REGULATORY FOCUS

Getting ready for the FDA's upcoming QMSR

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The FDA's Quality Management System Regulation (QMSR) proposal, paired with the International Organization for Standardization's ISO 13485:2016, is expected to deliver cost savings to medtech organizations that adhere to both requirements. This article covers the differences between QMSR, ISO 13485:2016, and the Medical Device Single Audit Program (MDSAP) so leaders can prepare for the upcoming changes.

Keywords – MDSAP, quality management, quality system regulation, QMSR

Introduction and background

The US Food and Drug Administration (FDA) has not significantly revised 21 CFR Part 820 since 1996.[1] That was also when the first edition of ISO 13485 was released, though it has since been updated twice and is currently available as ISO 13485:2016.[2] As the foundation for many regulatory authorities, the international standard specifies requirements on quality management systems for organizations involved in one or more lifecycle stages of medical devices.

ISO 13485 is also the basis for the International Medical Device Regulators Forum's (IMDRF's) Medical Device Single Audit Program (MDSAP).[3] In 2012, the same year the MDSAP working group was formed, FDA piloted a program to accept a manufacturer's ISO 13485:2003 certificate instead of the FDA's routine inspection. While that program is no longer operated, the FDA gained confidence in the application of ISO 13485 and concluded that Part 820 and ISO 13485 pose similar requirements. The FDA is proposing a change to the Quality System Regulation (QSR), 21 CFR Part 820, the primary difference being the inclusion of ISO 13485:2016 by reference.

The new title is Quality Management System Regulation (QMSR).[4] The FDA does not plan on issuing ISO 13485:2016 certificates, nor will such a certificate exempt a manufacturer from an FDA inspection, yet it does aim to rework the current QSIT (quality system inspection technique).

It is crucial for medtech companies to understand the additions to QMSR on top of ISO 13485:2016, and the difference between the proposed QMSR and current MDSAP requirements to ensure long-term compliance. This article provides information for organizations that are already ISO 13485:2016 certified or audited under MDSAP that are planning to do a gap analysis of the upcoming QMSR.

ISO 13485:2016 requirements vs. proposed QMSR

The QMSR proposal, specifically the high-level mapping provided by FDA in Table 1 of the document,[5] mentions that ISO 13485:2016 requirements are substantively similar to the current Part 820 in most respects, excluding four subparts of Part 820, which are addressed in the proposed § 820.35 and § 820.45. The three key differences between the proposed QMSR and ISO 13485:2016 are definitions, confidentiality, and the signature of records.

Definitions

The FDA suggests different definitions as part of the proposed QMSR. The term "customer," for example, is proposed by the FDA as "persons or organizations, including users, that could, or do, receive a product or a service that is intended for, or required by, this person or organization. A customer can be internal or external to the organization."

The first sentence is identical to the definition of ISO 9000:2015 (3.2.4),[6] which is included in ISO 13485:2016 by reference. The second sentence is also stated in ISO 9000:2015 as a clarifying note to this definition. It seems the FDA would benefit from explaining their intent in the QMSR preamble on how ISO notes should be interpreted and eliminate this country-specific definition.

Similar cases could be made for the differing definitions of "product" and "top management." Other differences in terminology are clearer. For example, FDA

retains the definition of “process validation” instead of using the term “validation of processes” used in ISO 13485:2016.

On the one hand, the FDA explicitly notes that some terms and definitions are retained without change as they are necessary for implementing Part 820: “component,” “finished device,” “human cell, tissue, or cellular or tissue-based product (HCT/P) regulated as a device,” “design validation,” “remanufacturer,” “nonconformity,” and “verification.[4] On the other hand, it will not retain the definition of device master record, as the medical device file of ISO 13485:2016 is substantively similar.[7]

Confidentiality

The approach to confidentiality between ISO 13485:2016 and the current Quality System Regulation (QSR) differs in documentation of internal audits and management reviews. FDA auditors are currently limited by QSR 820.180(c) in that respect, whereas ISO 13485:2016 does not take the same approach.

