Technical Information Report

AAMI TIR105: 2020

Risk management guidance for combination products

AAMI
Advancing Safety in Health Technology

Risk management guidance for combination products

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AAMI

Abstract: This technical information report provides recommendations and processes to assist manufacturers of combination products in identifying hazards associated with the combination product, assessing associated risks, selecting options for controlling these risks, and monitoring the effectiveness of the implemented controls.

Keywords: combination products, risk management

AAMI Technical Information Report

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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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Combination Products Committee

This technical information report (TIR) 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.

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NOTE Participation by federal agency representatives in the development of this TIR does not constitute endorsement by the federal government or any of its agencies.

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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- "can" and "cannot" are used as statements of possibility or capability;
- "might" and "might not" are used to express possibility;
- "must" is used for external constraints or obligations defined outside the document; "must" is not an alternative for "shall."

Suggestions for improving this document are invited. Comments and suggested revisions should be sent to Standards, AAMI, 901 N. Glebe Road, Suite 300, Arlington, VA 22203 or standards@aami.org.

NOTE This foreword does not contain provisions of the AAMI TIR105, *Risk management guidance for combination products* (AAMI TIR105:2020), but it does provide important information about the development and intended use of the document.

Introduction

This technical information report (TIR) is intended as an aid when assessing the risks of combination products[1] that include a drug/biologic[2] and a device throughout their total product lifecycle. It is intended to provide recommendations on best practices, recognizing that risk management requirements might vary across regulatory jurisdictions. AAMI TIR48:2015, *Quality management systems (QMS) recommendations on the application of the United States Food and Drug Administration's Current Good Manufacturing Practice (U.S. FDA's CGMP) final rule on combination products* [1], laid the foundation for risk management considerations for combination products by providing an overview of risk management, and identifying risk management as integral to the development process for these products. This risk management TIR leverages the overview presented in AAMI TIR48 and provides more detailed recommendations and considerations. For the purposes of this TIR, we have chosen to use the term "combination product" to describe the final, finished combination product for commercialization. A fundamental aspect of this TIR is highlighting the importance of comprehensively managing risks from the combination product throughout its total product lifecycle, which necessitates assessment of risks contributed by constituent parts, their interactions and how these risks interrelate.

The foundation for implementing a risk management process as described here is guidance from ISO 14971:2019 (*Medical devices–Application of risk management to medical devices*) (ISO 14971) [38], ISO TR 24971:2020 (*Medical devices–Guidance on the application of ISO 14971*) (ISO TR 24971) [39], ICH Q9:2005 (*Quality risk management*) [25], promulgated by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) (ICH Q9)[3]. The standards describe processes that enable management of the quality-related risks of a product "from cradle to grave." Users of this TIR should have a basic familiarity with ICH Q9 and ISO 14971/24971.

AAMI TIR105 highlights how an effective risk management process for a combination product can be achieved by systematic application of principles described in the ISO and ICH existing guidance. The expectations of ISO 14971/24971 and ICH Q9 have been considered in developing this TIR, with the goal of developing recommendations consistent with both standards and appropriate to support compliance with both.

AAMI TIR105 describes how principles of both ICH Q9 and ISO 14971/24971 can be applied and is intended to aid in identifying and addressing combination product-specific considerations and challenges in developing and implementing a risk management framework for these products.

This TIR is intended to be used in conjunction with ISO 14971, ISO TR 24971, and ICH Q9, but is not intended to interpret, replace, or change applicable national or regional legislation on risk management. Neither is it intended to alter ICH Q9, ISO 14971, or ISO TR 24971 or address application of risk management for single-entity medical devices, drugs, or biologics.

Either ICH Q9 or ISO 14971/24971 could serve as a basis for developing a suitable framework for risk management for combination products and reference to both can be helpful in developing such a framework. However, for combination products that include a device constituent part, use of an ISO 14971/24971-based framework is recommended to ensure a sufficiently robust risk management process consistent with current best practices and with

1 as defined in the U.S. under 21 CFR 3.2(e)

2 Unless otherwise stated, the term "drug" as used in this TIR is meant to include biological products as these terms are defined in the Federal Food, Drug, and Cosmetic Act, Public Health Services Act, and associated regulations.

