Technical Information Report

AAMI TIR48:2024

Quality management systems (QMS) recommendations on application of the U.S. FDA's CGMP final rule on combination products

AAMI

Advancing Safety in Health Technology

Quality management systems (QMS) recommendations on application of the U.S. FDA's CGMP final rule on combination products

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AAMI

Abstract: This Technical Information Report (TIR) provides information about how to effectively implement the FDA's regulation on current good manufacturing practices (CGMP) for combination products. Combination products are therapeutic or diagnostic medical products that combine drugs, devices, and/or biological products with one another. The FDA regulation became effective 22 July 2013 (21 CFR Part 4). Final guidance on CGMPs for combination products was issued in January 2017,[1] and a list of alternative or streamlined mechanisms for compliance with CGMPs for combination products was later issued in September 2022[2]. This TIR, where appropriate, also considers best practices, guidelines, and standards used in both the United States and other regions. The overall goal of the TIR is to aid informed, risk-based decisions in establishing CGMP operating systems that support development, manufacture, premarket regulatory evaluation, and commercialization of combination products. It should be noted that, while the information contained in the TIR has been carefully considered, it is up to the individual manufacturer to ensure compliance with all regulatory requirements that apply to its products.

Keywords: CGMP for combination products, combination product, constituent part, quality systems, 21 CFR Part 4, 21 CFR Part 211, 21 CFR Part 820, 21 CFR Parts 600-680, 21 CFR Part 1271, ISO 13485:2016, AAMI TIR 105:2020, ISO 14971:2019, ISO 24971:2020, CGMP, design controls, risk management, streamlined approach, single entity combination product, co-packaged combination product, cross-labelled combination product, FDA, Office of Combination Products (OCP), management responsibility, purchasing controls, corrective and preventive action (CAPA), installation, servicing, component testing, container testing, closure testing, calculation of yield, tamper-evident packaging, expiration dating, release and distribution testing, stability testing, special testing, reserve samples

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[1] FDA, Current Good Manufacturing Practice requirements for Combination Products (2017), accessed 23 March 2023 at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-manufacturing-practice-requirements-combination-products

[2] Alternative or Streamlined Mechanisms for Complying With the Current Good Manufacturing Practice Requirements for Combination Products; List Under the 21st Century Cures Act, 87 FR 56066, pp. 56066-56070 (2022), accessed 23 March 2023 at https://www.federalregister.gov/documents/2022/09/13/2022-19713/alternative-or-streamlined-mechanisms-for-complying-with-the-current-good-manufacturing-practice

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Comments on this technical information report are invited and should be sent to AAMI, Attn: Standards Department, 901 N. Glebe Road, Suite 300, Arlington, VA 22203.

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Committee representation

Association for the Advancement of Medical Instrumentation

Combination Products Committee

This AAMI Technical Information Report (TIR) was developed and approved by the AAMI Combination Products Committee. Committee approval of the TIR does not necessarily imply that all committee members voted for its approval.

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Foreword

The following verbal forms are used within AAMI documents to distinguish requirements from other types of provisions in the document:

“shall” and “shall not” are used to express requirements;

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“must” is used for external constraints or obligations defined outside the document; “must” is not an alternative for “shall.”

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Introduction

The U.S. Food and Drug Administration (FDA) terms therapeutic and diagnostic medical products that combine drugs, devices, and/or biological products with one another as combination products. Technological advances have continued to merge product types and further blur the historical lines separating traditional drugs, biologics, and medical devices. Combination products can raise challenging development, regulatory, and premarket review questions. Differences in the regulatory pathways and duties for combination products—compared to drugs, devices, or biological products alone—can affect virtually all aspects of product life cycle management, including development, clinical investigation, marketing application processes, manufacturing and quality controls, post market surveillance, adverse event reporting, promotion and advertising, and post-approval modifications.

Under the FDA's final rule, CGMP requirements that apply to drugs, devices, biological products, and HCT/Ps continue to apply when they are combined to make combination products.

The FDA issued its Current Good Manufacturing Practices (CGMP) regulation for combination products in January 2013 which became effective 22 July 2013, and is codified in Title 21 of the U.S. Code of Federal Regulations, Part 4A (21 CFR Part 4.A., or "the rule").[3,4,5] Final guidance on CGMPs for combination products[6] was issued in January 2017 and a list of alternative or streamlined mechanisms for compliance with CGMPs for combination products was issued in September 2022. For purposes of this Technical Information Report (TIR), "CGMP" requirements encompass CGMPs for drugs and biological products; quality system requirements for devices; and current good tissue practices for human cells, tissues, and cellular and tissue-based products (HCT/Ps). The FDA has explained that regulatory requirements for combination products arise from those associated with their constituent parts, that these constituent parts retain their regulatory identities, and that combination products are a distinct legal category of medical product in the United States and, as such, can be subject to specialized regulatory requirements. The CGMP rule addresses how to comply with CGMP requirements associated with constituent parts of a combination product. The rule does not establish any new CGMP requirements.

