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The Wait is Over (or is it?): Assessing the Proposed Rule Aligning FDA's Medical Device Quality System Regulation with ISO 13485:2016

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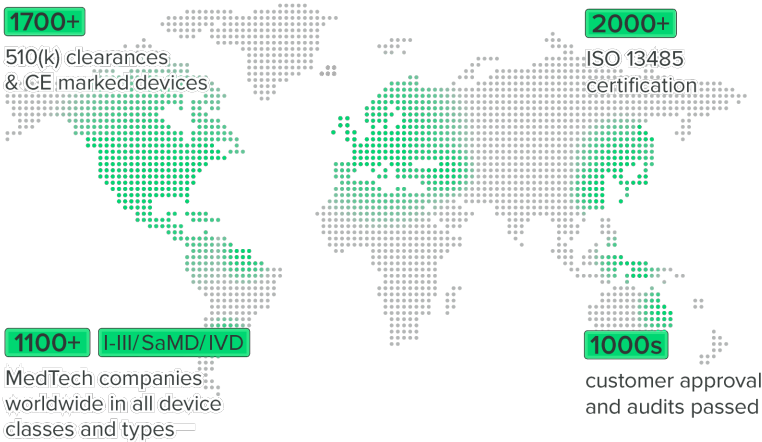

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Profile

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Eric Henry is a Senior Quality Systems and Compliance Advisor in the FDA and Life Sciences practice of the law firm King & Spalding. In this role Eric advises King & Spalding client staff, management, and boards on a variety of regulatory compliance matters including Quality System establishment and remediation, establishment of quality organizations, audit and inspection management and response, compliance-related due diligence reviews for M&A, training, and serving as expert witness during litigation.

Eric is an industry veteran, with over 33 years leading and coaching global organizations through a wide variety of quality and compliance challenges.

Prior to King & Spalding, Eric led global technical and quality organizations at Philips, Medtronic, GE Healthcare, Boston Scientific, and Hologic.

Prior to entering the medical device industry, Eric led a software quality management and program management office consulting capability in the Washington, DC area and held software design and development leadership roles in a small startup, a mid-size healthcare software company, a large financial services regulator and stock market, and a large retail organization.

The Quality System Regulation (QSR) (i.e. 21 CFR Part 820) and Its Scope

The Quality System Regulation

- Effective 1 June 1997
- Replaced 1978 GMP for medical devices
- Harmonized to ISO 13485:2003

Scope

- Domestic and foreign manufacturers of finished medical devices (FMDs) (not component manufacturers although supplier controls may influence expectations at this level)
- Methods and facilities involved in design, manufacturing, packaging, labeling, storage, installation, and servicing of FMDs (may extend beyond FMD manufacturers)
- Finished medical devices intended for use in the U.S. (including territories, DC, PR)

The One Fundamental Requirement (21 CFR §820.5)

- “Each manufacturer shall establish and maintain a quality system that is appropriate for the specific medical device(s) designed or manufactured, and that meets the requirements of this part.”
- A product not manufactured in compliance with the QSR is deemed “adulterated” and subject to regulatory action (even if it meets specifications and is safe and effective).

High-Level Walkthrough of 21 CFR Part 820 (1 of 2)

- ***Management Controls (*)***
  - Quality Policy
  - Organization
    - Manager with Executive Responsibility
    - Management Representative
  - Management Review
  - Quality Planning
  - Quality System
  - Quality Audit
  - Personnel (Training, Education, Experience)
- ***Design Controls (*)***
  - Design and Development Planning
  - Design Inputs
  - Design Outputs
  - Design Review
  - Design Verification
  - Design Validation
  - Design Transfer
  - Design Change
  - DHF
- ***Document Controls***
  - Approval
  - Changes
- ***Purchasing Controls***
  - Evaluation
  - Maintenance

(*) QSIT Element

High-Level Walkthrough of 21 CFR Part 820 (2 of 2)

- ***Production and Process Controls (*)***
  - Process changes
  - Environmental Controls, Personnel, Contamination Controls, Buildings, Equipment, Material Management
  - Software Validation
  - Inspection / Test Equipment, Calibration
  - Process Validation (or verification)
  - Nonconforming Product
  - Acceptance
- ***Corrective Action / Preventive Action (*)***
  - Investigation
  - Data Analysis (including statistical analysis)
  - Containment
  - Correction
  - Corrective Actions
  - Preventive Actions
  - Verification of Effectiveness
- ***Product Identification***
  - Identification
  - Traceability
- ***Packaging / Labeling***
- ***Handling, Storage, Distribution, Installation***
- ***Records***
  - DMR
  - DHR
  - Quality System Records
  - Complaints
- ***Service***
- ***Statistical Techniques***

(*) QSIT Element

What is Happening to the QSR?

