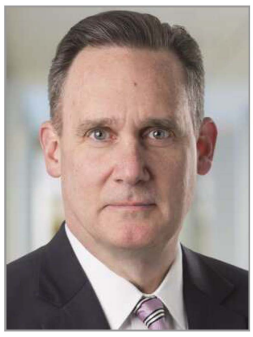
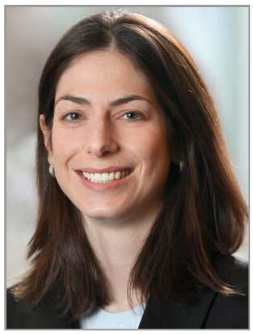
Comparing FDA Medical Device Proposal With Global Rules

By **William McConagha, Jennifer Bragg and Maya Florence** (March 10, 2022, 5:28 PM EST)



William McConagha

Jennifer Bragg



Maya Florence

On Feb. 22, the U.S. Food and Drug Administration proposed a long-awaited rule to amend its quality system regulation, which is codified at Title 21 of the Code of Federal Regulations, Part 820, and sets forth current good manufacturing practice standards for medical devices.

The new rule also proposes corresponding changes to Title 21 of the Code of Federal Regulations, Part 4, relating to current good manufacturing practice requirements for combination products that contain device constituent parts.

If adopted, the rule would bring U.S. standards more in line with the consensus international standard for medical device current good manufacturing practice standards, International Organization for Standardization 13485.

ISO 13485 is a medical device regulation established by the International Organization for Standards, an independent, nongovernmental organization that develops and publishes international standards with input from standards bodies around the world.

Like Part 820, ISO 13485 sets quality management system standards for the entire life cycle of a medical device, including design and development, production, storage and distribution, installation, servicing, and final decommissioning and disposal of medical devices. The current edition of ISO 13485, which received input and support from the FDA, was adopted in 2016 and has gained significant traction globally.

The medical device industry has been expecting the FDA to adopt ISO 13485 in some capacity since early 2018, when the plans to harmonize the quality system regulation with ISO 13485 first appeared in the agency's biannual unified agenda. If finalized, the rule would mark an important step toward global harmonization of medical device regulation.

Summary of the Proposed Rule

The rulemaking proposes to incorporate the current version of ISO 13485 into Part 820 by reference. If the quality system regulation amendment is finalized, the requirements of the current Part 820 would be withdrawn and replaced with ISO 13485, except for a few "definitions, clarifying concepts, and additional requirements" that the FDA has determined are necessary to preserve certain key elements of Part 820 and to ensure the rule conforms to the Federal Food, Drug and Cosmetic Act.

The new regime would become known as the Quality Management System Regulation. Only the current 2016 version of ISO 13485 would become part of the QMSR; any future revisions to the ISO standard would not alter the final rule, and would only become part of the FDA's regulatory regime if the agency adopted the revised standard by additional amendment through the rulemaking process.

In the preamble to the proposed rule, the FDA emphasizes that the requirements in ISO 13485 are,

when considered in totality, substantially similar to the requirements of the current Part 820. The agency recognizes, however, that adopting ISO 13485 without some modification could create inconsistencies with the FDA's broader statutory and regulatory framework. Accordingly, the rulemaking proposes several discrete changes to ISO 13485.

Some noteworthy deviations include:

Definitions

The rulemaking proposes to incorporate several FDA-specific definitions into ISO 13485 to avoid creating inconsistencies with the FD&C Act and its implementing regulations. For example, the definitions of "device" and "labeling" in Part 820 would supersede the correlating definitions of "medical device" and "labeling" in ISO 13485.

Design and Development

The rulemaking also proposes to clarify that Clause 7.3 of ISO 13485, concerning design and development, only applies to certain manufacturers of Class I devices, in addition to all manufacturers of Class II and III devices, i.e., the same scope as the current Section 820.30(a).

The FDA asserts this modification is consistent with Clause 1 of ISO 13485, which states that a regulatory authority may implement certain exclusions from the design and development requirements as it deems appropriate.

Traceability Requirements

While both the proposed rule and ISO 13485 contain traceability requirements, the requirements in ISO 13485 only apply to implantable devices. Consistent with current unique device identifier requirements under Part 820, the proposed rule would add a requirement to apply traceability requirements to all devices that support or sustain life, regardless of whether the device is implantable.

