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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 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;

f) 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)[79], Japanese Pharmacopoeia (JP)[103] and European Pharmacopoeia (EP)[98]].

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).

a) The inclusion of materials in the VDDCP, can require analysis and/or estimation of potential patient exposure, analysis of possible alternative substances, material or designs, and/or benefit risk assessments for the continued use of the materials.

b) Justification can be required for the continued use of materials or substances found in VDDCP (e.g. if these substances are identified as being of concern).

c) Additional testing to facilitate proper disposal or additional information in the instructions for use to facilitate safe disposal can be required by environmental regulations when listed substances have been included.

NOTE Some authorities with jurisdiction impose different requirements for the identification, marking and documentation of a medical device or accessory.

7 Design evaluation

7.1 General

The requirements of ISO 14630:2012, Clause 7, shall apply, where applicable and appropriate for the DP type (e.g. stent versus balloon).

A justification shall be provided for the properties outlined in Clause 7 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 Local regional authorities can require that alterations, including those that can be considered minor alterations to a VDDCP, a manufacturing process or a test procedure, are reported.

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 can be required by some regulatory authorities [e.g. US Food and Drug Administration (US FDA)].

For long-term stability testing of the VDDCPs, the stability indicating drug attributes should be defined. 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 are 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 may 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, Annex 1, Table 1, includes climate zones for each member country which can be appropriate to use for stability-testing conditions. Climate zone definitions in local standards and guidelines [e.g. Association of Southeast Asian Nations (ASEAN), USP[79], European Medicines Agency (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 can 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 (such as 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 can differ for characterization, release and stability testing.

It can 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

However, sterilization can 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 can 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 can affect the test results. Conditioning can include preconditioning of the VDDCP as recommended in the instructions for use. If the product is a single-use product, it can 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.

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

7.2.3 Pre-clinical in vitro test reports and additional information

For the purposes of this document, reporting relates to requests from a regional regulatory authority.

An executive summary of the preclinical in vitro testing shall be provided. This summary should include an identification of all the tests, with the justification for the omission of any tests included in Clause 7. 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 can be presented in a tabular form. The justification and clinical applicability of the acceptance criteria for each test shall be addressed. A table of contents should be provided, and pages should be numbered sequentially.

Individual test reports should include:

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

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

c) sampling information: 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;

e) the test method: describe in detail the method used to perform the test, including any prospectively defined inspection procedures, and provide a justification for critical test parameters;

f) protocol deviations: describe any deviations and their potential significance for the interpretation of the results;

g) the expression of results: state the test results, expressed in the units indicated in the test method;

h) conclusions: state the conclusions, based on comparing the results with the acceptance criteria and including any potential clinical significance of the results.

NOTE Some tests can also require submission of raw data and a detailed data analysis.

7.2.4 Pre-clinical in vitro evaluation

7.2.4.1 Testing the device part-related attributes of the VDDCP

Testing of the device part (DP)-related attributes of the VDDCP shall be conducted to evaluate the design attributes described in Clause 5, as applicable. Testing of each design attribute shall evaluate whether the design components perform as intended, and should consider potential failure modes.

If the DP is a temporarily placed product, such as a balloon, then testing shall also address issues in relevant guidance documents and standards for that specific device.

If the DP is an implant, such as a stent, coil, valve, or graft, then testing shall also address issues in relevant guidance documents and standards for those specific vascular implants.

NOTE An example of a recommended format for presentation of a summary of the test information for local regulatory authorities is provided in B.3.4.

7.2.4.2 Testing the drug-containing part-related attributes of the VDDCP

Testing of the drug-containing part (DCP)-related attributes of the VDDCP shall be conducted to evaluate the design attributes described in Clause 5, as applicable. Testing of each design attribute

— shall evaluate whether the design components perform as intended, and

— should consider potential failure modes.

NOTE For regional regulatory authorities, it can be helpful to document the evaluation of the drug-related attributes of the DCP using the common technical document (CTD). The CTD contains a format that is internationally accepted for reporting on medicinal products. See B.3.1 for more information on CTDs.

7.2.4.3 Requirements for the VDDCP related to the DCP

7.2.4.3.1 Ability to access

This subclause covers the ability of the VDDCP to permit the safe transport of the DCP to the target site.

