Medical Devices; Quality System Regulation Amendments Docket No. FDA-2021-N-0507

Comments submitted by International Society for Pharmaceutical Engineering (ISPE)

regualtorycomments@ispe.org

GENERAL COMMENTS ON THE DOCUMENT
We applaud the Agency in their work to harmonize and streamline 21 CFR 820 with the international consensus standard ISO 13485:2016 used by other regulatory authorities in an effort to simplify quality system requirements for medical device and combination product manufacturers worldwide.
Upon implementation, we request that FDA and ISO make available, at no cost to the public, ISO 13485 and the other recognized consensus standards that are required to implement ISO 13485, such as ISO 9000, ISO 14971 and IEC 62366.
We request the Agency state that any standards referenced refer to the current FDA recognized version of the standard (i.e., recognized consensus standard). Any references in this proposed amendment to a standard version be removed. Examples include ISO 13485 and 14971.
We strongly recommend a longer implementation time (e.g., 3 years), 1 year after the date of publication is not sufficient for manufacturers to incorporate the changes into their quality systems, especially given the number of organizations that are involved in combination products.

Specific Comments on the Text

ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
B. Definitions (Proposed § 820.3) Page 10125	"Among the definitions being withdrawn from the current part 820 is the term ''establish''. Though the term establish is not defined in the ISO standard, section 0.2 states that when a requirement is required to be ''documented'', it is also required to be established, implemented, and maintained. We believe the clarification of this concept within the standard is sufficient to convey the current requirement for manufacturers to establish and maintain the regulatory requirements of a QMS."	We recommend keeping the term "establish" in 820 as it indicates to define, document, and implement. Document alone does not capture this intent.	"Establish" per 820.3(k) indicates to define, document, and implement. "Document" alone does not capture this intent. In addition, the word "establish" is included in the proposed amendment in the following locations: § Scope 820.1(a) ""...must establish and maintain a quality management system that is appropriate for its specific device(s)." § 820.3 Definitions."*Top management* means those senior employees of a manufacturer who have the authority to establish or make changes to the manufacturer's quality policy and quality management system" § 820.45 Device labeling and packaging controls. "In addition to the requirements of Clause 7.5.1 of ISO 13485 (incorporated by reference, see § 820.7), Control of production and service provision, each manufacturer must establish and maintain procedures that..." If FDA intends to retain certain 820 definitions, "establish" should be included.
B. Definitions (Proposed § 820.3) Page 10125	"We are also proposing to replace the term ''management with executive responsibility'' (see § 820.3(n)) in the current part 820 with the term ''top management'', which is used in ISO 13485, but is defined in ''Quality Management Systems — Fundamentals and Vocabulary,'' ISO 9000:2015 (ISO	We propose to maintain the term "management with executive responsibility" in 820 along with the current definition, or use "top management" with the same definition as in ISO 9000:2015.	FDA's current proposal to change the term, but keep the original definition, doesn't harmonize with ISO 13485 and manufacturers will still have to manage two different definitions. Management with executive responsibility also conveys the intent of the term more clearly than top