1996 – Present: No significant changes to QSR

2018: FDA announced plans to reexamine the QSR to blend with requirements of ISO 13485 and align with other regulatory authorities

2018 – 2022: FDA missed at least five internal deadlines to modify the QSR

23 February 2022: FDA published a proposed rule to amend 21 CFR Part 820 and Part 4 (Combination Products) to incorporate by reference ISO 13485:2016 (QSR renamed QMSR)

2 March 2022: FDA convened the Device Good Manufacturing Practice (DGMP) Advisory Committee in a public meeting to review and make recommendations regarding the proposed rule (Section 520(f)(1)(B) of the FD&C Act)

24 May 2022: Comment period on the proposed rule closed

??? FDA will issue the final rule amending 21 CFR Part 820 (QMSR) and Part 4– more on this later

Why ISO 13485?

ISO 13485

- Initial version in 1996 as an adaptation of ISO 9001 (general quality management system requirements)
- Governs Quality Management System (QMS) requirements for medical device manufacturing
- Recognized in a variety of geographies (e.g., the European Union (harmonized under EU MDR), Canada, Australia, Japan)

Scope of ISO 13485

- Organizations that provide medical devices and related services including design and development, production, storage and distribution, installation, or servicing of a medical device and design and development or provision of associated activities (e.g., technical support).
- External parties that provide product, including quality management system-related services to such organizations.

Relationship Between FDA and ISO 13485

- FDA was a key participant in the 1996 initial release of ISO 13485
- FDA continues to be heavily involved in ISO/TC 210 through the American National Standards Institute (ANSI)
- FDA participates in the Medical Device Single Audit Program (MDSAP), which is based on ISO 13485:2016, and accepts MDSAP audit reports in lieu of routine FDA inspections
- ISO 13485:2016 remains “substantively similar” to the QSR

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.

FDA's Authority to Make this Change

"We are proposing to issue this rule under the same authority that FDA initially invoked to issue the current part 820 and combination product regulations…"
Preamble to the Proposed Rule

- "The Secretary may, in accordance with subparagraph (B), prescribe regulations requiring that the methods used in, and the facilities and controls used for, the manufacture, pre-production design validation … , packing, storage, and installation of a device conform to current good manufacturing practice, as prescribed in such regulations, to assure that the device will be safe and effective and otherwise in compliance with this Act …" — FD&C Act § 520(f)(1)(A)

What Does "Incorporate by Reference" Mean?

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.

Note: Incorporating ISO 13485 by reference also incorporates two other ISO standards (ISO 14971 (risk management) and ISO 9000 (definitions).

Propose Structure & Items of Interest (1)

21 CFR §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.

Propose Structure & Items of Interest (2)

21 CFR §820.3 (Definitions)

“Establish” replaced by the ISO 13485 term “documented.”
“Management with executive responsibility” replaced by the ISO 13485 term “top management.”
“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).
“Component,” “finished device,” “human cell, tissue, or cellular or tissue-based product (HCT/P),” “design validation,” “remanufacture,” “nonconformity,” and “verification” are retained.
“Device” and “labeling” in the Food Drug and Cosmetic Act (FD&C Act) are retained and supersede the ISO 13485 definitions.
“Manufacturer” and “product” 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.”

Propose Structure & Items of Interest (3)

21 CFR §820.7 (Incorporation by Reference)	
21 CFR §820.10 (Requirements of a Quality Management System)	Incorporates the quality system requirements of ISO 13485, while 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.
	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).
	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.
	Reminder that failure to comply with the requirements of 21 CFR Part 820 (and, by extension, ISO 13485) renders a device adulterated.

Propose Structure & Items of Interest (4)

21 CFR §820.15 (Clarification of Concepts)	"Organization" in the ISO standard equates to the QMSR term "manufacturer."
	"Safety and performance" in the ISO standard equates to the FD&C Act term "safety and efficacy."
	"Validation of processes" in the ISO standard equates to the QMSR term "process validation."
21 CFR §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.
21 CFR §820.45 (Device Labeling and Packaging Controls)	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.

