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The Wait is Over: FDA Releases Proposed Rule to Align the U.S. Medical Device Quality Regulation with International Standards

On February 23, 2022, the U.S. Food and Drug Administration (FDA) published in the Federal Register, 87 Fed. Reg. 10119, the long-awaited proposed rule, Medical Devices; Quality System Regulation Amendments (Docket No. FDA-2021-N-0507). The proposed rule seeks to amend the device good manufacturing practice (GMP) requirements of the Quality System Regulation (21 CFR Part 820) to incorporate by reference the International Organization for Standardization (ISO) - ISO 13485:2016 Medical devices – Quality management systems – Requirements for regulatory purposes, Third Edition 2016-03-01 ("ISO 13485"). The goal of the proposed rule is to streamline and harmonize FDA's Quality System Regulation (QSR) with the globally recognized Quality Management System requirements issued in 2016 by ISO, an independent, non-governmental international organization. ISO 13485 has been implemented throughout the global medical device industry and used by many regulatory authorities around the world as their standard for a Quality Management System (QMS).

FDA first announced its plans to reexamine the QSR in early 2018, providing that, in the spirit of global harmonization, the Agency would consider ways to blend the ISO 13485 requirements to the appropriate U.S. regulatory requirements. This effort became one of the Agency's top priorities, and for four years, the Agency promised to issue a revised rule, setting internal deadlines only to repeatedly—at least five times—miss them, much to Industry's frustration. The long wait is over; FDA finally issued the proposed rule. If finalized, the existing QSR will become the Quality Management System Regulation (QMSR).

As discussed in detail below, the proposed rule would remove most of the existing QSR and replace it with ISO 13485:2016, incorporated by reference. Future revision of the standard by ISO would not automatically

get incorporated into the QMSR. FDA would need to independently consider any future revisions of ISO 13485 and determine if the regulation should be amended.[1]

The proposed rule is an important step towards achieving FDA's goal of harmonization of international regulatory requirements and has the potential to have many positive impacts for the medical device industry. By FDA's own estimate, the proposed rule could result in cost savings of $439 million over ten years. Savings would largely come from a reduction in compliance efforts relating to medical device establishments having to comply with two sets of requirements. Currently, the vast majority of device manufacturers registered with FDA must comply with the current QSR as only limited numbers of devices are exempt from QSR compliance. They must also comply with ISO 13485 if they sell devices in jurisdictions that require compliance with ISO 13485, including the European Union, Australia, Canada, and Japan. The requirement to comply with both the current QSR and ISO 13485 creates redundancy and inefficiency for manufacturers, especially given that the current QSR and ISO standard are substantially similar. The proposed rule is a step at removing the current redundancy and inefficiency and to streamline how the medical device industry implements a Quality Management System.

WHAT IS THE STRUCTURE AND CONTENT OF THE PROPOSED RULE?

The proposed rule removes most of the contents of the existing 21 CFR Part 820 and replaces them with two elements:

(1) Reference to ISO 13485: Instead of rewriting the QSR section by section, FDA makes the proposed 21 CFR Part 820 a pointer to ISO 13485 content.

(2) Additional and clarified definitions and requirements: The QMSR identifies those limited areas in which FDA proposes to depart from ISO 13485.

ISO 13485:2016 STRUCTURE

Because references to ISO 13485 will replace the majority of quality system requirements in current 21 CFR Part 820, it is worth reproducing here the table provided by FDA in the preamble to the proposed rule, mapping the existing QSR sections to the ISO 13485 clauses and noting where the revised 21 CFR Part 820 will address differences in requirements:

Current part 820[1]	ISO 13485 requirements[1]	Proposed rule
Subpart A—General Provisions	Clause 1. Scope, Clause 4. Quality Management System.	Requirements substantively similar.
Subpart B—QS Requirements	Clause 4. Quality Management System, Clause 5. Management Responsibility, Clause 6. Resource Management, Clause 8. Measurement, Analysis, and Improvement.	Requirements substantively similar.
Subpart C—Design Controls	Clause 7. Product Realization	Requirements substantively similar.
Subpart D—Document Controls[2]	Clause 4. Quality Management System	Differences addressed in 820.35.
Subpart E—Purchasing Controls	Clause 7. Product Realization	Requirements substantively similar.
Subpart F—Identification and Traceability	Clause 7. Product Realization	Requirements substantively similar.
Subpart G—Production and Process Controls	Clause 4. Quality Management System, Clause 6. Resource Management, Clause 7. Product Realization.	Requirements substantively similar.
Subpart H—Acceptance Activities	Clause 7. Product Realization, Clause 8. Measurement, Analysis, and Improvement.	Requirements substantively similar.
Subpart I—Nonconforming Product	Clause 8. Measurement, Analysis, and Improvement.	Requirements substantively similar.
Subpart J—Corrective and Preventive Action	Clause 8. Measurement, Analysis, and Improvement.	Requirements substantively similar.
Subpart K—Labeling and Packaging Control	Clause 7. Product Realization	Differences addressed in 820.45.
Subpart L—Handling, Storage, Distribution, and Installation.	Clause 7. Product Realization	Requirements substantively similar.
Subpart M—Records	Clause 4. Quality Management System	Differences addressed in 820.35.
Subpart N—Servicing	Clause 7. Product Realization	Differences addressed in 820.35.
Subpart O—Statistical Techniques	Clause 7. Product Realization, Clause 8. Measurement, Analysis, and Improvement.	Requirements substantively similar.

PROPOSED 21 CFR PART 820 STRUCTURE

Below is the structure of the proposed new 21 CFR Part 820 and items of interest within each one:

a. Section 820.1 (Scope)

- Scope remains largely identical to the current Part 820, with finished devices and human cells, tissues, and cellular and tissue-based products (HCT/Ps) in-scope and components / parts, blood & blood components out-of-scope, and with the scope of manufacturers subject to the requirements to include contract sterilizers, installers, relabelers, remanufacturers, repackers, specification developers, and initial distributors of foreign manufacturers.
- The section clarifies how manufacturers are to address conflicts between Part 820 and other regulations and between the Federal Food, Drug, and Cosmetic Act (FDCA) and its implementing regulations and ISO 13485; importantly, in the event of a conflict with ISO 13485, the FDCA and its regulations will control.

b. Section 820.3 (Definitions)

In the preamble to the proposed rule and in the proposed 21 CFR § 820.3, FDA revises some definitions from the current 21 CFR § 820.3, adds some definitions beyond those in ISO 13485, and clarifies others.

- The current term "establish" is being replaced by the ISO 13485 term "documented."
- The current term "management with executive responsibility" is being replaced by the ISO 13485 term "top management."
- The current term "device master record (DMR)" is being removed in favor of the existing ISO 13485 requirement for a medical device file (clause 4.2.3).
- Neither the existing 21 CFR Part 820 nor ISO 13485 define the term "customer," but the proposed rule adds this definition as a means for clarifying the entities impacted by the ISO requirements for handling customer property (clause 7.5.10).
- Current terms for "component," "finished device," "human cell, tissue, or cellular or tissue-based product (HCT/P)," "design validation," "remanufacture," "nonconformity," and "verification" are retained in the proposed rule.
- The terms "device" and "labeling" in the Food Drug and Cosmetic Act (FD&C Act) are retained and supersede the ISO 13485 definitions.
- The terms "manufacturer" and "product" in the proposed rule will supersede definitions of these terms in the ISO standard. The definition of "manufacturer" remains the same as in the current 21 CFR § 820.3, but the proposed definition of "product" varies slightly from the current definition, replacing a reference to "manufacturing materials" with "process agents."

c. Section 820.7 (Incorporation by Reference)

As mentioned above, the proposed rule is not a complete rewrite of the QSR to align with ISO 13485. It is instead a full incorporation of the ISO standard by reference, with the primary content of the new 21 CFR Part 820 focused on limited areas of difference and clarification.

d. Section 820.10 (Requirements for a Quality Management System)

This section of the proposed rule incorporates the quality system requirements of ISO 13485, while also ensuring references to 21 CFR Part 821 (Medical Device Tracking Requirements), 21 CFR Part 803 (Medical Device Reporting), and 21 CFR Part 806 (Corrections and Removals) are maintained as required elements.

Proposed 21 CFR § 820.10(c) clarifies the scope of devices subject to the design and development requirements of ISO 13485, clause 7.3, which will replace design controls in 21 CFR § 820.30, and will include class II, class III, and certain class I devices. This scope is unchanged from the current 21 CFR § 820.30(a).

