Combination Products Coalition

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VIA ELECTRONIC SUBMISSION

May 24, 2022

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

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

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to provide comments on FDA's proposed rule "Medical Devices; Quality System Regulation Amendments," dated February 23, 2022 (the "proposed rule").

The CPC greatly appreciates FDA's efforts to provide this proposed rule which helps to harmonize the device current good manufacturing practice ("CGMP") requirements of the Quality System ("QS") Regulation with the international consensus standard for devices set by the International Organization for Standardization ("ISO"), the 2016 edition of ISO 13485 ("ISO 13485"). We are also appreciative of the Agency's efforts to clarify the expected impact on 21 CFR Part 4 for combination product CGMP requirements which the CPC advocated for upon FDA's first announcements of its intention to harmonize with ISO 13485.

The CPC's comments on the proposed rule are captured below. The comments are organized by section number, reference content, and proposed revision or clarification.

Comments Regarding Incorporation of ISO 13485 by Reference into 21 CFR 820 – Section V.C Incorporation by Reference (Proposed § 820.7)

Within Section V.C of the FDA's proposed rule, it is stated that "FDA is proposing to incorporate by reference the International Standard, ISO 13485:2016 Medical devices—Quality management systems—Requirements for regulatory purposes, Third Edition 2016–03–01." However, it is unclear from the proposed rule if FDA intends to alter the existing 21 CFR Part 820 subparts,

[1] The CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with FDA on issues affecting combination products and digital products to advance our common mission: providing the best possible health care to patients. Our diverse, cross-industry membership permits the CPC to bring a special, broad, and unique perspective to these issues.

specifically the titles and structure of the 21 CFR Part 820 clauses. The proposed rule outlines that the FDA intends to incorporate ISO 13485 by 'reference' within the existing 21 CFR Part 820 framework; however, it is unclear how this will impact the current titles and subparts of 21 CFR Part 820. The implications of any such changes should be explicitly stated such that industry, including combination product manufacturers, can adequately assess the impact of any such changes within existing compliant quality management systems. Ideally, the Agency would adjust the text of 21 CFR Part 820 in such a way that the titles and subparts remain the same, thus avoiding the need to substantially modify existing cross references and citations within industry and Agency systems.

Comments Regarding Mutual Recognition for cGMPs Pharmaceutical Products – Section V.G Proposed Conforming Amendments

Within Section V.G of the FDA's proposed rule, FDA states, "[W]e are proposing conforming amendments to the part 4 references to the corresponding clauses in ISO 13485. To that end, we are taking comment on the proposed conforming amendments and whether additional changes are necessary to assure compliance with part 4. The QS requirements outlined in part 4 are not fundamentally different than the corresponding requirements in ISO 13485."

The CPC agrees with the Agency's assessment that the QS requirements outlined in part 4 are not fundamentally different than the corresponding requirements in ISO 13485. However, it is unclear from these comments and the proposed rule more broadly if the Agency intends to advance the mutual recognition of Pharmaceutical GMPs[2] for combination product manufacturers that have aligned their quality management systems to 21 CFR Part 4.4(b)(2) to meet GMP requirements for the Combination Product.

Comments Regarding Proposed Revisions to § 4.4, paragraph (b)(1) and the introductory text to paragraph (b)(2) – Section V.G Proposed Conforming Amendments and Section X.II References

As noted above, within Section V.G of the proposed rule, FDA states, "[W]e are proposing conforming amendments to the part 4 references to the corresponding clauses in ISO 13485. To that end, we are taking comment on the proposed conforming amendments and whether additional changes are necessary to assure compliance with part 4. The QS requirements outlined in part 4 are not fundamentally different than the corresponding requirements in ISO 13485."

Furthermore, within Section XII of the proposed rule, it is stated that, for co-packaged and single entity Combination Products, there are clauses of ISO 13485 within the QMSR requirements for devices that must also be shown to have been satisfied, including 'Improvement' Clause 8.4 and Clause 8.5 and its subclauses of ISO 13485.

[2] *See* "U.S.-UK Mutual Recognition Agreement" and "U.S.-EU Mutual Recognition Agreement Sectoral Annex for GMPs," *available at* https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra.

However, it is unclear how the FDA intends for Combination Product manufacturers to interpret the term 'Improvement' in the context of compliance to 21 CFR Part 4 given that 'Improvement' has a separate specific heading within Clause 8.5 of ISO 13485, and also refers to separate clause, Clause 8.4 for 'Analysis of Data.' This may make it challenging for Combination Product manufacturers to interpret which of these requirements from ISO 13485 are applicable under the proposed rule impacting 21 CFR Part 820.

Similarly, within Section XII of the proposed rule, it is stated that, for co-packaged and single entity Combination Products, 'Management responsibility' Clause 4.1, Clause 5 and its subclauses, and Clause 6.1 of ISO 13485 within the QMSR requirements for devices must also be shown to have been satisfied.

However, it is unclear how the FDA intends Combination Product manufacturers to interpret the term 'Management responsibility' in the context of compliance to 21 CFR Part 4. Specifically, given that ISO 13485 Clause 4.1 'General Requirements' states Organizational Responsibilities, Clause 5 and its subclauses define Management Responsibilities, and Clause 6.1 'Provision of Resources' states Organizational Responsibilities, it may be challenging for Combination Product manufacturers to interpret which of these requirements from ISO 13485 are applicable under the proposed rule impacting 21 CFR Part 820.

The CPC recommends that, as the Agency is undertaking revision to 21 CFR Part 820 to account for the text of ISO 13485 requirements, it provides a clear lexicon of terms and phrases, and specifies where divergent terms and phrases used in 21 CFR Part 820 and ISO 13485 are intended to have the same meaning.

The CPC greatly appreciates FDA's efforts to provide this proposed rule and the opportunity to comment on elements which impact combination product manufacturers. We believe implementation of the comments and proposals suggested within this letter will assist the industry in harmonizing existing 21 CFR Part 4 processes with ISO 13485.

Yours truly,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition