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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

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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).

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For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

ISO 12417 consists of the following parts under the general title, *Cardiovascular implants and extracorporeal systems — Vascular device-drug combination products*:

— *Part 1: General requirements*

— *Part 2: Local regulatory guidance*

Introduction

This part of ISO 12417 was prepared in order to provide minimum requirements for vascular device-drug combination products (VDDCPs).

Only issues related to vascular devices combined with drug(s), wherein the drug serves an ancillary function of the VDDCP are covered by this part of ISO 12417.

It was impossible, when writing this part of ISO 12417, to take into consideration all future and emerging technologies. VDDCPs using such technologies will need to be evaluated following the basic requirements of this International Standard. Testing beyond the scope of this part of ISO 12417 might also be necessary to characterize these device systems. Consideration shall be given to the failure modes of the VDDCP and their effects on the performance in deciding what testing will be appropriate.

For issues related to the primary mode of action (PMOA) of the vascular VDDCP, 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 1: General requirements

1 Scope

This part of ISO 12417 specifies requirements for vascular device-drug combination products (VDDCPs) based upon current technical and medical knowledge. 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. With regard to safety, this part of ISO 12417 outlines requirements for intended performance, design attributes, materials, design evaluation, manufacturing, sterilization, packaging, and information supplied by the manufacturer. For implanted products, this International Standard should be considered as a supplement to ISO 14630, which specifies general requirements for the performance of non-active surgical implants. This International Standard should also be considered as a supplement to relevant device-specific standards, such as the ISO 25539-series specifying requirements for endovascular devices. Requirements listed in this part of ISO 12417 also address VDDCPs that are not permanent implants.

NOTE Due to variations in the design of combination products covered by this part of ISO 12417 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 part of ISO 12417 might be necessary.

Delivery systems or parts of the delivery system are included in the scope of this part of ISO 12417, if they comprise an integral component of the vascular device and if they are drug-covered (e.g. drug-covered balloon catheters and drug-covered guidewires).

Devices whose PMOA is to provide a conduit for delivery of a drug, are excluded from the scope of this part of ISO 12417 (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).

Procedures and devices used prior to and following the introduction of the VDDCP (e.g. balloon angioplasty devices) are excluded from the scope of this part of ISO 12417 if they do not affect the drug-related aspects of the device.

This part of ISO 12417 is not comprehensive with respect to the pharmacological evaluation of VDDCPs. Some information on the requirements of different national and regional authorities is given in Annex B.

Absorbable components of VDDCPs (e.g. coatings) are addressed by this part of ISO 12417 in their connection with drug-related aspects of the device. Degradation and other time-dependent aspects of absorbable implants and coatings are not completely addressed by this part of ISO 12417.

NOTE See also ISO/TS 17137 and ASTM F3036-13.

This part of ISO 12417 does not address issues associated with viable or non-viable biological materials such as tissues, cells, or proteins.

This part of ISO 12417 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, in whole or in part, are normatively referenced in this document and are indispensable for its application. 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 — Animal welfare requirements*

ISO 10993-7, *Biological evaluation of medical devices — 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 14971:2007, *Medical devices — Application of risk management to medical devices*

ISO 15223-1, *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied — Part 1: General requirements*

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

NOTE See the Bibliography for additional device-specific and regional information about standards and guidance documents.

3 Terms and definitions

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

NOTE Potential clinical events are defined in Annex A.

3.1
active pharmaceutical ingredient
API
drug
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 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 maintain the composition or performance of a VDDCP

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
compendial pharmaceutical reference standard
general term covering reference substances, reference preparations, and reference spectra that are recognized by a national pharmacopoeia

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 might be assisted in its function by such means

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

3.8
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

3.9
drug-containing part of the VDDCP
DCP
part of the VDDCP that consists of the API or matrix and associated device interfaces intended to assist in the PMOA 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 might have an incorporated medicinal or drug substance primarily intended to optimize the surface properties of the VDDCP.

3.10
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

a) the interface between the matrix containing the API and packaging materials with direct DCP contact;

b) the device surface(s);

c) the interface between the matrix and the API.