This section further specifies that the traceability requirements in ISO 13485 clause 7.5.9.2 extend to devices that support or sustain life, in addition to the implantable devices already covered by the ISO provision. Finally, proposed 21 CFR § 820.10(e) reminds that failure to comply with the requirements of 21 CFR Part 820 (and, by extension, ISO 13485) renders a device adulterated.

e. Section 820.15 (Clarification of Concepts)

FDA clarifies three terms existing in ISO 13485:

- The term "organization" in the ISO standard equates to the QMSR term "manufacturer."
- The term "safety and performance" in the ISO standard equates to the FD&C Act term "safety and efficacy."
- The term "validation of processes" in the ISO standard equates to the QMSR term "process validation."

f. Section 820.35 (Control of Records)

FDA adds signature requirements, specific content requirements for complaints and service records, clarification on the requirements for Unique Device Identification (UDI), and an admonition to mark confidential records (ref. proposed 21 CFR § 820.35) to the existing ISO 13485 documentation requirements.

g. Section 820.45 (Device Labeling and Packaging Controls)

One quality system element where FDA views ISO 13485 as inadequate is device labeling and packaging. The proposed rule addresses the FDA's concern that "ISO 13485 fails to provide additional requirements for labeling and packaging and does not specifically address the inspection of labeling by the manufacturer." The proposed 21 CFR § 820.45(a) specifically describes content requirements for packaging and labeling.

h. Additional structural and content takeaways:

- Where the existing regulation mentions risk management in 21 CFR § 820.30(g) as part of design validation, the proposed incorporation of ISO 13485 includes an explicit definition for risk management (clause 3.18) linking this standard with the ISO 14971 medical device risk management standard. The international standard also requires a documented risk management process (clause 7.1) and post-market feedback into the risk management process (clause 8.2.1).
- The quality system record, Device Master Record (DMR), Design History File (DHF), and Device History Record (DHR) will cease to exist as distinct buckets of documents and are replaced by the general set of documentation requirements in clause 4.2 of the ISO standard, including a new category of documents called the medical device file. FDA has explained that, "We are not proposing to retain separate requirements for these record types as we believe the elements that comprise those records are largely required to be documented by other ISO 13485 Clauses, such as Clause 4.2 and its subclauses."[2]

HOW AND WHEN WILL THE PROPOSED RULE BE ROLLED OUT?

Section 520(f)(1)(B) of the FD&C Act requires FDA to convene the Device Good Manufacturing Practice Advisory Committee (DGMP Advisory Committee), which FDA has scheduled to meet on March 2, 2022. At that meeting, the members of the DGMP Advisory Committee will review the proposed regulations and make recommendations to

FDA regarding their feasibility and reasonableness. As well, FDA shall schedule an oral public hearing to discuss this proposal prior to FDA's finalization of this rule.

FDA is also proposing conforming edits to 21 CFR Part 4, to clarify the device QMS requirements for combination products. The proposed edits would not impact the GMP requirements for combination products.

It is important to note that the proposed rulemaking does not impact FDA's inspectional authority under Section 704 of the FD&C Act. If and when the proposed rule is finalized, FDA inspections will not result in the issuance of certificates of conformance to ISO 13485, nor is FDA developing a certification program for ISO 13485. In addition, manufacturers with a certificate of conformance to ISO 13485 are not exempt from FDA inspections. However, participation in the Medical Device Single Audit Program (MDSAP) will continue to exempt manufacturers from routine surveillance inspections by FDA.

The comment period for the proposed rule closes on May 24, 2022. FDA proposes that any final rule based on this proposal become effective one (1) year after the date of publication of the final rule in the Federal Register. This approach is intended to provide adequate time for manufacturers to make any changes necessary to comply with the requirements of ISO 13485. We expect that FDA will receive a large number of comments on the proposed rule. The Agency must consider and respond to each comment received, so the delay between the close of the comment period in May and the issuance of the final rule could be lengthy.

HOW WILL THE PROPOSED RULE IMPACT INDUSTRY AND FDA?

a. Industry Considerations

For companies that already market devices in the U.S. as well as in the EU or other international markets where ISO 13485 is already the applicable GMP standard (e.g., Australia, Canada, Japan), the impact of FDA's new QMSR, as proposed, would be relatively small. For these companies, the primary task will be to update procedures and work instructions to remove obsolete references to QSR requirements. Overall, these firms should experience a net reduction in burden and costs associated with quality management system compliance.