Labeling and Packaging

The proposed rule would also retain current labeling and packaging requirements in Part 820, which are not meaningfully addressed by ISO 13485. Citing the fact that many device recalls in the U.S. are related to labeling and packaging, the FDA proposes to retain the labeling and packaging requirements in the quality system regulation in their current form.

The proposed rule also includes conforming edits to Title 21 of the Code of Federal Regulations, Part 4, which governs current good manufacturing practice for combination products, to ensure that Part 4 includes updated references to the corresponding clauses of ISO 13485 rather than the existing Part 820.

The FDA characterizes these edits as strictly technical and asserts they will not affect the current regulation of combination products that contain device constituent parts.

Advisory Committee Meeting

On March 2, the FDA's device good manufacturing practice advisory committee met to discuss the proposed rule and transition to ISO 13485.

Stakeholder comments during the meeting indicated that the proposed change has broad support across the industry, although there are concerns about FDA's proposals to preserve certain elements of the current quality system regulation as well as the amount of time regulated entities will need to effectuate the transition. We expect the committee will likely convene again prior to finalizing the rule.

Implications for the Industry

If finalized, the rule would support global harmonization of medical device regulation, which the FDA

stated is its primary purpose for adopting ISO 13485 into its regulations.

The agency reasoned that harmonization of regulatory compliance efforts not only benefits manufacturers from a cost-savings perspective, but also helps patients access newly developed medical devices sooner than patients can in a fractured regulatory environment.

But as expected, the FDA did not propose to adopt ISO 13485 without change, and many stakeholders in the industry are concerned that the FDA's proposed deviations from the international standard will limit the intended benefits of the QMSR.

One of the most notable differences between the regimes is that ISO 13485 places a greater emphasis on risk-management activities and risk-based decision making than the current Part 820 does.

Specifically, the current Part 820 only addresses risk management in the design validation requirements in Section 830.30(g), whereas risk management is more broadly integrated throughout ISO 13485.

As stated in the preamble to the rulemaking, risk management for device manufacturers is "the essential systematic practice of identifying, analyzing, evaluating, controlling, and monitoring risk throughout the product lifecycle to ensure that the devices they manufacture are safe and effective."

Many global medical device companies have enhanced their risk-management processes over the last decade in response to ISO, but for those who operate solely under the aegis of Part 820, adoption of ISO 13485 will necessitate a fresh look at these issues.

We also expect that, once the rule is finalized, the FDA will have a renewed focus on management controls. This includes a focus on how medical device companies attempt to integrate the updated rule into their new QMSRs as well as a focus on management's overall vigilance in life cycle oversight of its medical devices from a quality perspective.

The economic analysis in the proposed rule presumes adoption of ISO 13485 should not require an overhaul of a quality system, as QMSR and quality system regulation requirements already align, but we anticipate an emphasis on management's commitment to life cycle concepts such as risk management moving forward.

To this end, the FDA plans to change its quality system inspection program for devices in the new regime. In the rulemaking, the agency committed to replacing its current approach — the quality system inspection technique — with a new approach consistent with the updated regulations.

The rulemaking offered little detail on what the new inspections would involve, aside from stating that inspections will not result in the issuance of certificates of conformance to ISO 13485, and conversely, manufacturers with a certificate of conformance to ISO 13485 will not be exempt from FDA inspections.

Even so, as highlighted during the advisory committee meeting, ISO 13485 certification remains an ambiguous area under the new regime, including whether ISO 13485 certification will be required or expected.

As the FDA's approach to inspections evolves, we expect the agency to build on its experience with the Medical Device Single Audit Program, which allows an MDSAP-recognized auditing program to conduct a single regulatory audit that can be leveraged by all governmental bodies participating in the program.

The FDA has been a MDSAP member for several years and cites its experience with the program as an important factor in its decision to transition to ISO 13485. The FDA has accepted MDSAP audit reports as a substitute for routine agency inspections, and this should continue given the FDA's focus on global harmonization in the preamble to the proposed rule and the corresponding economic analysis.

MDSAP has published guidance on how to conduct audits, and we expect, and urge, the FDA to

clarify its own updated approach to QMSR investigations under the new ISO 13485 paradigm.