Additional Structural and Content Takeaways

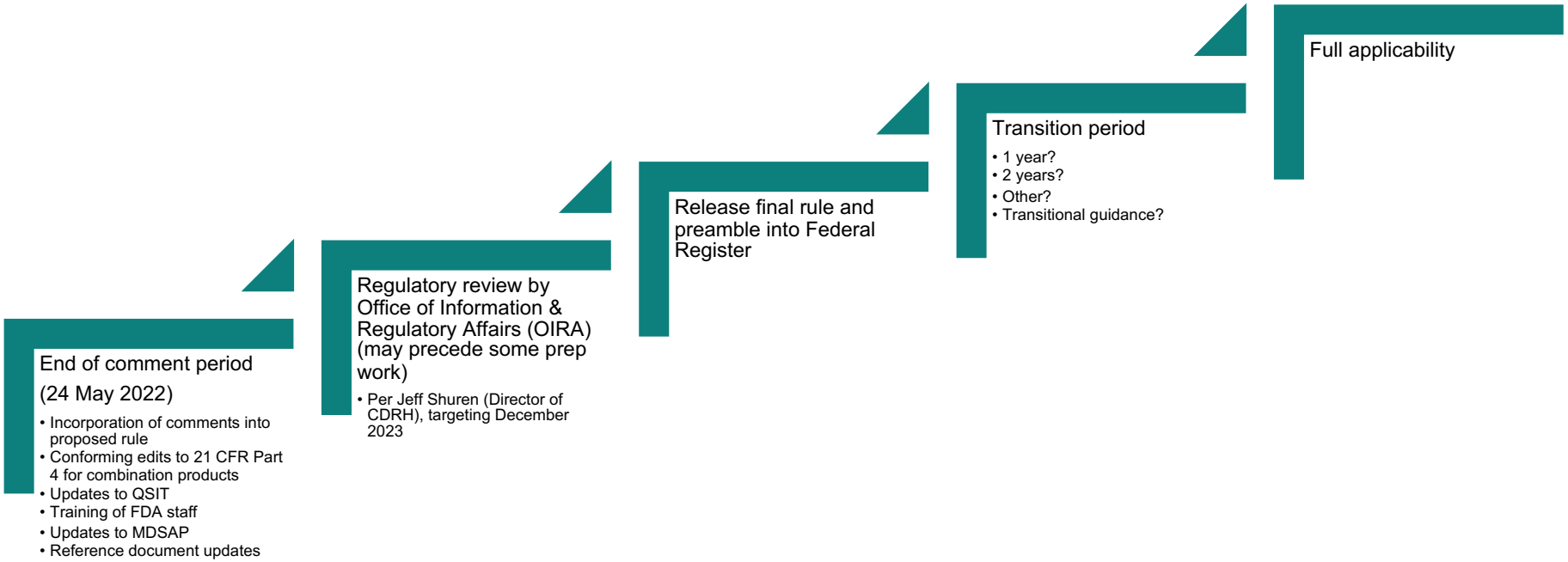
Risk Management

- The QSR 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.
- ISO 13485 requires a documented risk management process (clause 7.1) and post-market feedback into the risk management process (clause 8.2.1).

DMR/DHF/DHR

- 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
- DMR/DHF/DHR 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.
- "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."

The Rollout


End of comment period
(24 May 2022)
• Incorporation of comments into proposed rule
• Conforming edits to 21 CFR Part 4 for combination products
• Updates to QSIT
• Training of FDA staff
• Updates to MDSAP
• Reference document updates
Regulatory review by Office of Information & Regulatory Affairs (OIRA) (may precede some prep work)
• Per Jeff Shuren (Director of CDRH), targeting December 2023
Release final rule and preamble into Federal Register
Transition period
• 1 year?
• 2 years?
• Other?
• Transitional guidance?
Full applicability

Impacts

Industry

QMS changes
- If 13485 certified, relatively small changes to accommodate QMSR
- If not 13484 certified, possibly significant changes to accommodate QMSR (including adoption of ISO 14971)

Access to the standard
- Purchase from a variety of online standards stores (e.g., ISO, ANSI, AAMI)
- View-only version at the ANSI Standards Incorporated by Reference (IBR) site: ISO IBR Standards Available (ansi.org)

Leveraging ISO 13485:2016 certificates
- FDA inspections will not result in issuance of ISO 13485:2016 certificates
- FDA is not developing an ISO 13485:2016 certification program
- ISO 13485:2016 certificates do not exempt firms from FDA inspections

FDA

QSIT updates
- Office of Medical Deice & Radiological Health Operations (OMDRHO) training required
- Removal of restriction regarding the request of management review minutes, internal audit reports, and supplier audit reports

Potential conflicts with current statutory authority
- Implementation of ISO 13485:2016 may cause unforeseen conflicts with current statutory authority under the FD&C Act

Managing the transition period
- Transitional guidance similar to 1997?
- How to assess QMSR observations that would not have been QSR observations during transition
- How to assess QSR observations that are not QMSR observations during transition

Questions?