TECHNICAL SPECIFICATION

ISO/TS 12417

First edition
2011-06-01

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

Implants cardiovasculaires et systèmes extracorporels — Produits de combinaison médicament-dispositif vasculaire

Reference number
ISO/TS 12417:2011(E)

ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
Web 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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

In other circumstances, particularly when there is an urgent market requirement for such documents, a technical committee may decide to publish other types of normative document:

— an ISO Publicly Available Specification (ISO/PAS) represents an agreement between technical experts in an ISO working group and is accepted for publication if it is approved by more than 50 % of the members of the parent committee casting a vote;

— an ISO Technical Specification (ISO/TS) represents an agreement between the members of a technical committee and is accepted for publication if it is approved by 2/3 of the members of the committee casting a vote.

An ISO/PAS or ISO/TS is reviewed after three years in order to decide whether it will be confirmed for a further three years, revised to become an International Standard, or withdrawn. If the ISO/PAS or ISO/TS is confirmed, it is reviewed again after a further three years, at which time it must either be transformed into an International Standard or be withdrawn.

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.

ISO/TS 12417 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

Introduction

This Technical Specification was prepared in order to provide minimum requirements for vascular device-drug combination products (VDDCPs).

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

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

1 Scope

1.1 This Technical Specification 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 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. With regard to safety, this Technical Specification outlines requirements for intended performance, design attributes, materials, design evaluation, manufacturing, sterilization packaging, and information supplied by the manufacturer. For implanted products, this Technical Specification should be considered as a supplement to ISO 14630, which specifies general requirements for the performance of non-active surgical implants. This Technical Specification 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 Technical Specification also address VDDCPs that are not necessarily permanent implants.

NOTE Due to variations in the design of products covered by this Technical Specification and due to the relatively recent development of some of these products, acceptable standardized *in vitro* tests and clinical results are not always available. As further scientific and clinical data become available, appropriate revision of this Technical Specification will be necessary.

1.2 Delivery systems or parts of the delivery system are included in the scope of this Technical Specification 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).

1.3 Pumps and infusion catheters which do not contain drug coverings, and whose primary mode of action is to deliver a drug, are not addressed in this Technical Specification.

1.4 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 Technical Specification if they do not affect the drug-related aspects of the device.

1.5 This Technical Specification is not comprehensive with respect to the pharmacological evaluation of VDDCPs. Some information on the requirements of different related national and regional authorities is given in Annex B of this Technical Specification.

1.6 Bioabsorbable components of VDDCPs (e.g. coatings) are addressed by this Technical Specification in their connection with drug-related aspects of the device.

1.7 This Technical Specification does not address issues associated with viable tissues and non-viable biological materials.

2 Normative references

The following referenced documents are indispensable for the application 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 10993-7, *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals*

ISO 11135-1, *Sterilization of health care products — Ethylene oxide — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11137-1, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

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 14160, *Sterilization of health care products — Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives — Requirements for characterization, development, validation and routine control of a sterilization process for medical devices*

ISO 14630, *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, *Medical devices — Application of risk management to medical devices*

ISO 17665-1, *Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*

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, 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

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

NOTE Such events might not have clinical significance and might not be attributable to the VDDCP.

3.4
device part of the VDDCP
DP
that 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

3.5
drug product
medicinal product
active pharmaceutical ingredient, in its final formulation for administration to the patient, that is primarily intended to treat, prevent or diagnose disease and that achieves its principal intended action in or on the human body by pharmacological means

3.6
drug-containing part of the VDDCP
DCP
that 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

3.7
DCP interface
common boundary or interconnection between the various components of the device part(s) and the drug-containing part(s) of a VDDCP

EXAMPLES

a) the interface between the matrix containing the active pharmaceutical ingredient and packaging materials with direct DCP contact;

b) the device surface(s);

c) the interface between the matrix and the active pharmaceutical ingredient.

3.8
drug content
total labelled amount of active pharmaceutical ingredient in a VDDCP

NOTE Drug content could be expressed as µg/DCP of a certain size.