3.11
delivery system
transport device that physically or mechanically positions the VDDCP and/or the DCP 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 API in a VDDCP

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

3.13
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

3.14
drug-related impurity
any substance in the DCP of a VDDCP that is not the API or an excipient

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

3.15
drug release characterization
in vitro characterization of the API released from the DCP of a VDDCP over time

EXAMPLE The release might be determined by a drug elution test, and could 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) in accordance with the design specifications

3.17
efficacy
effectiveness
ability of the VDDCP to achieve the planned and desired physiological result

3.18
evaluate
appraise or analyse qualitatively

3.19
excipient
additional material(s), 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.

3.20
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).

3.21
matrix
any 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 might: be permanent or temporary (dissolvable, absorbable or degradable); include surface treatments such as primers; be a coating with or without an API, or consist of multiple excipients and/or multiple APIs.

3.22
particulates
particles
mobile matter, other than gas bubbles, present on, or arising from the use of the VDDCP

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

3.24
procedural fluids
blood and serum, saline, and contrast media that come into contact with a VDDCP

3.25
stability studies
tests undertaken according to a prescribed stability protocol to establish, support, or confirm the shelf life of a VDDCP

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 ICH Q1A.

3.26
uniformity of drug content
comparison of the uniformity of the drug content between individual VDDCPs within each batch as compared to the labelled claim

3.27
vascular device-drug combination product
VDDCP
vascular medical device (PMOA) that incorporates one or more APIs as an integral part (ancillary mode of action)

3.28
VDDCP deployment
physical or mechanical positioning of the VDDCP so that the drug-containing part is in contact with the intended anatomic treatment site

Note 1 to entry: The VDDCP might be permanently deployed (e.g. a drug-eluting stent) or temporarily deployed (e.g. a drug-eluting balloon).

3.29
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 ICH Q6A.

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 take into account at least the following:

a) 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) 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.

5.2 Drug-containing part of the VDDCP (DCP)

5.2.1 General

The design attributes of the VDDCP to meet the intended performance of the DCP shall additionally take into account at least the following:

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

b) 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) appropriate biocompatibility of the DCP;

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

e) 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) 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 take into account at least the following:

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

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

5.2.3 Active pharmaceutical ingredient (API)

The design attributes of the VDDCP to meet the intended performance of the API shall additionally take into account at least the following:

a) conformance of drug content, impurities, and degradants to the API specification on receipt and after storage and handling of the API during the VDDCP manufacturing process;

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

c) ability to apply the drug to the target site in accordance with the VDDCP specification;

d) conformance of drug content, drug impurities, and drug degradants to VDDCP specifications at the time of manufacture and after storage;

NOTE There might 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 might be other biologic 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;

f) appropriate interaction between the drug(s) and the tissue to which the drug(s) is(are) applied;

g) effect of imaging (e.g. MRI) on the drug of a VDDCP (e.g. heating).

NOTE Additional guidance on the drug-related specifications can be found in ICH Q6A as well as in general and individual monographs of pharmacopoeias of the different regions [e.g. the United States Pharmacopeia (USP), Japanese Pharmacopoeia (JP) and European Pharmacopoeia (EP)].

6 Materials

The requirements of ISO 14630:2012, Clause 6, shall apply when selecting the API, matrix, and DP materials used to design the VDDCP (e.g. metals, polymers, drugs).

7 Design evaluation

7.1 General

The requirements of ISO 14630:2012, Clause 7, shall apply.

For the properties outlined in this Clause, a justification shall be provided for the properties that are not assessed.

Whenever changes are made in materials, construction, configuration, application, or processing methods, an appropriate risk analysis of the potential impact of the change on the failure modes and performance of the VDDCP shall be performed. Appropriate testing shall be conducted, as deemed necessary.

NOTE Any alterations, including those that might be considered minor alterations to a VDDCP, a manufacturing process, or a test procedure might require reporting to local regional authorities.

The use of a control device for comparison can be informative in the evaluation of certain design attributes relevant to the performance of the VDDCP.