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
	9000) (Ref. 10). We propose to accomplish this by revising the name of the term to ‘‘top management’’ but retaining the definition in the current part 820.”		management (which is not as specific and is defined vaguely in ISO 9000:2015).
C. Incorporation by Reference (Proposed § 820.7) Page 10126	“We also propose to clarify that Clause 7.3 Design and Development applies only to the manufacturers of the class I devices that are listed in this provision in addition to all manufacturers of class II and III devices.”	“We also propose to clarify that Clause 7.3 Design and Development applies ~~only~~ to the manufacturers of the class I devices that are listed in this provision in addition to all manufacturers of class II and III devices.”	Recommend removing the word “only” since it may cause confusion as to which class of device the clause applies. Provide clarification in § Part 4 regarding design control exemptions for those Class I devices that are regulated as combination products. Per the FDA Guidance Current Good Manufacturing Requirements for Combination Products, Section III.C. Definitions and terminology, 3. *Drug containers and closures versus delivery devices,* Para 3. "...However, if a device that would ordinarily be exempt from all or certain provisions in is incorporated into a container closure system, for example if a dropper is incorporated into the cap of a bottle of a drug, this may be a new use of the device such that the exemptions from part 820 may not be applicable."
§ 820.3 Definitions Page 10133	*“Customer* means 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.”	“*Customer* means persons or organizations, including users, that **could receive, do receive, and/or use** 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.”	We recommend a revision to the definition of customer for clarity.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
B. Definitions (Proposed § 820.3) Page 10125	"Although FDA historically has not used the term ''customer'', we find it is a useful term and can encompass many types of individuals and organizations throughout the device manufacturing process, such as component manufacturers, contract manufacturers, and end users."	"Although FDA historically has not used the term ''customer'', we find it is a useful term and can encompass many types of individuals and organizations throughout the device manufacturing process, **in addition to the** ~~such as component manufacturers, contract manufacturers, and~~ end users."	Recommend not confounding definition of "customer" with definition of "supplier". Component manufacturers and contract manufacturers are suppliers, not customers. A supplier is subject to purchasing controls, a "customer" is not. Keeping this phrasing could generate confusion, especially when speaking to "customer property", as the language around customer property as the property of the end-user, not the CMO or component manufacturer that provided the component or part.
§ 820.3 Definitions Page 10133	**"***Finished device* means any device or accessory to any device that is suitable for use or capable of functioning, whether or not it is packaged, labeled, or sterilized."	Add the definition of "accessory" to 820.3	Accessory is not defined in the QMSR.

§ 820.3(a) and (b) Definitions Page 10133	**§ 820.3 Definitions** (a) "*Nonconformity* means the nonfulfillment of a specified requirement." "*Verification* means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled." (b) "*Product* means components, process agents, in-process devices, finished devices, and returned devices."	Replace the proposed 820 definitions of "nonconformity", "verification" and "product" with the ISO equivalents (including notes) and update the corresponding justification. • "nonconformity" - ISO 9000, Clause 3.6.9, including notes • "verification" - ISO 9000, Clause 3.8.12, including notes • "product" - ISO 13485, Clause 3.15, including notes	It is counterintuitive to have exceptions to definitions if the intent is to adopt by reference ISO 13485 as evidence of harmonization. Dual definitions could create confusion and challenges in compliance. In addition, some of the terms for which the FDA is proposing to retain their 820 definitions over the comparable ISO definition will result in conflicts when using a harmonized ISO/FDA term (e.g., corrective action) that references another term that is not harmonized. For example, "Nonconformity" is part of the definition of multiple ISO 13485 and 9000 terms (e.g., 3.12.11 preventive action; 3.12.2 corrective action; 3.12.9 repair). Changing the definition of nonconformity to refer to the FDA definition instead of the ISO definition will create significant confusion from the multiple terms and definitions. Regarding the Agency's comments on "verification": The only difference in the FDA definition is that it allows for "confirmation by examination" as well. Based on the referenced ISO 9000 definitions for "objective evidence", "inspection" and "determination", the concept of "confirmation by examination" appears to be covered. Regarding the Agency's comments on "product": It is not clear as to how the proposed FDA definition for "product" would clarify inclusion of "service" as compared to the ISO 13485 definition per 3.15 which clearly includes "service" as well as the clarification in Clause 0.2. In addition, the ISO 13485

