TECHNICAL REPORT

ISO/TR 12417-2

Second edition
2022-07

Cardiovascular implants and extracorporeal systems — Vascular device-drug combination products —

Part 2: Local regulatory information

Implants cardiovasculaires et circuits extra-corporels — Produits de combinaison médicament-dispositif vasculaire —

Partie 2: Directives règlementaires locales

Reference number
ISO/TR 12417-2:2022(E)

ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Email: copyright@iso.org
Website: www.iso.org

Published in Switzerland

Contents

Page

Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

This second edition cancels and replaces the first edition (ISO/TR 12417-2:2017), which has been technically revised.

The main changes are: editorial changes have been made regarding the use of requirements, recommendations, permissions and possibilities.

A list of all parts in the ISO 12417 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

This document was prepared in order to provide local regulatory information for vascular device-drug combination products (VDDCPs).

VDDCPs are medical devices with various clinical indications for use in the human vascular blood system. A VDDCP incorporates, as an integral part, substance(s) which, if in final formulation separately, can be considered to be a medicinal product (drug product) but the action of the medicinal substance is ancillary to that of the device and supports the primary mode of action of the device.

Only regulatory issues related to drug(s) combined with the vascular device based on the ancillary function of the VDDCP are covered by this document.

Although this document attempts to represent the state-of-the-art regarding regulatory requirements for pre and post-approval changes, these requirements are evolving and as such, it is strongly suggested that the applicant consult with the regulatory authority under which whose jurisdiction the VDDCP falls. This is most easily done by accessing the local authorities' current webpage.

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

NOTE 1 For issues related to the primary mode of action of the vascular device, the reader can find it useful to consider a number of other International Standards given in the Bibliography.

NOTE 2 Potential clinical events are defined in ISO 12417-1:2015, Annex A.

Cardiovascular implants and extracorporeal systems — Vascular device-drug combination products —

Part 2: Local regulatory information

1 Scope

This document provides region-specific information for:

— local submissions and approvals for vascular device-drug combination products (VDDCPs) in countries and regions around the world;

— changes related to the drug-containing part and how they are evaluated by different local regions.

For implanted products, this document is considered as a supplement to ISO 14630, which specifies general requirements for the performance of non-active surgical implants.

This document is considered also as a supplement to ISO 12417-1, and any relevant device-specific standards, such as the ISO 25539 series specifying requirements for endovascular devices. This document also addresses VDDCPs that are not necessarily permanent implants.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 12417-1, *Cardiovascular implants and extracorporeal systems — Vascular device-drug combination products — Part 1: General requirements*

ISO 14630, *Non-active surgical implants — General requirements*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 12417-1, ISO 14630 and the following apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
active pharmaceutical ingredient
API
drug substance
pharmacologically active (drug or medicinal) substance used as a raw material, which is coated on, bound to or incorporated into the device to achieve an ancillary device function, such as minimizing vascular restenosis

3.2
batch
quantity of VDDCP at the final stage or pre-final stage of manufacture which has undergone the same manufacturing cycle, using the same components (e.g. same coating solution, same device size), and meets the same specifications

3.3
change
alteration to an activity or to the VDDCP to improve or to maintain the composition or performance of a VDDCP

Note 1 to entry: This term includes small alterations to a VDDCP, a manufacturing process or a test procedure, even if it is not necessarily captured by a corrective action/preventative action (CAPA) system, and can require reporting to local regional authorities.

3.4
clinical event
complication, failure or device-related observation that can be observed with clinical use of a VDDCP

Note 1 to entry: Such events can possibly not have clinical significance and can possibly not be attributable to the VDDCP.

3.5
critical component
component whose specifications, if not met, can result in unacceptable risk to the patient, clinician or others, or can have a significant impact on performance

3.6
device part of the VDDCP
DP
part of the VDDCP intended to treat vascular disease by temporary or long-term intervention or implantation that does not achieve its PMOA in or on the human body by pharmacological, immunological, or metabolic means, but can be assisted in its function by such means

3.7
drug product
medicinal product
API, in its final form for administration to the patient (e.g. tablet, solution, spray), that is intended to prevent, diagnose or treat disease, and that achieves its principal intended action in or on the body by pharmacological, immunological or metabolic means

3.8
drug-containing part of the VDDCP
DCP
part of the VDDCP that consists of the active pharmaceutical ingredient or matrix and associated device interfaces intended to assist in the primary mode of action of the device and/or diminish or ameliorate an unintended effect that placement of the device part can stimulate

Note 1 to entry: Some VDDCPs can have an incorporated medicinal or drug substance primarily intended to optimize the DP properties of the VDDCP.