Testing to establish the labelled shelf life shall be conducted by repeating appropriate device and drug tests on the final aged VDDCP. Justification for the selection of tests shall be provided.

NOTE If different finished-product manufacturing sites are used, the generation of appropriate batch release/stability data to ensure the consistency and equivalency of the finished product across manufacturing sites might be required by some regulatory authorities (e.g. US FDA).

For VDDCPs, long-term stability testing shall be used to define drug attributes for product shelf life. Prior to the completion of these long-term stability tests, accelerated stability testing should be considered. Additional guidance on stability testing of VDDCPs can be found in ICH Q1A(R2), ICH Q1B(R2), ICH Q1D, and ICH Q1E. In addition, ICH Q3B(R2) and ISO 10993 provide guidance on how to test for identification of impurities and/or degradation products. ICH guidelines include specific testing time frames and environmental conditions that might not be appropriate for all product designs, storage conditions, and climate zones. Testing intervals for identification of degradation products will depend on the potential degradation characteristics of the API and/or matrix, as well as the shelf life of the VDDCP. As a result of the stability testing, the final release specification for a particular VDDCP attribute might be modified to ensure that product performance is maintained throughout shelf life.

Testing appropriate to climatic zones should also be considered with respect to where the VDDCP will be marketed. World Health Organization (WHO) Technical Report 953, 2009, Annex 2, Appendix 1, Table 1, includes climate zones for each member country which might be appropriate to use for stability-testing conditions. Climate zone definitions in local standards and guidelines (e.g. ASEAN, USP, EMA) should also be considered.

7.2 Pre-clinical evaluation

7.2.1 Sampling

For each test, a sampling plan shall be utilized which will ensure that adequate representation of the data has been obtained for each parameter measured. The DCP design characteristics of the VDDCP shall be verified to be representative of the products to be released for distribution, including all sizes, configurations, and components.

The sampling shall represent the worst-case relevant VDDCP parameters (e.g. drug content, drug-related impurities, durability), and should fully represent the range of VDDCP designs. A justification shall be provided for sample selection. It might be necessary to conduct an analysis to identify the design(s) of the VDDCP with the greatest potential for failure.

NOTE Additional guidance on a use of a mixed bracketing/matrix design for stability testing (e.g. minimum, intermediate [e.g. worst-case design], and maximum sizes of the VDDCP) can be found in ICH Q1D.

Sampling shall ensure adequate representation of the expected variability in the manufacture of devices. For drug-related aspects of the VDDCP, at least three batches of each of the representative samples of the drug-containing part of the VDDCP shall be tested over the shelf life.

Where possible, different batches of the API should be used. See ICH Q1A(R2).

The sampling plan might differ for characterization, release, and stability testing.

It might be appropriate to assess some properties only at manufacture, if changes are not expected over the shelf life.

For those tests with specified confidence and reliability parameters, the sample size shall have a statistical basis. For all tests, the number of samples shall be justified.

7.2.2 Conditioning of test samples

Because sterilization could affect the performance of the VDDCP, all samples shall be subjected to sterilization, unless justification is provided for the use of non-sterilized products. If the VDDCP can be sterilized multiple times prior to release for marketing, then the test samples shall also be sterilized multiple times, as appropriate.

Maximum and minimum tolerances for the conditioning-process parameters within a cycle could result in different properties for the VDDCP. Additionally, the impact of any change to sterilization (e.g. number of cycles, types of sterilization, or process parameters within a cycle) on VDDCP properties should be considered.

Samples shall be subjected to conditions that are normally encountered prior to use that might affect the test results. Conditioning might include preconditioning of the VDDCP as recommended in the instructions for use. If the product is a single-use product, it might be necessary to consider whether multiple attempts (e.g. tracking) with the same product should be included in a simulated-use test.

If the product is labelled for multiple-use, the simulated-use test shall incorporate this concept into the test protocol.

For *in vitro* simulated-use testing, issues associated with clinical access, deployment, and withdrawal, if applicable, of the VDDCP and/or the delivery system shall be considered.