

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

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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 2022². 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

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.

At the time this document was published, the **AAMI Combination Products Committee** had the following members:

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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:

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“should” and “should not” are used to express recommendations;

“may” and “may not” are used to express permission;

“can” and “cannot” are used as statements of possibility or capability;

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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.

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 products⁶ 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.

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.

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**

4.1.2 Examples of single-entity combination products (21 CFR 3.2(e)(1)) include:

- a monoclonal antibody combined with a therapeutic drug;
- a device that is coated or impregnated with a drug or biologic, for example:
 - drug-eluting stent; pacing lead with steroid-coated tip; catheter with antimicrobial coating; condom with spermicide;
 - orthopedic implants containing antimicrobials; or
- devices prefilled with a drug or biological product, including prefilled syringes, insulin injector pens, metered dose inhalers, transdermal delivery system, IV bags.

4.1.3 Examples of co-packaged combination products (21 CFR 3.2(e)(2)) include:

- a drug or biological product packaged with a delivery device;
- a surgical tray with surgical instruments, drapes, and lidocaine or alcohol swabs; or
- ophthalmic drugs co-packaged with eye cups, eye droppers, or other dispensers.

4.1.4 Examples of products that can comprise cross-labelled combination products (21 CFR 3.2(e)(3) and (4)) include:

- a light-activated drug and activating light source; or
- an iontophoretic drug delivery patch and controller.

4.2 CGMP requirements

4.2.1 When constituent parts of a combination product are manufactured separately, as may be the case for cross-labelled combination products, the constituent parts are subject to the CGMP regulations applicable to that type of constituent part (e.g., drug or device). For single-entity and co-packaged combination products, the rule describes a streamlined regulatory framework (Figure 1) for demonstrating compliance with CGMP requirements associated with each constituent part for a combination product. The FDA has stated that such an approach can also be used at facilities that manufacture more than one constituent part type for a cross-labelled combination product. Manufacturers may demonstrate compliance with drug CGMPs and quality system (QS) regulation by either:

- fully implementing the device QS regulation (21 CFR Part 820) and the drug CGMPs (21 CFR Part 211); or
- following the streamlined approach:
 - fully implementing the device QS regulation and the provisions of 21 CFR Part 211 specified in the rule; or
 - fully implementing the drug CGMPs and also provisions of Part 820 specified in the rule.

4.2.2 Where multiple facilities bear responsibility for different aspects of the manufacturing process, each facility is responsible for the CGMP requirements applicable to the activities performed at that facility. The combination product marketing authorization holder (or legal manufacturer)⁹ is ultimately responsible for ensuring compliance with all aspects of CGMP requirements applicable to the entire manufacturing process and across all facilities.

The combination product marketing authorization holder is ultimately responsible for ensuring compliance with all aspects of CGMP requirements applicable to the entire manufacturing process and across all facilities.

⁹ The Combination Product Marketing Authorization Holder (or Legal Manufacturer) is the entity that introduces the combination product onto the market under a product-specific premarket authorization or some other marketing authorization.

4.2.3 Manufacturers may opt for the full quality management system (QMS) implementation approach or for either of the streamlined approaches.

4.2.4 Regardless of the CGMP approach selected, manufacturers of combination products that include a biologic or a human cells, tissues, and cellular and tissue-based product (HCT/P) must comply with biological product CGMPs and CGTPs for HCT/Ps, respectively.¹⁰

4.2.5 Manufacturers are responsible for ensuring compliance with the CGMP requirements applicable to the manufacturing activities at their facilities. These manufacturing activities may vary based upon the type or types of constituent part or parts being manufactured and the specifics of their manufacturing processes.

For “single-entity” and “co-packaged” combination products, the rule describes a streamlined regulatory framework for demonstrating compliance with CGMP requirements.

¹⁰ Combination products with a biologic constituent part must meet the CGMP expectations of 21 CFR 210 and 211, as well as biological product CGMPs (21 CFR 600 through 680). The current good tissue practice (CGTP) requirements (21 CFR 1271) apply, including donor eligibility requirements, for Human Cells, Tissues, and Cellular & Tissue-based Products (HCT/Ps).