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
			definition for “purchased product” per Clause 3.16 means “product provided by a party outside the organization’s quality management system”. As a result, "purchased product" includes "services".
B. Definitions (Proposed § 820.3) Page 10125 AND § 820.3(a) Definitions Page 10133	**§ 820.3 Definitions** (a) “*Rework* means action taken on a nonconforming product so that it will fulfill the specified requirements before it is released for distribution."	Replace the “rework” definition with the ISO definition in ISO 9000:2015 3.12.8	The definition of “rework” in ISO 9000:2015 3.12.8 appears adequate for harmonization and should replace the current FDA definition of “rework” per (§ 820.3(x). The ISO definition of rework does not reference "DMR". As a result, the ISO definition of rework as written appears to be aligned with the FDA proposed definition of rework.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
III. Background A. Introduction Sixth paragraph Page 10122 AND VI. Proposed Effective Date and Implementation Strategy Second paragraph Page 10127	III. Background A. Introduction "Under MDSAP, audits are conducted based on core ISO 13485 requirements with additional country-specific requirements. In determining whether to participate in MDSAP and which FDA specific provisions were needed for the United States, FDA conducted a thorough review and comparison of ISO 13485 and part 820 and concluded that very few FDA-specific requirements needed to be added to this audit model, demonstrating not only the similarities between the current part 820 and ISO 13485, but the comprehensive QMS approach provided by ISO 13485. This has allowed FDA to participate in MDSAP and accept certain MDSAP audits as a substitute for its own routine surveillance of device quality systems." "Although this rule does not impact FDA's authority to conduct inspections under section 704 of the FD&C Act, FDA intends to replace its current inspection approach for medical devices, the Quality System Inspection Technique (QSIT), with an inspection approach that will be consistent with the requirements of the proposed part 820 as finalized."	"Although this rule does not impact FDA's authority to conduct inspections under section 704 of the FD&C Act, FDA intends to replace its current inspection approach for medical devices, the Quality System Inspection Technique (QSIT), with an inspection approach that will be consistent with the requirements of the proposed part 820 **and Part 4** as finalized."	Could the Agency please clarify the applicability of MDSAP to combination products in consideration of the proposed amendment. We recommend FDA consider accepting the MDSAP inspection model in lieu of QSIT, for device-led combination products. What is the FDA's intent for updating MDSAP to align with this proposed amendment and subsequent revisions to QSIT? Could the Agency please clarify if a drug product inspection conducted under a Mutual Recognition Agreements with EU and UK would be acceptable in lieu of an FDA GMP inspection for a drug-led combination product.
§ 820.35 Control of records Page 10134	N/A	**(e) *Exceptions.* This section does not apply to the reports required by § 820.20(c) Management review, § 820.22 Quality audits, and supplier audit**	Retain record exceptions as written in § 820.180 (c)

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
		reports used to meet the requirements of § 820.50(a) Evaluation of suppliers, contractors, and consultants, but does apply to procedures established under these provisions. Upon request of a designated employee of FDA, an employee in management with executive responsibility shall certify in writing that the management reviews and quality audits required under this part, and supplier audits where applicable, have been performed and documented, the dates on which they were performed, and that any required corrective action has been undertaken.	
§ 4.4(b)(1) Page 10131	"If the combination product includes a device constituent part and a drug constituent part, and the current good manufacturing practice operating system has been shown to comply with the drug CGMPs, the following clauses of ISO 13485 within the QMSR requirements for devices must also be shown to have been satisfied; upon demonstration that these requirements have been satisfied, no additional showing of compliance with respect to the QMSR requirements for devices	"If the combination product includes a device constituent part and a drug constituent part, and the current good manufacturing practice operating system has been shown to comply with the drug CGMPs, the following clauses of ISO 13485 within the QMSR requirements for devices must also be shown to have been satisfied; ~~upon~~	Clauses 8.5.2 and 8.5.3 rely on compliance with 8.3 Control of nonconforming product and 8.2.2 Complaint handling. In addition, if a complaint meets the criteria for adverse event reporting per 803, compliance with 8.2.3 is required. Inclusion of the phrase "no additional showing of compliance with respect to the QMSR requirements for devices need be made" appears to exclude ISO 13485 clauses which are necessary to