The rule is intended to promote public health by clarifying which CGMP requirements apply when a drug, device, or biological product are combined to create a combination product. The rule establishes a streamlined regulatory framework for manufacturers to use when demonstrating compliance with CGMP requirements for combination products. The FDA has also issued final guidance on how to comply with the rule.[7]

This AAMI TIR was developed at the request of combination product manufacturers, the primary users of 21 CFR Part 4.A. The TIR is intended to provide guidance on best practices to those addressing manufacturing questions, including design, quality, and regulatory personnel.

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[3] On 31 January 2024, the FDA issued a final rule , "Quality Management System Regulation" (QMSR), to align 21 CFR 820 more closely with ISO 13485:2016, with conforming edits to 21 CFR Part 4 to clarify the device CGMP requirements for combination products. These edits do not impact the CGMP requirements for combination products. The QMSR rule is effective February 2, 2026.

[4] See AAMI TIR:102:2019 Comparison of ISO 13485:2016 with 21 CFR 820.

[5] Definitions and applicable regulatory frameworks differ from country to country and region to region for medical products containing more than one constituent part type intended for combined use. Regulated entities need to understand unique interpretations in light of regulatory definitions and constructs in the jurisdictions in which the medical devices and combination products are made available.

[6] Current Good Manufacturing Practice Requirements for Combination Products Guidance for Industry and FDA Staff, accessed January 2017, at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-manufacturing-practice-requirements-combination-products.

[7] See Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (January 2017) (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-manufacturing-practice-requirements-combination-products).

Where appropriate and in addition to the rule and the Final Guidance for Industry and FDA Staff,[8] consideration has been given to best practices, guidelines, and standards used both in the United States and other regions. With this knowledge, users may more effectively establish CGMP operating systems to support manufacture for product development, premarket regulatory evaluation, and marketing.

The information contained in this document has been carefully considered. It is up to the individual manufacturer to ensure compliance with all regulatory requirements that apply to its products.

[8] Ibid.

Quality management system (QMS) recommendations on application of the U.S. FDA's CGMP final rule on combination products

1 Scope

1.1 Inclusions

This Technical Information Report (TIR) provides recommendations on the application of current good manufacturing practices (CGMPs) for drugs, devices, biologics, and human cells, tissues, and cellular and tissue-based products during development and marketing of combination products (drug-device, biologic-device, drug-biologic, or drug-device-biologic), in accordance with the FDA's final rule (21 CFR Part 4.A; 78 FR 4307, 2013—hereafter "the rule" or "the FDA's final rule") and "Alternative or Streamlined Mechanisms for Complying With the Current Good Manufacturing Practice Requirements for Combination Products; List Under the 21st Century Cures Act" (87 FR 56066, 2022). These recommendations are intended to inform the adoption and application of CGMPs for combination products.

1.2 Exclusions

The TIR does not address topics outside the realm of CGMPs. Additionally, the TIR may inform practices for combination products marketed outside the United States, but it is not intended or considered to address non-U.S. requirements comprehensively.

2 Normative references

This TIR contains no normative references.

3 Terms and definitions

For reference in review of this TIR and in relation to regulations and guidance discussed therein, terms, definitions, and regulatory references are included in Annex A.

4 Applying CGMPs in accordance with the FDA's final rule on combination products (21 CFR Part 4.A.)

4.1 Combination product definitions and examples

4.1.1 Combination products include two or more different types of medical products (e.g., a drug and a device, not a drug and a drug). Combination products can take several forms. In the United States, three categories of combination products have been identified: Single entity, co-packaged, and cross-labelled combination products. "Single-entity" combination products comprise two or more drugs, devices, or biological products that are physically, chemically, or otherwise combined or mixed with one another to produce a single entity. "Co-packaged" combination products consist of drugs, devices, or biological products packaged together with one another. Some drugs, devices, and biological products that are packaged separately from one another and need to be used together to achieve the intended use, indication, or therapeutic effect also together constitute a combination product. These are termed "cross-labelled" combination products.

Combination product types:

- **Single-entity**
- **Co-packaged**
- **Cross-labelled**