INTERNATIONAL STANDARD

ISO 12417-1

Second edition

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

Part 1: General requirements

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

Partie 1: Exigences générales

PROOF/ÉPREUVE

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Contents

Page

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 document 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).

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This document was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems,* in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 285, *Non-active surgical implants,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This second edition cancels and replaces the first edition (ISO 12417-1:2015), which has been technically revised.

The main changes are as follows:

— the text regarding ethylene oxide sterilization limits has been revised,

— references have been updated, and

— terms and definitions have been revised.

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

Vascular device-drug combination products (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 used separately, can be considered to be a medicinal substance or product (drug substance, drug product) but the action of the medicinal substance is ancillary to that of the device and supports the primary mode of action (PMOA) of the device.

Many vascular device-drug combination products have been shown to be safe and effective in clinical use. This revision is not intended to require additional evaluation of these products as the testing would not provide useful information regarding the expected clinical performance of the product. Manufacturers can rely on historical data gathered in the previous edition of this document (i.e. ISO 12417-1:2015). Similarly, for product modifications or changes in intended clinical use, this edition of this document (i.e. ISO 12417-1:202X) is not intended to require additional evaluation of any aspects of the product that are not expected to change clinical performance.

When developing this document, it was impossible to consider all future and emerging technologies. VDDCPs using such technologies need to be evaluated following the basic requirements of this document. Testing beyond the scope of this document can also be necessary to characterize these future and emerging device systems.

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

Part 1: General requirements

1 Scope

This document specifies requirements for vascular device-drug combination products (VDDCPs).

With regard to safety, this document outlines requirements for intended performance, design attributes, materials, design evaluation, manufacturing, sterilization, packaging and information supplied by the manufacturer.

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

NOTE 1 Due to variations in the design of combination products covered by this document and due to the relatively recent development of some of these combination products, acceptable standardized in vitro test results and clinical study results are not always available. As further scientific and clinical data become available, appropriate revision of this document can be necessary.

This document applies to delivery systems or parts of the delivery system that are an integral component of the vascular device and that are drug-covered (e.g. drug-covered balloon catheters and drug-covered guidewires).

This document does not apply to devices whose PMOA provide a conduit for delivery of a drug (e.g. infusion catheters), unless they contain a drug component that is intended to have an ancillary action to the device part (e.g. antimicrobial coated infusion catheter).

This document does not apply to procedures and devices used prior to and following the introduction of the VDDCP (e.g. balloon angioplasty devices) that do not affect the drug-related aspects of the device.

This document does not provide a comprehensive pharmacological evaluation of VDDCPs.

NOTE 2 Some information about the requirements of certain national and regional authorities is given in Annex B.

The connection of absorbable components of VDDCPs (e.g. coatings) with drug-related aspects of the device are addressed in this document. This document does not provide an exhaustive list of the degradation and other time-dependent aspects of absorbable implants and coatings.

NOTE 3 For more information on absorbable coatings, refer to ISO/TS 17137 and ASTM F3036-13.

This document does not address issues associated with viable or non-viable biological materials such as tissues, cells or proteins.

This document does not address issues associated with active surgical implants (i.e. implants that require power not generated by the human body or gravity).

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 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-2, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

ISO 10993-7, *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals*

ISO 11070, *Sterile single-use intravascular introducers, dilators and guidewires*

ISO 11607-1, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

ISO 14155, *Clinical investigation of medical devices for human subjects — Good clinical practice*

ISO 14630:2012, *Non-active surgical implants — General requirements*

ISO 14937, *Sterilization of health care products — General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices*

ISO 14971:2019, *Medical devices — Application of risk management to medical devices*

ISO 15223-1, *Medical devices — Symbols to be used with information to be supplied by the manufacturer — Part 1: General requirements*

ISO 25539-2, *Cardiovascular implants — Endovascular devices — Part 2: Vascular stents*

3 Terms and definitions

For the purposes of this document, the terms and definitions provided in 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 (e.g. minimizing vascular restenosis)

3.2
batch
quantity of *vascular device-drug combination product* (3.27) 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 *vascular device-drug combination product* (3.27) to improve or maintain the composition or performance of a vascular device-drug combination product

Note 1 to entry: Certain local regional authorities require that changes are reported, including small alterations to a vascular device-drug combination product, a manufacturing process or a test procedure, even if it is not necessarily captured by a corrective action/preventative action (CAPA) system.

3.4
clinical event
complication, failure or device-related observation that can be observed with clinical use of a *vascular device-drug combination product* (3.27)

Note 1 to entry: It is possible events will not have clinical significance and cannot be attributable to the vascular device-drug combination product.

