Technical Information Report

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Quality Management System (QMS) Recommendations on the Application of the U.S. FDA's CGMP Final Rule on Combination Products

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Quality Management System (QMS) Recommendations On the 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 on how to effectively implement 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, and the FDA regulation became effective July 22, 2013 (21 CFR Part 4).The TIR, where appropriate, also considers best practices, guidelines, and standards used both in 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 ultimately 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 11,21 CFR Part 211,21 CFR Part 820,21 CFR Parts 600-680,21 CFR Part 1271,CGMP, Design Controls, Risk management, Streamlined Approach, Single entity combination product, Co-packaged combination product, Cross-labeled 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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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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Glossary of Equivalent Standards

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www.aami.org/standards/glossary.pdf

Committee Representation

Association for the Advancement of Medical Instrumentation

Combination Products Committee

This Technical Information Report was developed 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:

Cochairs:
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John Weiner, FDA/OCP

Members:
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NOTE—Participation by federal agency representatives in the development of this Technical Information Report does not constitute endorsement by the federal government or any of its agencies.

Introduction

The U.S. Food and Drug Administration (the 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, as 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 (the Rule), which became effective July 22, 2013 and is codified in Title 21 of the U.S. Code of Federal Regulations, Part 4 (21 CFR Part 4 or the Rule). 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 explained in the rulemaking that constituent parts of a combination product retain their regulatory status (as a drug or device, for example) after they are combined. Accordingly, the CGMP requirements that apply to each of the constituent parts continue to apply when they are combined to make combination products. The Rule did 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 with t 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 is currently developing guidance on how to comply with the Rule.[1]

This AAMI TIR was developed at the request of combination product manufacturers, the primary users of 21 CFR Part 4. The TIR is intended to provide guidance to those addressing manufacturing questions, including design, quality, and regulatory personnel. In addition to the Rule and the Draft Guidance for Industry and FDA Staff,[2] where appropriate, 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.

Although 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.

Under 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.

[1] See Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (Draft) (Jan. 2015) (www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf).
[2] Ibid.

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1 Scope

1.1 Inclusions

This Technical Information Report (TIR) provides recommendations on the application of 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; 78 FR 4307, 2013—hereafter "The Rule" or "FDA's Final Rule"). 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.

Combination product types:

- Single-entity
- Co-packaged
- Cross-labeled

2 Applying CGMPs in accordance with the FDA's Final Rule for Combination Products (21 CFR Part 4)

2.1 Combination product definitions and examples

2.1.1 Combination products must 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. "Co-packaged" combination products consist of drugs, devices, and or/ biological products packaged together with one another. "Single entity" combination products comprise two or more drugs, devices, and/or biological products that are physically, chemically, or otherwise combined or mixed with one another to produce a single entity. 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 constitute combination products. These are termed "cross-labeled" combination products.

2.1.2 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