3 Unless otherwise specified, throughout this guidance, references to ISO 14971 also refer to ISO TR 24971. NOTE: Both of these documents have been adopted by AAMI. Several ICH guidances, including Q9, collectively relate to risk management: Q8 addresses collecting the knowledge base related to the product and process, utilizing the principles of quality-by-design; Q9 addresses the application of this knowledge to managing risk; Q10 [26] addresses the need to maintain the process and product quality throughout the product lifecycle; and Q12 (currently in draft) [27] will provide a framework to facilitate the management of post-approval Chemistry Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle. Although this TIR recommends an ISO 14971-based risk management process for combination products that include a device, and these additional ICH guidances are not a focus of this TIR, reference to them is intended to inform risk management, as well as guide design and quality control, particularly for drug-led combination products.

global regulatory trends and norms. An ISO 14971/24971-based framework can be applied for the combination product even if other paradigms are applied to its constituent parts (as described in later sections of this TIR).

This TIR is organized around the risk management process step identified in AAMI TIR48, *Quality management systems (QMS) recommendations on the application of the U.S. FDA's CGMP final rule on combination products*. Key elements of TIR105 include the following:

- Emphasis on the importance of risk management planning, providing details on the planning phase and on how to ensure applicable considerations are addressed during appropriate lifecycle phases for each constituent part and for the combination product.

- A special focus on the "identification" of risk data, including failure modes, hazards, hazardous situations, and harms from a variety of sources of information. The section contains a table with examples of internal sources of risk data (i.e., what can be mined from your own company's data) and external sources (e.g., publicly available information).

- Examples to help illustrate and elucidate the concepts addressed as well as describe the value of using a Risk Management Trace Matrix.

In summary, this TIR addresses how existing risk management standards like ICH Q9 and ISO 14971 and ISO TR 24971, and the principles upon which they are based, can inform and guide risk management for combination products to establish an effective risk management process and be incorporated into a manufacturer's existing QMS.

NOTE This technical information report is not a standard, and the material contained herein is not normative in nature. The committee has used the term "shall" in a few instances, based on their knowledge of requirements contained in relevant standards and regulatory requirements.

Risk management guidance for combination products

1 Scope

1.1 Inclusions

This TIR provides recommendations on the application of risk management principles and processes during development and marketing of combination products that include a device constituent part (drug−device, biological drug−device, or drug−device−biologic), in accordance with FDA's final rule (21 CFR Part 4) [B1].[4] These recommendations are intended to inform the adoption and application of established risk management processes during all phases of the lifecycle of combination products.

The recommendations and processes described in this TIR are intended to assist manufacturers of combination products in identifying hazards associated with the combination product, assessing associated risks, selecting options for controlling these risks, and monitoring the effectiveness of the implemented controls.

1.2 Exclusions

The TIR does not address drugs, biologics, or devices that are not part of a combination product, nor does it address drug−biologic combination products as risk management considerations for these are similar to those for drugs or biologics alone. Additionally, the TIR also does not address topics outside the realm of risk management for combination products. Finally, while the TIR might inform risk management practices for combination products marketed outside the United States, it is not intended, nor considered, to address non-U.S. practices or recommendations in all risk management considerations in a comprehensive fashion.

2 Normative references

There are no normative references in this document.

3 Terms and definitions

For the purposes of this document, the following definitions apply.

3.1
combination product
therapeutic and diagnostic medical product that combines drugs and/or biological products with devices

3.2
co-packaged combination product
two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products

3.3
constituent part
a drug, device, or biological product that is part of a combination product

[4] Among other things, Part 4 requires combination product manufacturers to comply with design control requirements, including requirements for risk management, consistent with 21 CFR 820.