This is a preview edition of an AAMI guidance document and is intended to allow potential purchasers to evaluate the content of the document before making a purchasing decision.

For a complete copy of this AAMI document, contact AAMI at +1-877-249-8226 or visit www.aami.org.
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:
A technical information report (TIR) is a publication of the Association for the Advancement of Medical Instrumentation (AAMI) that addresses a particular aspect of medical technology.

Although the material presented in a TIR may need further evaluation by experts, releasing the information is valuable because the industry and the professions have an immediate need for it. A TIR differs markedly from a standard or recommended practice, and readers should understand the differences between these documents.

Standards and recommended practices are subject to a formal process of committee approval, public review, and resolution of all comments. This process of consensus is supervised by the AAMI Standards Board and, in the case of American National Standards, by the American National Standards Institute.

A TIR is not subject to the same formal approval process as a standard. However, a TIR is approved for distribution by a technical committee and the AAMI Standards Board.

Another difference is that, although both standards and TIRs are periodically reviewed, a standard must be acted on—reaffirmed, revised, or withdrawn—and the action formally approved usually every five years but at least every 10 years. For a TIR, AAMI consults with a technical committee about five years after the publication date (and periodically thereafter) for guidance on whether the document is still useful—that is, to check that the information is relevant or of historical value. If the information is not useful, the TIR is removed from circulation.

A TIR may be developed because it is more responsive to underlying safety or performance issues than a standard or recommended practice, or because achieving consensus is extremely difficult or unlikely. Unlike a standard, a TIR permits the inclusion of differing viewpoints on technical issues.

CAUTION NOTICE: This AAMI TIR may be revised or withdrawn at any time. Because it addresses a rapidly evolving field or technology, readers are cautioned to ensure that they have also considered information that may be more recent than this document.

All standards, recommended practices, technical information reports, and other types of technical documents developed by AAMI are voluntary, and their application is solely within the discretion and professional judgment of the user of the document. Occasionally, voluntary technical documents are adopted by government regulatory agencies or procurement authorities, in which case the adopting agency is responsible for enforcement of its rules and regulations.

Comments on this technical information report are invited and should be sent to AAMI, Attn: Standards Department, 4301 N. Fairfax Drive, Suite 301, Arlington, VA 22203-1633.
Glossary of equivalent standards

Committee representation

Introduction

1 Scope

1.1 Inclusions

1.2 Exclusions

2 Applying CGMPs in Accord with FDA’s Final Rule for Combination Products (21 CFR Part 4)

2.1 Combination Product Definitions and Examples

2.2 CGMP Requirements

3 Considerations in transitioning to ‘Streamlined Approach’

3.1 Overview of considerations

3.2 Transition from device to combination product

3.3 Transition from drug or biologic to combination product

4 Application of Design Controls and Risk Management for a Combination Product

4.1 Overview

4.2 Additional Design Control Considerations and Initiating the Design Controls Process

4.3 Risk Management Considerations for Combination Products

4.4 Exemplary Combination Product Risk Management Process Steps

4.5 Drug/Biologic (ICH Q9) focused Risk Assessment

Annex A: Terminology

Bibliography
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: Jon Cammack, AstraZeneca/MedImmune
           John Weiner, FDA/OCP

Members: Nolan Baird, Abbvie
         Jessica Ballinger, Biogen Idec
         Steven Binion, Becton Dickinson & Company
         Joe Braido, EdgeOne Medical Inc
         Mark Brueckl, Academy of Managed Care Pharmacy
         Melissa Burns, FDA/OCP
         Stephanie Del Paine, MED Institute Inc
         Dean Elliott, American Association of Tissue Banks
         Andrew Emmett, Biotechnology Industry Organization
         Plamena Entcheva-Dimitrov, Regulatory Consultant
         Bryant Foster, Research Collective
         Jeffrey Francer, PhRMA
         Rosemary Gonzales, Combination Product Partners
         Dan Gottlieb, MHealth Regulatory Coalition
         Rich Hall, Eli Lilly & Company
         Dale Herbranson, West Pharmaceutical Services
         Steven Hertz, FDA/CDER
         Marcia Howard, Consumer Healthcare Products Association
         Maura Kibbey, US Pharmacopeia Convention Inc
         Kristi Kistner, Amgen Inc
         Mark Leahey, Medical Device Manufacturers Association
         Lee Leichter, P/L Biomedical
         Debbie Levine, Johnson & Johnson
         Rich Levy, FDA
         Elizabeth Mahoney, Baxter Healthcare Corporation
         Jan Frank Nielsen, Novo Nordisk
         Lisa Olson, WuXi AppTec Inc
         Nitin Patil, CR Bard
         Sara Radcliffe, Biotechnology Industry Organization
         Michael Sansoucy, Shire Pharmaceuticals
         Pam Schaub, GE Healthcare
         Sharon Segal, AdvaMed
         Brenda Seidman, Seidman Regulatory Toxicology, LLC
         Christy Skinner, WL Gore & Associates Inc
         Dave Sterry, CLSI
         J.S. Wiley, Draeger Medical Systems Inc

Alternates: Lismarie Alamo, Amgen Inc
            Stephen Fournier, Novo Nordisk
            Sunny Gill, Combination Product Partners
            Russ Gray, Anson Group
            Kathleen O’Sullivan, Becton Dickinson & Company
            Nancy Regulski, Johnson & Johnson
            Isabel Tejero Del Rio, FDA/CDRH
            Anthony Trupiano, Shire Pharmaceuticals
            Tony Watson, Biogen Idec
            John Williams, Baxter Healthcare Corporation

Liaisons: Patricia Love, FDA/OCP
          Thinh Nguyen FDA/OCP
          Susumu Nozawa, Becton Dickinson & Company
          Atul Patel Biogen, Idec
          Edward Patten, FDA/CBER
          Pat Picariello, ASTM Standardization News
          Suzette Roan, Biogen Idec
          Carsten Schaufuss-Feddersen, Novo Nordisk
          Melissa Torres, FDA/CDRH

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 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 is currently developing guidance on how to comply with the Rule.

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, 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.

2 Ibid.
Quality Management System (QMS) Recommendations on the 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 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.

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