For manufacturers currently operating under the QSR but not already compliant with ISO 13485, the new rule will necessitate revisions to procedures and documentation to address distinctions between the former and the latter. For example, as FDA observes, "ISO 13485 has a greater emphasis on risk management activities and risk-based decision making than the current part 820."[3] FDA expects that "the explicit integration of risk management throughout the clauses of ISO 13485…should help industry develop more effective total product life-cycle risk management systems."[4] Firms that are not already subject to ISO 13485 compliance will need to understand this and other areas where their procedures should be shored up or otherwise revised to conform to the international standard, while retaining or adding provisions to ensure compliance with Part 820 insofar as it will be revised to include FDA-specific provisions that clarify or add to those of ISO 13485. These firms will need to first obtain a copy of ISO 13485. Because ISO 13485 is published by a non-governmental organization, the International Organization for Standardization, it is not available for free. It can be purchased from ISO for $170.[5] Alternately, the material can also be found in a read-only format at the American National Standards Institute (ANSI) Incorporated by Reference (IBR) Portal. Because compliance with ISO 13485 will form the crux of FDA's revised regulations, even pending finalization of the QMSR, it will be important for manufacturers not yet experienced with the ISO requirements to carefully determine the distinctions between their current QSR procedures and the provisions of the ISO standards.

b. Anticipated Impacts on FDA

FDA intends to replace its current inspectional approach for medical devices, the Quality System Inspection Technique (QSIT), with an inspectional approach that will be consistent with the revised Part 820 and ISO 13485.

We expect the inspectional approach to remain similar to the QSIT format, and, as currently, inspections would involve the collection of information to support observations noted during the inspection and, where appropriate, listed on a Form FDA-483. However, the roll-out of a new inspectional approach will also require the retraining of all FDA Investigators working within the Office of Medical Device and Radiological Health Operations (OMDRHO). As well as retraining Investigators, FDA has indicated that it may also need to update internal procedures, processes, and policies to address the new QMSR when finalized.[6] We expect these to be time- and resource-consuming efforts, but the Agency has stated that it intends to complete these activities while continuing to carry out inspections. It remains to be seen how the completion of FDA's internal activities to ensure appropriate implementation of the new QMSR will align with the effective date of the new regulations, which, as noted above, is proposed to fall one year after the date of their publication. We also anticipate the possibility that the added efforts to complete internal retraining and related activities may have ramifications for FDA's ability to address current inspectional backlogs resulting from the COVID-19 pandemic.

Another potential impact arises from the fact that currently, notified bodies auditing firms for ISO 13485 certification or MDSAP certification have access to internal audits, supplier audits, and management review material. FDA, by policy, has denied its Investigators access to these documents. There is a growing consensus—and concern—that FDA will remove this restriction in the new QSIT and allow FDA Investigators access to these quality system records. Although only speculative at this point, such a change would be significant and could provide Investigators a direct roadmap in an inspection to the weakest areas of a firm's quality management system.

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Although the final rule may not take the same format as the proposed rule in all respects, there is no question that compliance with ISO 13485 will be required in the coming years for medical devices sold on the US market. Additionally, as FDA recognizes, simply integrating ISO 13485 into the existing QSR "by reference" without clarification or modification to the existing standard could create some inconsistencies with FDA's statutory and regulatory framework, and, as explained above, has proposed modifications, additions, and revisions to certain ISO 13485 provisions. We, therefore, strongly encourage firms to become familiar with additional definitions, clarifying concepts, and additional requirements being proposed, all of which would require compliance within a manufacturer's QMS in addition to ISO 13485.

We encourage clients to submit comments to the docket as appropriate, and welcome the opportunity assist with any questions you may have as you transition your QMS to conform with the ISO 13485 standard.

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[1] Although FDA intends to incorporate ISO 13485:2016, specifically, into the QSMR, for convenience and consistency with FDA's Federal Register notice, this Client Alert refers to the current version of the standard simply as ISO 13485.
[2] FDA, Medical Devices; Quality System Regulation Amendments; Proposed Rule, 87 Fed. Reg. 10119 at 10127 (Feb. 23, 2022).
[3] Id at 10126.
[4] Id.
[5] At current exchange rates. The ISO's online store is priced in Swiss Francs.
[6] FDA, Proposed Rule: Quality System Regulation Amendments - Frequently Asked Questions.