3.9
drug-containing part interface
DCP interface
interface between the matrix containing the API and packaging materials with direct DCP contact or device surface(s), or interface between the matrix and the API

3.10
drug content
total labelled amount of active pharmaceutical ingredient in a VDDCP

Note 1 to entry: Drug content can be expressed as µg/DCP of a certain size.

3.11
drug delivery
local interaction between the VDDCP drug and the in vivo environment, whether the drug is released from, eluted from or remains bound to the VDDCP

3.12
drug release profile
in vitro characterization of the active pharmaceutical ingredient released from the DCP of a VDDCP over time

Note 1 to entry: For example, the drug release can be characterized by a drug elution test and can include either a curve shape (or profile) or a drug release rate, or both.

3.13
efficacy
ability of the VDDCP to achieve the planned and desired physiological result

3.14
evaluate
appraise or analyse qualitatively

3.15
excipient
additional material, other than the API, that are intentional components of the drug-containing part of a VDDCP

EXAMPLE Filler, extender, diluent, wetting agent, solvent, colorant, stabilizer, antioxidant, preservative, pH maintainer, polymers, adhesives.

3.16
functionality
ability of the VDDCP to perform either physically, chemically or mechanically, or all, as designed

Note 1 to entry: Functionality does not include the physiological response to the VDDCP (i.e. efficacy).

3.17
matrix
organic or inorganic material, other than living cells, intentionally applied by a manufacturer to a vascular device and designed for the purpose of drug storage, local drug activity at the surface and/or enabling, retarding, delaying or modifying drug release

Note 1 to entry: The matrix can be permanent or temporary (dissolvable, absorbable or degradable), include surface treatments such as primers, be a coating with or without an active pharmaceutical ingredient, or consist of multiple excipients and/or multiple active pharmaceutical ingredients.

3.18
mode of action
means by which a product achieves an intended therapeutic effect or action

Note 1 to entry: This can be a primary or ancillary mode of action.

3.19
pharmacokinetics
absorption, distribution, metabolism and elimination of a drug in vivo

3.20
primary mode of action
single mode of action of a combination product that provides the most important therapeutic action of the combination product

Note 1 to entry: The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product

Note 2 to entry: Additional guidance on the drug-related aspects of the drug-containing part of the VDDCP can be found in International Conference on Harmonization Guideline IC H Q1A[29].

3.21
uniformity of drug content
comparison of the uniformity of the drug content between individual VDDCPs within each batch as compared to the labelled claim

3.22
vascular device-drug combination product
VDDCP
vascular medical device that incorporates one or more APIs as an integral part (ancillary mode of action) to that of the device, but not necessarily to the VDDCP PMOA

Note 1 to entry: The VDDCP can be permanently deployed (i.e. it can be an implant like a drug-eluting stent) or temporarily deployed (i.e. it can be a drug-eluting balloon).

3.23
vascular device-drug combination product specification
VDDCP specification
required list of test procedures and appropriate acceptance criteria which are numerical limits, ranges or other criteria for the tests described

Note 1 to entry: A specification is a critical quality standard. It establishes the set of criteria to which a VDDCP has to conform.

Note 2 to entry: Additional guidance on the drug-related aspects of the drug-containing part of the VDDCP can be found in International Conference on Harmonization Guideline IC H Q6A[37].

4 Information on device- and drug-related aspects — Applicable documents for local guidance

4.1 General

The following region-specific information identifies the regional regulatory authorities responsible for VDDCPs and provides general clinical evaluation and audit requirements for VDDCPs.

NOTE 1 Region-specific requirements can deviate from harmonized International Standards.

NOTE 2 At the publication of this document, the following information is believed to be accurate and can change over time. Current guidance can be directly obtained from the regulatory authorities in the region of interest.

4.2 Australia

4.2.1 General

VDDCPs are approved by the department of health through the Therapeutic Goods Administration (TGA).

NOTE For more information, see the Therapeutics Goods Administration website and for Australian regulatory guidelines for medical devices, see Reference [136].

4.2.2 Australia: Managing changes

See the website of the local authority above for the responsibilities of deciding whether a submission or change notification is subject to requirements.

It is the responsibility of the manufacturer to decide if a submission or change notification is subject to requirements. This information is then communicated to the TGA by the Australian sponsor.