Hazards to be evaluated shall include, but are not limited to:

a) the introducer (if necessary, for the procedure) and DCP not matching the access site (i.e. size mismatch);

b) the unintended lack of mechanical (structural) integrity of the DCP during advancement to the target site/tissue (i.e. particle shedding by API/matrix);

c) the unintended lack of chemical stability of the DCP (i.e. lack of stability of either API or matrix materials and impact of release of degradation products);

d) the unintended effects of API outside target site/tissue due to loss of material before API reaches target site/tissue;

e) the procedural bleeding due to unintended anti-coagulation effects caused by API;

f) the chemical incompatibility of the DCP with procedural fluids.

These hazards can result in clinical events.

NOTE Potential clinical events that can be evaluated are given in Annex A.

7.2.4.3.2 Dimensional compatibility of components

Evaluate the dimensions of the DCP for compatibility with the dimensions of recommended accessories. All components shall be dimensionally compatible.

7.2.4.3.3 Ability to deploy the VDDCP and deliver the API from the DCP

This subclause covers the ability of the VDDCP to deploy safely and deliver the intended amount of API at the target site within the intended time frame.

Drug delivery can occur over a short period of time (as in the case of burst release from a drug-coated balloon) or over a longer period of time (as in the case of sustained drug release by an implanted drug-eluting stent until that release is exhausted) or the deliver can have continued local interaction (as in the case of a graft with a bound drug, such as covalently bound heparin).

Hazards to be evaluated shall include, but are not limited to:

a) the unintended lack of mechanical (structural) integrity of the DCP due to undesirable material degradation (API/matrix particle generation) (see 7.2.4.3.9);

b) the unintended lack of chemical stability of the DCP (i.e. lack of stability of either API or matrix materials and impact of release of degradation products);

c) the procedural bleeding due to unintended anti-coagulation effects caused by API;

d) the excessive API delivery;

e) the inadequate API delivery;

f) the unintended variability in localized API delivery;

g) the chemical incompatibility of the DCP with procedural fluids;

h) the lack of appropriately justified/conducted biocompatibility.

These hazards can result in clinical events.

NOTE Potential clinical events that can be evaluated are given in Annex A.

Testing shall include the following items listed, as appropriate to the design of the DCP.

7.2.4.3.4 Drug content

Determine the quantity of drug on the DCP (assay and content uniformity testing).

NOTE Additional guidance on the determination of content uniformity (or uniformity of dosage units within a lot) can be found in EP 2.9.5, EP 2.9.6[98], and USP < 905 >[79].

7.2.4.3.5 Drug distribution

Evaluate the drug distribution along the DCP surfaces or throughout the DCP matrix, as appropriate.

NOTE This test is commonly done for product characterization.

7.2.4.3.6 Drug release characterization

Determine the amount of drug that elutes over the desired time period, if applicable.

In vitro drug release profile testing can consider:

a) the characterization of the rate of drug release and of the amount of drug remaining on the VDDCP at any given time;

b) the relative solubility of the drug (e.g. more lipophilic drugs can exhibit a longer elution time);

c) the optimization of in vitro elution methodology and the developmental parameters (i.e. equipment/apparatus, in vitro release media, agitation/speed, temperature, pH, assay);

d) the method validation information showing that the selected method is able to detect manufacturing changes (under meaningful testing) that can have an effect on the release of the drug.

NOTE 1 This information is sometimes requested during audits by some regional regulatory authorities.

NOTE 2 Additional guidance on the dissolution procedure, dissolution profiles and drug release testing can be found in USP 711, USP 724, USP 1092[79], JP 6.09, JP 6.10[103], EP 2.9.1, EP 2.9.3, and EP 2.9.4[98].

Validation studies identifying critical formulation and manufacturing variables during development, establishing relevant controls for manufacturing, and developing a relevant stability-indicating test method for final product testing. Knowledge of the mechanism of drug release can facilitate the development of an appropriate in vitro release test. Similarly, drug-device compatibility is a consideration under storage conditions over time (e.g. leaching of undesirable impurities from device components).

The US Food and Drug Administration and the National Medical Products Administration (NMPA) currently have recommendations for the setting of in vitro drug release/elution (or transfer from the DP)/acceptance criteria for product release testing which include the following points:

— in vitro drug release specifications encompass the time frame over which at least 80 % of the intended drug is released is recommended (if in vitro drug release is intended to be incomplete, the in vitro drug release specifications should encompass the time frame up to the point when the plateau of drug release is reached, as demonstrated by no additional release);

— data from lots used in the clinical studies and stability studies, and also on to-be-marketed batches, should be used;

— at least three sampling times covering the initial, middle, and terminal phases of the complete in vitro drug release characterization should be selected (the acceptance criteria ranges should be based on the overall in vitro drug release data generated at these times);

— acceptance criteria should be set in a way which will ensure consistent performance from lot to lot;

— chosen acceptance criteria should not allow the release of any lots with elution rates or profiles outside those that were tested clinically.