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
	need be made: (i) Management responsibility. Clause 4.1, Clause 5 and its subclauses and Clause 6.1 of ISO 13485; (ii) Design and development. Clause 7.3 and its subclauses of ISO 13485; (iii) Purchasing. Clause 7.4 and its subclauses of ISO 13485; (iv) Improvement. Clause 8.4, Clause 8.5 and its subclauses of ISO 13485; (v) Installation activities. Clause 7.5.3 of ISO 13485; and (vi) Servicing activities. Clause 7.5.4 of ISO 13485 and § 820.35(b).”	~~demonstration that these requirements have been satisfied, no additional showing of compliance with respect to the QMSR requirements for devices need be made:~~ (i) Management responsibility. Clause 4.1, Clause 5 and its subclauses and Clause 6.1 of ISO 13485; (ii) Design and development. Clause 7.3 and its subclauses of ISO 13485; (iii) Purchasing. Clause 7.4 and its subclauses of ISO 13485; (iv) Improvement. Clause 8.4, Clause 8.5 and its subclauses of ISO 13485; (v) Installation activities. Clause 7.5.3 of ISO 13485; and (vi) Servicing activities. Clause 7.5.4 of ISO 13485 and § 820.35(b).”	demonstrate compliance with the clauses that are referenced for Part 4 compliance. In addition, this phrase conflicts with the following statement that appears in both the FDA Guidance for Combination Products (Section III., C.,3.) and the FDA Compliance Program 7356.000, Inspections of CDER-led or CDRH-led Combination Products (Part III,1., (6)): “If the exemptions for a device constituent part of a drug-device combination product cover all of the 21 CFR Part 820 provisions included in 21 CFR 4.4(b)(1), then FDA will consider the combination product manufacturer CGMP compliant.”
§ 820.3 Definitions Page 10133	“(a) The following terms are necessary for the purposes of this part and do not appear in ISO 13485: *Component* means any raw material, substance, piece, part, software, firmware, labeling, or assembly that is intended to be included as part of the finished, packaged, and labeled device.”	(a) The following terms are necessary for the purposes of this part and do not appear in ISO 13485: *Component* means any raw material, substance, piece, part, software, firmware, labeling, or assembly that is	Per Section 201(h) of the Food, Drug, and Cosmetic Act, a device is: An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
		intended to be included as part of the finished, packaged, and labeled device. **A component that meets the definition of a device as defined in Section 201(h) of the FD&C Act shall be subject to the same provisions of this part, as appropriate, for a "device".**	Request clarification regarding when a component is considered a part of a device and not subject to the requirements of this part vs. a component that is a device and is subject to the requirements of this part, including its manufacturer.
§ 4.4 Page 10131	**"§ 4.4 How can I comply with these current good manufacturing practice requirements for a co-packaged or single-entity combination product?** (b) * * * "(1) If the combination product includes a device constituent part and a drug constituent part, and the current good manufacturing practice operating system has been shown to comply with the drug CGMPs, the following clauses of ISO 13485 within the QMSR requirements for devices must also be shown to have been satisfied; upon demonstration that these requirements have been satisfied, no additional showing of compliance with respect to the QMSR requirements for devices need be made: (i) *Management responsibility*. Clause 4.1, Clause 5 and its subclauses and Clause 6.1 of ISO 13485; (ii) *Design and development*. Clause 7.3 and its subclauses of ISO 13485; (iii) *Purchasing*. Clause 7.4 and its subclauses of ISO 13485;	"(iv) **Analysis of data,** Clause 8.4, **and** Improvement, Clause 8.5, and its subclauses of ISO 13485."	Corrective and Preventive Action (CAPA) has been replaced with 'improvement' and has expanded scope (e.g., Analysis of Data, Statistical Techniques and CAPA) under ISO 13485. To align with 13485:2016, we propose to add Clause 8.4 under a different heading called "Analysis of data" and only reference Clause 8.5 under "Improvement".