3.5
compendial pharmaceutical reference standard
reference substance, reference preparation or reference spectrum recognized by a national pharmacopoeia

3.6
device part of the vascular device-drug combination product
device part of the VDDCP
device part
DP
part of the *vascular device-drug combination product* (3.27) intended that treats vascular disease by temporary or long-term intervention or implantation that does not achieve its primary mode of action in or on the human body by pharmacological, immunological or metabolic means, but that can be assisted in its function by such means

3.7
assay
biological or chemical method to determine the activity or potency of a substance

3.8
drug product
medicinal product
active pharmaceutical ingredient (3.1), 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

3.9
drug-containing part of the vascular device-drug combination product
drug-containing part
DCP
part of the *vascular device-drug combination product* (3.27) that consists of the *active pharmaceutical ingredient* (3.1) or *matrix* (3.21) and associated device interfaces intended to assist in the primary mode of action of the device by diminishing or ameliorating, potential unintended effects that placement of the *device part* (3.6) can potentially stimulate

Note 1 to entry: Some vascular device-drug combination product can incorporate medicinal or drug substances that are primarily intended to optimize the DP properties of the vascular device-drug combination product.

3.10
DCP interface
drug-containing part interface
common boundary or interconnection between the various components of the *device part(s)* (3.6) and the *drug-containing part(s)* (3.9) of a *vascular device-drug combination product* (3.27)

EXAMPLE 1 Interface between the *matrix* (3.21) containing the *active pharmaceutical ingredient* (3.1) and packaging materials with direct drug-containing part contact.

EXAMPLE 2 Device surface(s).

EXAMPLE 3 Interface between the matrix and the active pharmaceutical ingredient.

3.11
delivery system
transport device that physically or mechanically positions the *vascular device-drug combination product* (3.27) and/or the *drug-containing part* (3.9) at the intended anatomic location

EXAMPLE The delivery system of a drug-coated balloon would position the balloon in the lumen of the lesion intended to be treated.

3.12
drug content
total labelled amount of *active pharmaceutical ingredient* (3.1) in a *vascular device-drug combination product* (3.27)

Note 1 to entry: Drug content can be expressed as µg per *drug-containing part* (3.9) of a certain size.

3.13
drug delivery
local interaction between the *vascular device-drug combination product* (3.27) drug and the in vivo environment, whether the drug is released from, eluted from, or remains bound to the vascular device-drug combination product

3.14
drug-related impurity
substance in the *drug-containing part* (3.9) of a *vascular device-drug combination product* (3.27) that is not the *active pharmaceutical ingredient* (3.1) or an *excipient* (3.19)

Note 1 to entry: Drug-related impurities can include drug degradation products or degradants, drug-synthesis-related impurities, isomers of the drug, residual drug solvents or biological contaminants (e.g. occurring with drugs derived from biological systems).

3.15
drug release characterization
in vitro characterization of the *active pharmaceutical ingredient* (3.1) released from the *drug-containing part* (3.9) of a *vascular device-drug combination product* (3.27) over time

EXAMPLE The release can be determined by a drug elution test and can include a curve shape (or profile), a drug release rate, or both.

3.16
durability
ability to maintain adequate integrity and robustness during procedural (i.e. access, deployment, withdrawal), post-procedural and long-term use (i.e. over time) according to design specifications

3.17
efficacy
effectiveness
ability of the *vascular device-drug combination product* (3.27) to achieve the planned and desired physiological result

3.18
evaluate
analyse qualitatively

3.19
excipient
additional material(s), other than the *active pharmaceutical ingredient* (3.1), that are intentional components of the *drug-containing part* (3.9) of a *vascular device-drug combination product* (3.27)

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

3.20
functionality
ability of the *vascular device-drug combination product* (3.27) to perform physically, chemically, and/or mechanically, as designed

Note 1 to entry: Functionality does not include the physiological response to the vascular device-drug combination product [i.e. *efficacy* (3.17)].

3.21
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* (3.1), or consisting of multiple *excipients* (3.19) and/or multiple active pharmaceutical ingredients.

3.22
particulate
particle
mobile matter, other than gas bubbles, present on, or arising from the use of the *vascular device-drug combination product* (3.27)

3.23
pharmacokinetics
absorption, distribution, metabolism and elimination of a drug in vivo

3.24
procedural fluid
blood and serum, saline, and contrast media that come into contact with a *vascular device-drug combination product* (3.27)

3.25
stability testing
tests undertaken according to a prescribed stability protocol to establish, support or confirm the shelf life of a *vascular device-drug combination product* (3.27)

Note 1 to entry: Additional guidance on the drug-related aspects of the *drug-containing part* (3.9) of the vascular device-drug combination product can be found in ICH Q1A.

3.26
content uniformity
uniformity of drug content
comparison of the uniformity of the *drug content* (3.12) between individual *vascular device-drug combination products* (3.27) within each *batch* (3.2) as compared to the labelled claim

3.27
vascular device-drug combination product
VDDCP
vascular medical device that incorporates one or more *active pharmaceutical ingredients* (3.1) as an integral part of the device that is not necessarily part of the device's primary mode of action(i.e. ancillary mode of action)

Note 1 to entry: The vascular device-drug combination product can be permanently deployed (e.g. an implant like a drug-eluting stent) or temporarily deployed (e.g. a drug-eluting balloon).