Establishing an in vitro-in vivo correlation may be used to validate the clinical relevance of an in vitro drug release test which can aid to establish a drug release specification and may be used to justify post-approval process changes or manufacturing site changes (see also 7.2.5.2).

In vitro drug release characterization testing used for developing stability and batch release testing of manufactured product may incorporate parameters that help accelerate the method, as compared to real-time characterization testing.

7.2.4.3.7 Drug identity and purity

Confirm the API-specific identity and determine the purity by characterizing the types and amounts of drug-related impurities and degradation products. If available, compendial pharmaceutical reference standards shall be employed in identification and purity testing (API and VDDCP). Otherwise, non-compendial reference standards shall be validated and justified.

NOTE Additional guidance on such drug-related aspects can be found in national and regional pharmacopoeias such as the USP[79] and EP[98] [see also ICH Q3B(R2) and ICH Q6A].

7.2.4.3.8 Ability to withdraw

This subclause covers the ability of the VDDCP to permit safe withdrawal of any product components not intended to remain in the body.

Hazards to be evaluated shall include, but are not limited to:

a) unintended lack of mechanical (structural) integrity due to loss of residual material (i.e. particle generation by API/matrix);

b) unintended API effects outside target site/tissue due to loss of residual material;

c) procedural bleeding due to unintended anti-coagulation effects caused by API;

d) chemical incompatibility with procedural fluids.

These hazards can result in clinical events.

NOTE Potential clinical events that can be evaluated are given in Annex A.

7.2.4.3.9 Functionality

The ability of the DCP to be safe and meet specifications as intended at the target site shall be evaluated after VDDCP positioning at the target site.

Hazards to be evaluated shall include, but are not limited to, the following:

a) unintended lack of mechanical (structural) integrity due to material degradation (i.e. particle generation by API/matrix);

b) unintended lack of chemical stability of the DCP (i.e. lack of stability of either API or matrix materials and impact of release of degradation products);

c) excessive API delivery;

d) inadequate API delivery;

e) unintended variability in localized API delivery;

f) misplacement or movement of VDDCP from intended target site;

g) procedural bleeding due to unintended anti-coagulation effects caused by API.

These hazards can result in clinical events.

NOTE Potential clinical events that can be evaluated are given in Annex A.

Testing shall include the items given from 7.2.4.3.10 to 7.2.4.3.17, as appropriate to the design of the DCP.

7.2.4.3.10 Durability

Evaluate the durability of the VDDCP due to procedural use (i.e. access, deployment and withdrawal), post-procedural use and over the expected lifetime of the VDDCP, if applicable, as changes in product performance can affect patient safety.

For the device part of the VDDCP, product performance shall also be evaluated in accordance with device-specific standards such as ISO 10555-4, if the VDDCP includes a balloon catheter, or ISO 25539-2, if the VDDCP includes a stent.

For the drug containing part of the VDDCP, the ability to resist unintended integrity loss (e.g. delaminations, flaps, or bare spots) shall also be evaluated at pre-specified intervals. The expected lifetime of the DCP shall be described (e.g. 5 min or 5 years). Accelerated test conditions may be employed provided justification is given.

Results shall be analysed with respect to available preclinical in vivo and clinical data.

7.2.4.3.11 Particulates

Evaluate any particulate released and/or generated by the VDDCP to assess potential embolic risk to the patient during the procedure, through post-procedure hospitalization, and after release from the hospital, as appropriate. The testing time frames will depend on VDDCP type and related clinical use.

Determine the size and amount of particles generated when the VDDCP is subjected to simulated-use testing conditions. Results should be analysed with respect to available preclinical in vivo and clinical data to develop specifications.

Further characterization of the particles (e.g. their identity and solubility) can be helpful when particulate levels have exceeded specifications and as necessary to better derive the source of particles and their potential clinical relevance.

NOTE Additional guidance on particulate testing can be found in ASTM F3320-18 and AAMI TIR42.

7.2.4.3.12 Degradable matrix

If the matrix is intended to be degradable, the degradation behaviour (e.g. mechanism of breakdown, decomposition and/or dissolution), including the intermediate and final degradation products, shall be described and evaluated.