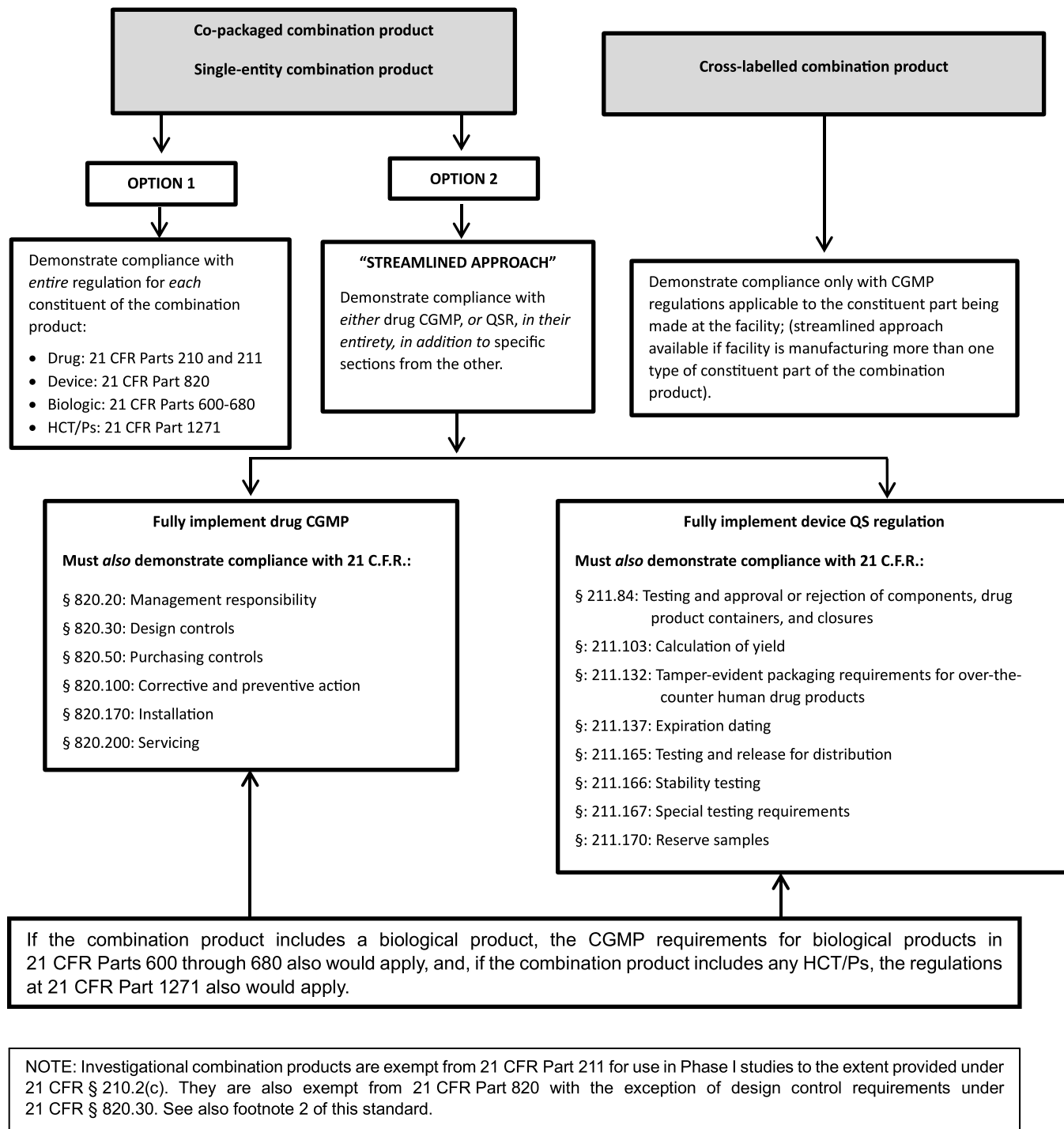


Figure 1—Applying CGMPs in accord with the FDA’s final rule on combination products

5 Considerations in adopting a 'Streamlined Approach'

5.1 Overview of considerations

5.1.1 With the release of the Rule, the FDA codified the 'Streamlined Approach' for compliance with combination product CGMPs. Tables 1 and 2 highlight considerations (technical or practical) that may arise when transitioning from manufacture of a device, drug, or biological product to manufacture of a combination product. The "considerations" address particular topics for combination products relating to specific CGMP requirements ("elements").

5.1.2 The assessment provided is not intended to be comprehensive, and the element discussed may focus on specific aspects of a broader issue. Users of this AAMI TIR should refer to relevant cGMP regulations, guidance, and standards for additional information on how to address the identified elements. Guidance documents and recognized standards related to specific aspects of cGMPS can be found on the FDA website through the Office of Combination Products home page and the home pages for the Center for Biological Products Evaluation and Research, Center for Drug Evaluation and Research, and Center for Devices and Radiological Health. Guidance documents of international organizations focusing on regulatory harmonization and convergence in which the FDA participates (e.g., International Medical Device Regulators Forum [IMDRF] and International Conference on Harmonisation [ICH]) should also be reviewed. See examples of relevant guidance and references in the Bibliography to this AAMI Technical Information Report.

Tables 1 and 2 highlight considerations (technical or practical) that may arise when transitioning from manufacture of a device, drug, or biological product to manufacture of a combination product.

5.2 Transition from device to combination product

For a manufacturer of a combination product operating under a 21 CFR part 820-based quality system, Table 1 reflects key considerations for demonstrating compliance with provisions of 21 CFR part 211¹¹ as required under the streamlined approach.

Table 1—Considerations under 21 CFR Part 211 for products operating under a 21 CFR Part 820 quality system transitioning to the streamlined approach

21 CFR Section	Element	Considerations
211.84	Testing and approval or rejection of components, drug product containers, and closures.	1. Components, drug product containers, and closures should be quarantined until representative samples of each shipment of each lot are examined, specifically identified, and tested to written specifications, including identity testing for drug components, then released by the quality control unit with all relevant information recorded/documented. If the specifications are not met, the component should be rejected and all relevant testing information included in documentation of the rejection of the component. 2. Sample collection for testing or examination should be based on statistical principles. With samples collected in such a manner as to prevent

¹¹ Generally, the 21 CFR 211 called-out provisions are prescriptive and testing-based. Given their explicit expectations, this standard does not delve deeply into each of the 21 CFR 211 called-out provisions. In contrast, the Quality Management System Regulations are less prescriptive, intended to accommodate the wide range of device complexities. Accordingly, while the provisions specified from each as applicable under a streamlined CGMP operating system are addressed, specified provisions of the QMS are reviewed in greater depth in this report, in sections 6 through 10.