See also Table 2 for managing changes that can impact the DCP.

4.2.3 Australia: Clinical evaluation requirements

VDDCPs are subject to requirements for a clinical study (but it need not be a local study). If the study is conducted in Australia, an exemption is granted by TGA prior to initiation of the study which allows products not included on the Australian Register of Therapeutic Goods to be supplied as part of the clinical trial.

NOTE The TGA has two pathways in Australia for clinical trials – Clinical Trial Notification (CTN) which involves a notification to the TGA and Clinical Trial Exemption (CTX) which requires a formal approval from the TGA. The CTX is generally for studies where the experimental device introduces a new technology, a new material or a new concept or for trials that are considered high risk.

4.2.4 Australia: Audit requirements

An appropriate quality system audit can be required prior to market approval.

NOTE For more information, see ARGMD[81] on the Therapeutics Goods Administration website.

4.3 Brazil

4.3.1 Brazil: Managing changes

VDDCPs are approved by the National Health Surveillance Agency (ANVISA). In Brazil, medical devices are regulated by

a) the national law ”Lei 6360/1976” which regulates drugs, medical devices, cosmetics and other sanitary products,

b) the decree ”Decreto 79094/1977” which regulates the law ”Lei 6360/1976” and the ANVISA Board Collegiate Resolutions,

   — RDC 185/2001 for the Registration, post-market changes, revalidation and cancellation of registration of medical devices in the Brazilian Health Surveillance Agency;

   — RDC 14/2011 for Establishing the technical regulations with requirements for grouping of medical device.

NOTE For more information, see the ANVISA website.

ANVISA expects that APIs are in compliance with the Brazilian Pharmacopoeia (or other specified compendia).

The pharmaceutical products, medicines and other products subject to sanitary surveillance are expected to meet the standards and specifications established in the Brazilian Pharmacopoeia (see ANVISA website).

In the absence of an official Brazilian monograph, the use of a foreign official monograph is allowed.

See website of the local authority above for the responsibilities of deciding whether a submission or change notification is subject to requirements.

See also Table 2 for managing changes that can impact the DCP.

4.3.2 Brazil: Clinical evaluation requirements

VDDCPs are subject to requirements for a clinical study (but it need not be a local study) according RDC 56/2001. If the study is conducted in Brazil, the clinical study protocol needs to be approved, prior to initiation of the study, by ANVISA according RDC 39/2008. The final report for the study primary end point(s) is completed prior to submission to ANVISA.

4.3.3 Brazil: Audit requirements

A manufacturing audit is subject to requirements prior to market approval. The manufacturing site is certified under RDC 59/2000 (Brazil quality system requirement) prior to submitting the product to ANVISA for registration. An audit can be required prior to market approval if the product is not within the current scope of the corresponding quality assurance system approval certificate.

The manufacturing RDC 59/2000 certificate or ISO 13485 MDSAP certificate is presented together with the submission dossier.

4.4 Canada

4.4.1 Canada: Managing changes

VDDCPs are approved by Health Canada.

NOTE For more information, refer to the Health Canada website[137].

See the website of the local authority given above for the responsibilities of deciding whether a submission or change notification is subject to requirements.

It is the responsibility of the Health Canada to decide if a submission or change notification is subject to requirements based on information provided by the manufacturer.

See also Table 2 for managing changes that can impact the DCP.

4.4.2 Canada: Clinical evaluation requirements

VDDCPs are subject to requirements for a clinical study (but it need not be a local study). It is suggested that a pre-CTA submission be scheduled with Health Canada (see website for Pre-CTA details). If the study is conducted in Canada, the clinical study protocol needs to be approved by Health Canada prior to initiation of the study per the Clinical Trial Application (CTA) process (see Health Canada website for more information of the CTA process).

4.4.3 Canada: Audit requirements

An audit can be required prior to market approval if the product is not within the current scope of the corresponding quality assurance system approval certificate.

4.5 European Union (EU)

4.5.1 EU: Managing changes

VDDCPs are assessed for conformity by a Notified Body before approval as medical devices according to Medical Device Regulation (EU) 2017/745. The Notified Body seeks a scientific opinion or consultation from one of the competent authorities (national regulatory authorities designated by member states) or the European Medicines Agency and from an Expert Panel review ((56) of Regulation (EU) 2017/745.). MEDDEV 2.1/3 is a guideline explaining the consultation process for VDDCPs as well as the necessary documentation to be provided for consultation.