NOTE Additional guidance on degradation testing can be found in ISO 13781. Additional guidance on degradation and other time-dependent aspects of cardiovascular absorbable implants can be found in ISO/TS 17137.

7.2.4.3.13 Compatibility with procedural fluids

Evaluate the ability of the VDDCP to resist unintended modifications to the VDDCP (e.g. API decomposition, matrix degradation or absorbable device degradation) when exposed to procedural fluids, such as contrast media or saline. Bench tests, such as API stability and drug release tests or preclinical in vivo tests to assess the compatibility with procedural fluids, can be appropriate.

7.2.4.3.14 Corrosion

Evaluate the susceptibility of metal-containing, implantable VDDCPs to corrosion in an actual or simulated environment. Possible corrosion mechanisms include pitting, fretting, crevice corrosion and galvanic corrosion.

NOTE Additional guidance on corrosion testing can be found in ISO 16428, ISO 16429, ISO 17475, ASTM F746, ASTM F2129, ASTM G5, ASTM G15, ASTM G61 and ASTM G102.

If the DCP is absorbable, additional corrosion testing of any metal-containing, implantable DPs should be considered.

7.2.4.3.15 Magnetic resonance imaging safety

Evaluate the ability of the DCP to maintain safety and performance during and after exposure to a magnetic resonance imaging (MRI) environment.

Hazards to be evaluated regarding VDDCP-related aspects shall include, but are not limited to:

a) magnetically induced displacement force and torque;

b) RF-induced heating causing tissue damage and/or API/matrix degradation.

While image artefact is unlikely to alter the safety or performance of the VDDCP itself, image artefact of the VDDCP in the MRI environment should also be characterized.

These hazards can result in clinical events.

NOTE 1 Potential clinical events that can be evaluated are given in Annex A.

NOTE 2 Additional guidance on evaluating magnetically-induced displacement, torque, RF heating and imaging artefacts can be found in ASTM F2052, ASTM F2213, ASTM F2182, and ASTM F2119.

NOTE 3 Additional guidance on evaluating the marking of medical devices for safety in the magnetic resonance environment can be found in ASTM F2503.

7.2.4.3.16 Biocompatibility

Biocompatibility of the manufactured VDDCP shall be evaluated in accordance with ISO 10993-1 and other relevant parts of ISO 10993. If different subcomponents of the VDDCP, such as the matrix or DP, become exposed to the body over time, additional subcomponent biocompatibility testing can be needed.

If VDDCP biocompatibility testing is conducted and results in toxic responses that can be attributed to a particular chemical substance of concern, such as the drug or a manufacturing excipient, it can be necessary

to also test portions of the VDDCP without that substance. This data can be used in conjunction with the data from the toxicity literature to confirm that the toxicity is a result of that chemical substance.

NOTE 1 If the omission of certain types of biocompatibility test is desired, ISO 10993-12 (extraction) and ISO 10993-18 (characterization) provide information on how to identify chemicals of concern that can be present in extracts of the VDDCP. Assessment of extracts, in conjunction with toxicity data from the literature, can be helpful in justifying the omission of recommended tests.

NOTE 2 For unstudied drug substances, matrix materials or device materials, additional biocompatibility testing of the VDDCP or the individual materials can be necessary.

NOTE 3 If components of the VDDCP are absorbable, sample preparation for biocompatibility testing may utilize some non-standardized techniques. Additional guidance on absorbable VDDCPs can be found in ISO/TR 37137.

NOTE 4 Additional guidance on drug toxicology issues can be found in ICH M3(R2), ICH S1A, ICH S1B, ICH S1C(R2), ICH S2(R1), ICH S3A, ICH S3B PK, ICH S4, ICH S5(R2), ICH S6, ICH S6(R1), ICH S7A, ICH S7B, and ICH S8.

7.2.4.3.17 Additional accessory-related considerations

The specific considerations regarding compatibility with accessory devices listed in ISO 25539-1 and ISO 25539-2 also apply to VDDCPs with a device component consisting of an endovascular prosthesis or vascular stent, respectively.

7.2.5 Preclinical in vivo evaluation

7.2.5.1 Purpose

The purpose of preclinical in vivo testing is to evaluate the positioning, deployment, withdrawal and follow-up of the VDDCP according to the instructions for use and to determine the response of both the host and the VDDCP. In particular, preclinical in vivo testing shall provide data pertaining to safety. The testing shall evaluate the suitability of the VDDCP for its intended use in clinical investigation.