3.9
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

3.10
drug-related impurity
any substance in the drug-containing part of a VDDCP that is not the active pharmaceutical ingredient or an excipient, such as unintended drug degradation products, drug-synthesis-related impurities, isomers of the drug, or residual drug solvents

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 processing aids, such as monomers, catalysts, residual matrix-related solvents or residual processing solvents.

3.11
drug release profile
in vitro characterization of the active pharmaceutical ingredient released from the drug-containing part of a VDDCP over time

NOTE For example, the release can be determined by a drug elution test.

3.12
durability
ability of a VDDCP to maintain adequate product robustness during procedural (i.e. access, deployment, withdrawal), post-procedural and long-term use (i.e. over time) in accordance with the design specifications

3.13
evaluate
appraise or analyse qualitatively

3.14
excipient
additional material(s) used for manufacturing the drug-containing part of a VDDCP

EXAMPLES Polymers, adhesives.

3.15
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 The matrix can be permanent or temporary (dissolvable or degradable), can include surface treatments such as primers, and can be a coating with or without an active pharmaceutical ingredient. The matrix can consist of multiple excipients and/or multiple active pharmaceutical ingredients.

3.16
pharmacokinetics
absorption, distribution, metabolism and elimination of a drug *in vivo*

3.17
procedural fluids
blood and serum, saline, contrast media, anticoagulants and antiplatelet medications that come into contact with a VDDCP

3.18
reference standard
general term covering reference substances, reference preparations and reference spectra

NOTE Reference standards are employed in the identification, purity testing and assay of substances.

3.19
stability studies
studies undertaken according to a prescribed stability protocol to establish, support or confirm the shelf life of a VDDCP

NOTE Additional guidance on the drug-related aspects of the drug-containing part of the VDDCP can be found in International Conference on Harmonisation Guideline ICH Q1A.

3.20
uniformity of drug content
comparison of the uniformity of the drug content between individual VDDCPs within each batch as compared to the labelled claim

3.21
vascular device-drug combination product
VDDCP
medical device (primary mode of action) that incorporates one or more active pharmaceutical ingredients as an integral part (ancillary mode of action)

3.22
VDDCP delivery
physical or mechanical positioning of a VDDCP at the intended anatomic location by a transport device such as a catheter

3.23
VDDCP deployment
physical or mechanical release of the drug-containing part of a VDDCP from a transport device such as a catheter

NOTE 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).

3.24
VDDCP specification
list of procedures and appropriate acceptance criteria which are numerical limits, ranges or other criteria for the tests described

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

NOTE 2 Additional guidance on the drug-related aspects of the drug-containing part of the VDDCP can be found in International Conference on Harmonisation Guideline ICH Q6A.

4 General requirements

4.1 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. It is classified as a medical device, provided that the action of the medicinal 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.

4.2 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 Intended performance

The requirements of ISO 14630 shall apply.

6 Design attributes

6.1 General

The requirements of ISO 14630 shall apply.

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

a) the ability of the device part of the VDDCP (i.e. the device without the active pharmaceutical ingredient and matrix) to fulfil all product-specific requirements for the primary mode of action (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 fulfil the drug-specific function and requirements of the VDDCP as defined in 6.2.

6.2 Drug-containing part of the VDDCP (DCP)

6.2.1 General

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

a) the ability of the DCP to be consistently, accurately and safely deployed;

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 compliance of the DCP with the requirements of ISO 10993-1 and other relevant parts of ISO 10993 (biocompatibility);

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

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

NOTE The fulfilment of the requirements of this specification (see 6.2.3) is a function of the interaction of all interfaces.

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

6.2.2 Matrix

The design attributes to meet the intended performance of the matrix used to store and/or release the drug shall additionally take into account at least the following:

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

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

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

d) the 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 to control the solubility or degradation behaviour and the interaction of the solubilized or degradation products with the body (mechanism of solubility or degradation, biocompatibility of the matrix as well as the degradation products);

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

6.2.3 Active pharmaceutical ingredient (API)

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

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

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

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

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

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

g) the 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)].