This approach can prove challenging since open insights, and especially findings in internal audits, can be positive as long as corrections are underway to address the findings of investigations. A culture in which quality teams are error-evasive is far riskier than openly discussing errors and tracking improvements across departments.

Signature of records

The addition to Clause 4.2.5 in ISO 13485:2016 in the proposed § 820.35[8] notes a significant change for quality leaders, specifically “... the manufacturer must obtain the signature for each individual who approved or re-approved the record, and the date of such approval, on that record (...).”[2] This new requirement will likely lead to modifications and revalidation efforts among many organizations’ quality management systems.

Modern quality systems can make this process seamless through workflow customizations. They also add 21 CFR Part 11 compliant e-signatures and the respective dates without compromising the existing system validation.

Current MDSAP requirements vs. proposed QMSR

The latest MDSAP audit approach (April 2022)[9] lists 21 country-specific requirements for the US, of which 12 reference the current 21 CFR Part 820. The following list covers these 12 items in order of appearance in the MDSAP audit, including a comment on the differences between the respective country-specific MDSAP requirement and the proposed QMSR.

Chapter 1, Task 8 – Document and record controls

What it says Verify that electronic records and documents have backups [21 CFR 820.180]

Analysis This requirement has not been transferred to the proposed QMSR. For business continuity purposes, it is good to check with your platform provider to understand how your electronic quality system is backed up. Platforms that are

not life-science-specific often struggle to fulfil this requirement or only provide this service at additional costs.

Chapter 3, Task 1 – Procedures for measurement, analysis, and improvement of QMS effectiveness and product conformity

What it says Verify procedures ensure that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of problems [21 CFR 820.100(a)(6)]. Confirm procedures provide for the submission of relevant information on identified quality problems, as well as corrective and preventive actions, for management review [21 CFR 820.100(a)(7)].

Analysis This requirement was not transferred to the proposed QMSR. The FDA views Part 820 Subpart J (Sec. 820.100) and ISO 13485:2016 (Clause 8.5) as "substantively similar." [5]

Chapter 3, Task 12 – Evaluation of information from post-production phase, including complaints

What it says See MDSAP Audit Approach, page 74, 75[9]

Analysis This country-specific requirement was partially transferred to the proposed § 820.35 of QMSR,[10] which also references 21 CFR Part 803[11] on medical device reporting. The requirement to keep a record of "any reply to the complainant" was already present in 21 CFR Part 820.198[12] and transferred to the proposed § 820.35 of QMSR. However, the reply to the complainant was not explicitly mentioned in the MDSAP country-specific requirement. The MDSAP still notes the requirement from the current 21 CFR Part 820.198 to record the "dates and results of investigation," which was not explicitly transferred to the proposed QMSR.

Chapter 5, Task 4 – Implementation of the design and development process

What it says Verify that the design input procedures contain a mechanism for addressing incomplete, ambiguous, or conflicting requirements [21 CFR 820.30(c)].

Analysis This requirement was not transferred to the proposed QMSR. While not mentioning the mechanism as part of the design input procedures directly, ISO 13485:2016 covers this in Clause 7.3.3: "Requirements shall be complete, unambiguous, able to be verified or validated, and not in conflict with each other."

Chapter 5, Task 8 – Risk management activities applied throughout the design and development project

What it says Confirm that the manufacturer has identified the possible hazards associated with the device in both normal and fault conditions. The risks associated with the hazards, including those resulting from user error, should be calculated in both normal and fault conditions. If any risk is judged to be unacceptable, it should be reduced to acceptable levels by the appropriate

means. Ensure changes to the device to eliminate or minimize hazards do not introduce new hazards [21 CFR 820.30(g); preamble comment 83].

Analysis This requirement has not been transferred to the proposed QMSR. One topic of the QSR that the FDA specifically called out in the preamble of the proposed QMSR was that ISO 13485:2016 "has a greater emphasis on risk management activities and risk-based decision making than the current Part 820." As such, this country-specific requirement on product risks (hazards leading to harm) is covered by ISO 13485:2016 and its reference to ISO 14971.