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
	(iv) *Improvement*. Clause 8.4, Clause 8.5 and its subclauses of ISO 13485; (v) *Installation activities*. Clause 7.5.3 of ISO 13485; and (vi) *Servicing activities*. Clause 7.5.4 of ISO 13485 and § 820.35(b)."		
§ 4.2	**§ 4.2 How does FDA define key terms and phrases in this subpart?**	***Component* means any (i) Functional elements, formulations, and compositions (e.g., including raw material, substance, piece, part, software, firmware, labelling, or assembly) intended to be included as part of the finished, packaged, and labelled device and/or (ii) ingredients intended for use in the manufacture of a medicinal product, including those that may not appear in such medicinal product (e.g., water, excipients).**	Recommend FDA consider taking this opportunity to align, where possible, with 21 CFR 210 and 211, given the increase in combination products being investigated and marketed in the US; for example, the definition of the word "component". 21 CFR 210.3 defines this term as: *Component* means any ingredient intended for use in the manufacture of a drug product, *including those that may not appear in such drug product* 21 CFR 820.3 defines this term as: *Component* means any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device.
V. Description of the Proposed Rule A. Scope (Proposed § 820.1) First paragraph Page 10124	FDA is not proposing to modify which establishments or products are subject to part 820. As before, the requirements would apply to manufacturers of finished devices; however, FDA notes that the legal authority exists to cover manufacturers of components or parts of finished devices under this regulation should the need arise (see 61 FR 52602 at 52606).	FDA is not proposing to modify which establishments or products are subject to part 820. As before, the requirements would apply to manufacturers of finished devices~~; however, FDA notes that the legal authority exists to cover manufacturers of components or parts of~~	The referenced FR page states "FDA notes that the legal authority exists to cover component manufacturers under the CGMP regulation should the need arise". It is not clear that this legal authority under CGMP supersedes the defined scope per § 820.1 for which component manufacturers are excluded.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
		~~finished devices under this regulation should the need arise (see 61 FR 52602 at 52606)~~.	
VI. Proposed Effective Date and Implementation Strategy Page 10127	FDA proposes that any final rule based on this proposal become effective 1 year after the date of publication of the final rule in the Federal Register.	FDA proposes that any final rule based on this proposal become effective ~~1 year~~ **3 years** after the date of publication of the final rule in the Federal Register.	1 year after the date of publication is not sufficient for manufacturers to incorporate the changes into their quality systems, especially given the number of organizations that are involved in combination products.
Part 820 - Quality Management System Regulation § 820.1 Page 10132	N/A	820.1(a) Applicability(a) **(5) In this regulation the term "where appropriate" and "as appropriate" is used. When a requirement is qualified by "where appropriate," or "as appropriate" it is deemed to be "appropriate" unless the manufacturer can document justification otherwise. A requirement is "appropriate" if nonimplementation could reasonably be expected to result in the product not meeting its specified requirements or the manufacturer not being able to carry out any necessary corrective action.**	The current regulation includes an explanation in section 820.1(a) of the term "where appropriate"; this is not in the proposed regulation, and the proposed regulation uses both "where appropriate" and "as appropriate" as follows; therefore, maintaining clear expectation on what the FDA means by "where appropriate" and "as appropriate" is important. Page 10132 820.1(a)(2) Components or parts. The provisions of this part do not apply to manufacturers of components or parts of finished devices, but such manufacturers are encouraged to consider provisions of this regulation as appropriate. Page 10133 820.10(b) Applicable regulatory requirements. Comply, as appropriate, with the other applicable regulatory

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
			requirements in this title, including, but not limited to the following, to fully comply with the listed ISO 13485 Clause... Page 10134 820.10(d) Devices that support or sustain life. Manufacturers of devices that support or sustain life, the failure of which to perform when properly used in accordance with instructions for use provided in the labeling can be reasonably expected to result in a significant injury, must comply with the requirements in Traceability for Implantable Devices, Clause 7.5.9.2 in ISO 13485, in addition to all other requirements in this part, as appropriate Page 10134 820.45 In addition to the requirements of Clause 7.5.1 of ISO 13485 (incorporated by reference, see § 820.7), Control of production and service provision, each manufacturer must establish and maintain procedures that provide a detailed description of the activities to ensure the integrity, inspection, storage, and operations for labeling and packaging, during the customary conditions of processing, storage, handling, distribution, and where appropriate, use of the device.