7 Materials

The requirements of ISO 14630 shall apply. Additional testing specific to certain materials (e.g. metals, polymers, drugs) shall be performed to determine the appropriateness of the material for use in the design.

8 Design evaluation

8.1 General

The requirements of ISO 14630 shall apply. A risk analysis shall be carried out and the requirements of ISO 14971 shall apply.

For the properties outlined in the design evaluation clause of this Technical Specification, a justification shall be provided for the properties that are not assessed.

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

Whenever changes are made in materials, construction, configuration, application or processing methods, an appropriate 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.

The use of a control device for comparison should be considered in the evaluation of the 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.

If different finished-product manufacturing sites will be used, the generation of appropriate batch release/stability data to ensure the consistency and equivalency of the finished product across manufacturing sites should be considered. Some regulatory authorities will require this (e.g. in the US — see also Annex B).

For VDDCPs, long-term stability testing augmented by accelerated stability testing, such as defined by ICH guidelines, shall be used to define drug attributes for product shelf life. 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 medical device.

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

8.2 Sampling

A sampling plan should be utilized which will ensure that adequate representation of the data has been obtained for each parameter measured. The drug- and/or matrix-related 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 should fully represent the range of device designs and might not necessarily require the stability testing of each size (e.g. by bracketing or matrixing to incorporate the worst-case design). The VDDCP sizes selected for testing shall represent the worst-case combination(s) of relevant VDDCP dimensions for each test. A rationale should be provided for sample selection. It might be necessary to conduct an analysis to identify the size(s) of the VDDCP with the greatest potential for failure.

Additional guidance on a mixed bracketing/matrix design [e.g. minimum, intermediate (e.g. worst-case design), and maximum sizes of the VDDCP] can be found in ICH Q1D. Samples of the extremes of certain design factors (e.g. strength) should be tested at all time points.

Sampling should 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 should be tested over the shelf life.

NOTE 1 The sampling plan might differ for characterization, release and stability testing.

NOTE 2 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 should be justified.

8.3 Conditioning of test samples

All samples should be subjected to sterilization, including multiple sterilizations, if appropriate, unless justification is provided for the use of non-sterilized products.

Maximum and minimum tolerances for the conditioning-process parameters within a cycle could result in different properties for the VDDCP. Additionally, changes in sterilization cycles or process parameters within a cycle could impact the properties of the VDDCP and this should be borne in mind.

Samples should be subjected to conditions that are normally encountered that could 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 with the same product should be included in a simulated-use test. If the product is a multiple-use product, the simulated-use test should 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 should be considered.

A simulated physiological environment (e.g. a temperature-controlled water bath) should be used when appropriate.

8.4 Reporting

For the purposes of this Technical Specification, reporting relates to requests from a national regulatory authority.

The test report for the preclinical *in vitro* testing should include an executive summary of all testing. This summary should include an identification of all the tests, with the rationale for the omission of any tests. The information provided in each test report should be based upon a prospectively defined test protocol.

A summary of results, with the acceptance criteria and any potential clinical significance of the results, should be included and may be in tabular form. Consideration should be given to the anatomical, physiological and morphological conditions of the intended use in establishing the acceptance criteria. The justification and clinical applicability of the acceptance criteria for each test should be provided. A table of contents should be provided and pages should be numbered sequentially.

Individual test reports should include the following information:

a) purpose: state the purpose of the test as it corresponds to this Technical Specification;

b) materials: list all materials (e.g. test articles with lot/serial numbers or other appropriate means of traceability, equipment) used in performing the test, using figures and diagrams as appropriate;

c) sampling: state the sampling plan, including the basis for sampling and the number of samples tested, and justifying the selection of the test articles (e.g. choice of sizes, use of conditioning);

d) acceptance criteria: state the criteria for acceptance of the test results;