3.28
vascular device-drug combination product deployment
VDDCP deployment
physical or mechanical positioning of the *vascular device-drug combination product* (3.27) so that the *drug-containing part* (3.9) is in contact with the intended anatomic treatment site

Note 1 to entry: The vascular device-drug combination product may be permanently deployed (e.g. a drug-eluting stent) or temporarily deployed (e.g. a drug-eluting balloon).

3.29
vascular device-drug combination product specification
VDDCP specification
list of required 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 *vascular device-drug combination product* (3.27) has to conform.

Note 2 to entry: Additional guidance on the drug-related aspects of the *drug-containing part* (3.9) of the vascular device-drug combination product can be found in ICH Q6A.

3.30
primary mode of action
PMOA
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* (3.9) of the *vascular device-drug combination product* (3.27) can be found in ICH Q1A.

4 Intended performance

4.1 General

The requirements of ISO 14630:2012, Clause 4, shall apply.

4.2 Classification

A VDDCP is a product that is considered to be a medical device but which incorporates, as an integral part, substances which, if used separately, can be considered to be a medicinal product or drug product. It is classified as a medical device, provided that the action of the medicinal or drug substance is

ancillary to that of the device, as reflected in the product claim and as supported by the scientific data provided by the manufacturer of the device.

4.3 Intended clinical location

The intended clinical location shall be identified as one or more of the following:

a) abdominal aorta;

b) arterio-venous shunt for vascular access;

c) carotid;

d) coronary;

e) femoral;

f) iliac;

g) popliteal;

h) intracerebral;

i) renal;

j) thoracic aorta;

k) thoraco-abdominal aorta;

l) tibial;

m) other arterial or venous vessels to be specified.

5 Design attributes

5.1 General

The design attributes to meet the intended performance of the VDDCP shall consider at least:

a) the ability of the device part of the VDDCP (i.e. the device without the API and matrix) to fulfill all product-specific requirements for the PMOA (e.g. the mechanical function), which are defined in the device-related standards;

b) the ability of the drug-containing part of the VDDCP to fulfill the drug-specific function and requirements of the VDDCP as defined in 5.2;

c) the ability of the VDDCP to meet defined chemical, physical, mechanical or compatibility specifications after interaction with the DCP/matrix and device or manufacturing processes;

d) the ability of the VDDCP to meet applicable interactional (ergonomic, connections, coupling) requirements, unless justified.

5.2 Drug-containing part of the VDDCP

5.2.1 General

The design attributes of the VDDCP to meet the intended performance of the DCP shall additionally consider at least:

a) the ability of the DCP to be consistently, accurately, and safely brought into contact with the intended anatomic treatment site;

b) the appropriate physical and chemical compatibility of the DCP interfaces (i.e. the device, the drug, the matrix and any packaging with direct DCP contact);

c) the appropriately justified/conducted biocompatibility of the DCP;

d) conformance of the DCP to VDDCP specifications at the time of manufacture and after storage;

e) the ability of the DCP to deliver or maintain the intended amount of drug safely at the target site in accordance with the specification of the VDDCP at product release and for the duration of the labelled shelf life;

f) the appropriate interaction between the VDDCP and procedural fluids.

5.2.2 Matrix

The design attributes of the VDDCP to meet the intended performance of the matrix shall additionally consider at least:

a) the ability of the matrix to maintain adequate integrity during procedural use in accordance with the design specifications (e.g. freedom from significant delamination, flaps, and bare spots) and over time as applicable for the VDDCP;

b) the ability of the matrix to maintain adequate resistance to unintended generation of particles;

c) conformance of the matrix to VDDCP specifications at the time of manufacture and after storage;

d) conformance of the matrix dimensions, physical and chemical properties, and other matrix parameters (e.g. porosity, mass, density, distribution, glass transition temperature, melting temperature, fragmentation point) to the design requirements;

e) if soluble or degradable, the ability of the matrix to control the release of drug and the interaction of any solubilized or degradation products with the body (i.e. biocompatibility of the matrix as well as the degradation products);

f) the effect of imaging (e.g. the heating caused by magnetic resonance imaging [MRI]) on the matrix.

5.2.3 Active pharmaceutical ingredient

The design attributes of the VDDCP to meet the intended performance of the API shall additionally consider at least:

a) conformance of drug content, impurities and degradants to the API specification upon receipt and after storage and handling of the API before introduction into the VDDCP manufacturing process;

b) the ability to reproducibly incorporate, as demonstrated by content uniformity, the desired drug and amount within the VDDCP;

c) the ability to release the drug in accordance with the VDDCP specification as applicable for devices that intended to release drug;

d) conformance of drug content, drug impurities and drug degradants to VDDCP specifications for finished devices after manufacturing (e.g. batch release) and after storage;

NOTE There can be other impurities, evaluated separately from the drug-related impurities, that are related to manufacture of the matrix or other components of the VDDCP or come from sterilization or processing aids, such as monomers, catalysts, residual matrix-related solvents, residual processing solvents or matrix-related degradation products or degradants. There also can be other biological impurities such as endotoxin, evaluated separately from the drug-related impurities.

e) appropriate interaction between the drug(s) and the matrix and/or the device to which the drug(s) is(are) applied;