This does not change the FDA's philosophy of "expected risk management throughout a QMS and the total product lifecycle."[4]

For additional guidance on integrating risk-based approaches in your quality management system beyond product risks, read the GHTF SG3 N15[13] document and review the information provided by MDIC's Case for Quality CAPA program.[14]

Chapter 5, Task 14 – Design review

What it says Verify that procedures ensure that participants include representatives of all functions concerned with the design stage being reviewed and an individual(s) who does not have direct responsibility for the design stage being reviewed, as well as any specialists needed [21 CFR 820.30(e)].

Analysis This requirement has not been transferred to the proposed QMSR. ISO 13485:2016 Clause 7.3.5 already covered most of this country-specific requirement. The only difference was that ISO 13485:2016 does not mention the "individual(s) who does not have direct responsibility for the design stage being reviewed."

Chapter 6, Task 7 – Identification of processes subject to validation

What it says Process validation is required for sterilization, aseptic processing, injection molding, and welding [21 CFR 820.75; preamble comment 143].

Analysis This requirement was not transferred to the proposed QMSR. The FDA views Part 820 Subpart G (820.75 and preamble comment 143) and ISO 13485:2016 (clauses 7.5.6 and 7.5.7) as "substantively similar."[5]

This specificity on process validation never made its way into 21 CFR 820.75 but is likely present in MDSAP due to the preamble comment 143 of QSR mentioning "sterilization, aseptic processing, injection molding, and welding" as an explanation and examples of processes that "cannot be fully verified by subsequent inspection and test." As such, QSR (without the preamble comment) has already been aligned with the flexible wording in ISO 13485:2016.

Chapter 6, Task 16 – Device master file

What it says If a control number is required for traceability, confirm that a control number is on or accompanies the device throughout distribution [21 CFR 820.120(e)].

Analysis This is an important new country-specific requirement, as it has not been translated 1:1 into the proposed QMSR but included by a different approach, referencing ISO 13485:2016 Clause 7.5.9.2 (proposed § 820.10(d)).[15]

The MDSAP requirement originates in the current 21 CFR Part 820.120(e), which references 820.65, wherein traceability is required throughout distribution for implants and devices that "support or sustain life."[12] ISO 13485:2016 has further traceability requirements mentioned in Clause 7.5.9.2. These go beyond ensuring that a control number is attached throughout distribution, adding, for example, the two requirements of (a) requiring "that suppliers of distribution services or distributors maintain records of the distribution of medical devices" and (b) maintaining records "of the name and address of the shipping package consignee."

It is important to note that Clause 7.5.9.2 of ISO 13485:2016 only applies to implants. The FDA proposes to expand this to devices that support or sustain life, which has seen a lot of debate in the public comments.[16] It will be intriguing to see how the FDA will react to the comments on this matter.

Chapter 6, Task 17 – Production record; evidence of compliance of released devices

What it says Verify that labelling is not released for storage or use until a designated individual has examined the labelling for accuracy, including, where applicable, the correct unique device identifier (UDI) or universal product code (UPC), expiration date, control number, storage instructions, handling instructions, and any additional processing instructions [21 CFR 820.120(b)].

Confirm that labelling is stored in a manner that provides proper identification and prevents mix-ups. Verify labelling and packaging operations are controlled to prevent labelling mix-ups [21 CFR 820.120(c) and (d)].

Verify that the label and labelling used for each production unit, lot, or batch are documented in the batch record, as well as any control numbers used [21 CFR 820.120(e), 820.184(e)].

Analysis FDA sees a gap in Clause 7.5.1 of ISO 13485:2016 to "specifically address the inspection of labelling by the manufacturer."[4] Therefore, this country-specific requirement was transferred to the proposed § 820.45 of QMSR.[17]

The first and third sections of this MDSAP requirement are almost identical to the proposed QMSR. The second section on control of labelling instead references Clause 4.2.5 of ISO 13485:2016 but also fulfills the same purpose.

Chapter 6, Task 21 – Acceptance activities

What it says Verify that the manufacturer establishes and maintains procedures to ensure that sampling methods are adequate for their intended use and

ensure that when changes occur, the sampling plans are reviewed [21 CFR 820.250(b)].