Those hoping the transition to ISO 13485 might offer a reprieve from certain unique aspects of Part 820 should temper expectations. The FDA has clearly weighed the differences between the regimes and retained those essential elements of Part 820 it feels are not adequately addressed in the ISO standard. The agency proposes to retain current controls for labeling and packaging in the proposed Section 820.45 and to strengthen language related to medical device reporting and servicing activities in the proposed Section 820.35.

The proposed language on records controls also underscores the FDA's enduring focus on data integrity as a hallmark of a healthy quality system. The FDA's emphasis on data integrity and contemporaneous documentation has been well documented over the last decade, and the specific language on recordkeeping signals that trend should continue.

While the FDA is intent on preserving these essential elements of quality system regulation, the rulemaking does not appear designed to otherwise extend the reach of Part 820 or revisit current risk-based distinctions based on device classification.

As noted, the proposed rule reaches into certain aspects of medical device reporting under Title 21 of the Code of Federal Regulations, Part 314, but the FDA has generally been careful to keep application of ISO 13485 from being overbroad.

For example, the FDA proposes to retain the current distinctions in Title 21 of the Code of Federal Regulations, Part 820.30(a), related to design controls, and it seems inclined to preserve current distinctions between manufacturing and servicing such that the latter does not get swept under ISO 13485.

There is also no suggestion in the proposal that the FDA is revisiting any prior decision to exempt Class I medical devices from the quality system regulation, or aspects of the quality system regulation, in its classification regulations.

One important consideration moving forward, as highlighted by comments from stakeholders at the advisory committee meeting, is the adequacy of the transition period once the rule is finalized. The FDA proposes the regulation should become effective one year after the date the rule is finalized, which we view as an ambitious timeframe given the scope of work involved.

Medical device manufacturers steeped in compliance with Part 820 will need to evaluate the QMSR and assess how differences may apply to their product lines. Standard operating procedures and work instructions will need to be updated and the army of employees touched by quality system regulation will need to be trained on new procedures and new vocabulary.

Iconic terms like "device master record," will disappear from the industry vernacular to be replaced by terms like "medical device file." The transition may prove even more challenging for smaller domestic manufacturers that do not sell globally and thus have much less current experience with ISO 13485 than multinational corporations, especially if the FDA decides to require ISO 13485 certification as part of the new regime.

In other contexts, the FDA has given the industry longer periods of time to adjust to major new rulemakings. Examples include track and trace requirements for prescription drugs as well as the current good manufacturing practice and adverse event reporting requirements for combination products. We urge the FDA to give the industry the time it needs to overhaul its systems, even if the concepts in the new Part 820 generally align with the old.

A transition of this magnitude also takes time for the FDA, regardless of how closely the Part 820 and ISO 13485 align.

The rulemaking process alone will be resource-intensive for the agency, and the updated regulation will require training on the new requirements, development of new guidance documents to internal and external audiences, and enhanced coordination between program officers at the Center for Devices and Radiological Health, the Office of Regulatory Affairs, and the Office of the Commissioner.

The FDA itself acknowledges the need to update IT systems, refine its inspection approach and revise relevant regulations affected by the new rule.

As it relates to combination products, we also urge industry to carefully track how the incorporation of ISO 13485 affects the corresponding amendments made to Title 21 of the Code of Federal Regulations, Part 4.

The current hybrid current good manufacturing practice requirements for drug-device combination products are grounded in an exacting comparison between Title 21 of the Code of Federal Regulations, Parts 211 and 820.

How the changes to Part 820 will impact the approach is yet unclear. The FDA has specifically asked for feedback on this issue, and we encourage participation. The proposed changes reinforce that the impact of the new rules will reach well beyond medical device manufacturers.

Drug and biological manufacturers who combine or co-package their products with drug delivery systems will have to account for, and respond to, the changes under ISO 13485, even though they are manufacturers of medicinal products in the first instance.

For example, the enhanced focus on life cycle risk management in ISO 13485 could have impacts for drug companies that sell lifesaving medicines in autoinjectors or inhalers.

Next Steps

The rule's public comment period will remain open until May 24. If finalized, the rule would take effect one year after the final rule's publication in the Federal Register, unless the FDA decides to extend the transition period in response to industry concerns.

William McConagha, Jennifer Bragg and Maya Florence are partners at Skadden Arps Slate Meagher & Flom LLP.

Skadden associate Michael Darling contributed to this article.