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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 réglementaires locales

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Foreword

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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).

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For an explanation on 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 the following URL: 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*.

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

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 Technical Report.

Although this document attempts to represent the state-of-the-art regarding regulatory requirements for pre/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 For issues related to the primary mode of action of the vascular device, the reader might find it useful to consider a number of other International Standards (see Bibliography).

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 the 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. Requirements listed in this document also address 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 in ISO 12417-1, ISO 14630 and the following apply.

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

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

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

NOTE Potential clinical events are defined in Annex A of ISO 12417-1.

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 is manufactured according to a single manufacturing order and has undergone the same manufacturing cycle, using the same components (e.g. same coating solution, same device size), and meets the same specifications

Note 1 to entry: Validation testing can be conducted to demonstrate that manufacturing variables do not impact specifications such as drug content or drug release, and thereby permit such manufacturing variables within a batch.

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

Note 1 to entry: This include 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 may require reporting to local regional authorities

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

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

3.5
critical component
component whose specifications, if not met, could result in unacceptable risk to the patient, clinician or others, or could 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 principal intended action in or on the human body by pharmacological, immunological or metabolic means, but might be assisted in its function by such means

3.7
drug product
medicinal product
active pharmaceutical ingredient, in its final formulation for administration to the patient (e.g. tablet, solution, spray), that is intended to prevent, diagnose, or treat disease and that achieves its principle intended action in or on the human 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 might stimulate

Note 1 to entry: Some VDDCPs have medicinal substance(s) bound with the primary intent to optimize the surface properties of the device.

3.9
DCP interface
common boundary or interconnection between the various components of the device part(s) and the drug-containing part(s) of a VDDCP

EXAMPLE The interface between the matrix containing the active pharmaceutical ingredient and packaging materials with direct DCP contact, the device surface(s), the interface between the matrix and the active pharmaceutical ingredient.

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

Note 1 to entry: Drug content could 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 might be characterized by a drug elution test, and could include a curve shape (or profile), 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 physically, chemically and/or mechanically, 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

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. 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 1 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.

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 (primary mode of action) that incorporates one or more active pharmaceutical ingredients as an integral part (ancillary mode of action)

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, for instance).

3.23
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.

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

4.1 Australia

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 might deviate from harmonized International Standards.

NOTE 2 As of the publication of this document, the following information is believed to be accurate and can change over time. Always seek current guidance directly from the regulatory authorities in the region of interest for up to date requirements

VDDCPs must be approved by the Department of Health through the Therapeutic Goods Administration (TGA).

NOTE For more information, see Therapeutics Goods Administration website and for Australian regulatory guidelines for medical devices, (ARGMD) Part 2–Pre-market Section 14. Medical devices incorporating a medicine.

4.1.1 Australia: managing changes

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

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

See also Table B.1 for managing changes that can impact the DCP.

4.1.2 Australia: clinical evaluation requirements

VDDCPs will require a clinical study (but it need not be a local study). If the study is conducted in Australia, an exemption must be 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.

4.1.3 Australia: audit requirements

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

NOTE For more information, see the Australian regulatory guidances for medical devices (ARGMD) on the Therapeutics Goods Administration website.

4.2 Brazil

4.2.1 Brazil: managing changes

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

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

2) 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

More guidance for non-active medical device registration will be given in:

“Agência Brasileira de Desenvolvimento Industrial. Manual de registro e cadastramento de materiais de uso em saúde / ABDI. Brasília: ABDI, 2011. 306 p.”

ANVISA expects APIs must be 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, use of a foreign official monograph is allowed. This is regulated by the “Resolution of the Directory Collegiate (RDC) Nº 49, November 23th, 2010”

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

See also Table B.1 for managing changes that can impact the DCP.

4.2.2 Brazil: clinical evaluation requirements

VDDCPs will require 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 to be completed prior to submission to ANVISA.

4.2.3 Brazil: audit requirements

A manufacturing audit is required prior to market approval. The manufacturing site must be 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 RDC 59/2000 certificate must be presented together with the submission dossier.

4.3 Canada

4.3.1 Canada: managing changes

VDDCPs must be approved by Health Canada.

NOTE For more information, see Health Canada website http://www.hc-sc.gc.ca

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

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

See also Table B.1 for managing changes that can impact the DCP.

4.3.2 Canada: clinical evaluation requirements

VDDCPs will require a clinical study (but it need not be a local study). It is recommended 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).

4.3.3 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.

4.4 European Union (EU)

4.4.1 EU: managing changes

VDDCPs must be assessed for conformity by a Notified Body before approval as medical devices according to Medical Device Directive 93/42/EC. The Notified Body must seek a scientific opinion or consultation from one of the competent authorities (national regulatory authorities designated by member states) or the European Medicines Agency. MEDDEV 2.1/3 is a guideline explaining the consultation process for VDDCPs as well as the necessary documentation to be provided for consultation.