Analysis This requirement was not transferred to the proposed QMSR. The FDA views Part 820 Subpart O and ISO 13485:2016 (clauses 7 and 8) as "substantively similar."[5]

Chapter 6, Task 25 – Review of customer requirements, distribution records

What it says Verify that the manufacturer maintains distribution records which include or refer to the location of the name and address of the initial consignee, the identification and quantity of devices shipped; and any control numbers used [21 CFR 820.160(b)].

Analysis This requirement was not transferred to the proposed QMSR. The FDA views Part 820 Subpart L and ISO 13485:2016 (Clause 7) as "substantively similar."[5]

Chapter 6, Task 27 – Servicing activities

What it says Verify that each manufacturer who receives a service report that represents an event that must be reported to FDA as a medical device report automatically considers the report a complaint [21 CFR 820.200(c)].

Confirm that service reports are documented and include the name of the device serviced, any unique device identifier (UDI) or universal product code (UPC), and any other device identification(s) and control number(s) used; and the date of service [21 CFR 820.200(d)].

Analysis This requirement was partially transferred to the proposed QMSR. FDA addresses the differences between Part 820 Subpart N (Sec. 820.200) and ISO 13485:2016 (Clause 7) in the proposed § 820.35 of QMSR.[10]

Specifically, the first part of this country-specific requirement is already covered under ISO 13485:2016 Clause 7.5.4: "The organization shall analyse records of servicing activities carried out by the organization or its supplier: a) to determine if the information is to be handled as a complaint."

The second part has been transferred to the proposed § 820.35(b) of QMSR[10] and is a representation of the details also listed in 21 CFR Part 820.200.[18] It extends MDSAP's country-specific requirement by adding the individual(s) who serviced, information on the service performed, as well as test and inspection data on the service report.

Conclusion

Bringing all these details together for a holistic comparison between MDSAP and QMSR, it becomes clear that the FDA is stepping closer to international alignment by removing eight country-specific requirements. In some areas, it is fair to ask why legacy requirements from 21 CFR Part 820 are being transferred to QMSR, especially in cases where these requirements have not been country specific in MDSAP.

If the FDA works through IMDRF, that can help ensure future consistency in both QMSR and MDSAP approaches. As it stands right now, these slight differences in requirements do not change the fact that it makes absolute sense to track these explicitly mentioned data points on a single technology platform to ensure a holistic perspective. After all, proactive real-time tracking and data analysis in regular quality management reviews ensures faster reactions to quality events and can directly impact the bottom line.

More work lies ahead for everyone involved in this transition, and a few foundational questions remain:

- How realistic is the proposed 12-month transition period? Due to the similarities, it might be more straightforward for organizations already familiar with ISO 13485 and MDSAP but transitioning to QMSR without prior experience with ISO 13485 seems unrealistic in the suggested timeframe.
- How will the FDA handle updates to ISO 13485:2016? ISO usually reviews and updates standards more frequently than the FDA has done with its legislation.

Companies can better prepare for the upcoming changes with valuable insights and good reference points for gap analysis towards transitioning to QMSR. Evaluating and reworking the current QSR delivers an excellent opportunity for medical device and diagnostic organizations to harmonize quality systems with a focus on product effectiveness and patient safety.

Acronyms and abbreviations

CAPA, corrective action and preventative action; **CFR**, Code of Federal Regulations; **FDA,** [US] Food and Drug Administration; **GHTF**, Global Harmonization Task Force**; ISO**, International Organization for Standardization; **IMDRF,** International Medical Device Regulators Forum; **MDIC**, Medical Device Innovation Consortium; **MDSAP**, Medical Device Single Audit Program; **QMS**, quality management system; **QMSR**, quality management system regulation; **QSIT**, quality system inspection technique; **QSR**, quality system inspection technique; **UDI**, unique device identifier; **UPC**, universal product code;

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Citation Brehm P. Getting ready for the FDA's upcoming QMSR. Regulatory Focus. Published online 29 August 2022. https://www.raps.org/news-and-articles/news-articles/2022/8/getting-ready-for-the-fdas-upcoming-qmsr

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