resources or companies that have concentrated their efforts on completing resource-intensive preclinical and clinical studies and other work required for the PMA. However, it should be clearly understood that companies must comply with all aspects of the QS regulation that apply to them before placing their products on the US market. There is some flexibility during the PMA process regarding compliance, but the guidance document states that during a preapproval inspection, FDA may assess any of the requirements of the QS regulation, not just the ones referenced in the guidance document.

English translations. Although limited to the essential elements of a quality system, the requested design and manufacturing information is detailed and voluminous. Companies located in countries where English is not the primary language that are submitting PMA applications will need to provide English translations of the documentation requested. According to FDA officials, English summaries of some procedures instead of the entire procedure may be acceptable unless the OC reviewer requests additional information. However, FDA strongly encourages nonUS manufacturers to have English translations of some of the more important procedures. This would help companies avoid the request for additional information or deficiency letters before the scheduling of the preapproval inspection and would also significantly facilitate the preapproval inspection process.

First 510k. This author believes that the guidance document, which provides extremely concise guidance on the major elements of the QS could be of interest to companies that have submitted a premarket notification or 510(k) submission for the first time. It must be stressed that the guidance document does not involve the 510(k) submission process. However, too often companies involved in the work of submitting a 510(k) for the first time have not placed adequate emphasis on complying with the QS regulation. Although these companies will have to comply with all QS regulatory provisions that apply to them, the QS information guidance document could be helpful in their initial efforts to understand the type of information that FDA expects to see if these companies are inspected. This does not in any way min-

imise the importance of companies being fully aware of the QS regulation and relevant standards and guidance documents that apply to the products that are the subject of the submission.

References

1. US Federal Register (FR) Notice, 64 FR 42137, 3 August 1999, Medical Devices; Draft Guidance on Quality Systems Regulation Information for Various Premarket Submissions; Availability, <http://www.accessdata.fda.gov/scripts/oc/ohrms/index.cfm>
2. M.E. Donawa, "New FDA Draft Guidance on Premarket Submissions," *Med. Dev. Technol.*, **10**, 8, 12 (October 1999).
3. US FR Notice, 68 FR 5198, 3 February 2003, Medical Devices; Final Guidance on Quality System Information for Certain Premarket Application Reviews; Availability, <http://www.accessdata.fda.gov/scripts/oc/ohrms/index.cfm>
4. US FR Notice, 7 October 1996, 21 CFR Parts 808, 812, and 820 Medical Devices; Current Good Manufacturing Practice (CGMP); Final Rule, <http://www.fda.gov/cdrh/comp/gmp.html> **mdt**

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