7.2.5.2 Specific aims

The specific aims of the study shall be stated and may include the following, as appropriate:

a) the evaluation of the ability to position the DCP at the target location;

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

c) the evaluation of the position of the DCP of the VDDCP during procedural use and over time according to the design specifications, if applicable;

d) the evaluation of the ability of the VDDCP to maintain adequate integrity during procedural use and over time according to the design specifications;

e) the evaluation of the presence of the drug in the blood, in the treated tissue and in other relevant tissues over time;

f) the evaluation of appropriate haematological and biochemical laboratory parameters;

g) the assessment of local biological responses (e.g. vascular trauma, thrombus deposition, inflammation, endothelialization, necrosis, neointimal proliferation or aneurysm formation) and downstream and systemic effects (e.g. embolism or infarction) through an evaluation of the histology and pathology of explants and pertinent tissues/organs;

h) the recording of adverse events and potential contributing factors (for instance, in order to understand better whether an adverse event was caused by the VDDCP or the delivery system).

More than one study may be used to address the specific aims above.

For an in vitro-in vivo correlation (IVIVC), consider the correlation between an in vitro property of an extended-release dosage form (if applicable) and the in vivo response. The correlation should describe the in vitro rate or the extent of drug dissolution or release and the measured in vivo effect (e.g. the drug tissue level). Due to local application, low drug doses and the potential for drug uptake into the tissue, IVIVC evaluation with systemic blood plasma level measurements in some cases is not feasible. Additionally, local tissue measurements often cannot be obtained or validated because of measurement variability (i.e. inconsistent quantification and/or sample preparation issues). In the absence of appropriate methods for systemic blood or local tissue sampling, evaluation of the amount of drug remaining on the VDDCP can be used to estimate the in vivo release rate.

Animal studies are primarily designed to demonstrate safety. However, end points that can be related to the relative benefit of the VDDCP should also be included, if possible. In the event that the animal studies provide a signal of relative effectiveness, this can help support a risk-benefit determination, such as whether or not to proceed with a clinical study. This can be particularly important if the animal studies also demonstrate delays in healing or other minor effects of drug delivery using a VDDCP.

7.2.5.3 Protocol

Each VDDCP shall be tested at the intended vascular site or at an anatomically analogous site, providing justification for the alternative site, if used. Whenever possible, animal models shall be chosen to most closely mimic the clinical site, vascular anatomy, physiology (e.g. coagulation system) and drug metabolism as compared to humans. The number of animals used for testing shall also be justified.

When identifying study follow-up time points, consideration shall be given to how long the device and drug-containing parts of the VDDCP are expected to remain in the body (e.g. for a limited period [≤24 h], for a prolonged period [>24 h to 30 d], or permanently [>30 d]). Long-term in-dwelling VDDCPs or VDDCPs with absorbable components, can necessitate additional study follow-up time points.

Long-term studies for VDDCP implants lasting at least 26 weeks in each animal can be necessary, unless a justification for a shorter-term study can be provided. The type of interim assessment and the intervals between assessments shall be specified and justified. For novel technologies, interim sacrifices and longer implant durations may be indicated.

For VDDCP studies of both implanted and non-implanted products, at least one study (in multiple animals) should characterize the release, retention, distribution and absorption of the drug. This data may include drug plasma levels, drug tissue levels and the amount of drug left on the VDDCP, over time. Alternatively, qualitative methods can be useful to address these issues (e.g. fluorescent labelling).

As far as permitted by the limitations of the animal model, all VDDCPs used shall be of clinical quality and size, and of the design intended for clinical use.

At least one safety study of the VDDCP shall include assessment of dose-dependent effects, including the effect of overdosing (with no drug, the nominal drug dose and overdose) unless justification can be provided for omission of this type of testing. Local, regional (downstream) and systemic toxicities shall be assessed.

If patients are to be treated with multiple VDDCPs clinically, there can be additive dose and/or product compatibility issues that may need to be considered for animal study design.

If the proposed VDDCP is intended for use with an already implanted VDDCP (i.e. another product), there can be product compatibility issues that may need to be considered for the animal study design.

Interpretation of animal study results may be enhanced by the use of at least a small number of control devices for comparison purposes. A justification shall be provided if no control devices are used in the study. Both control devices and drugless VDDCPs (e.g. matrix without the drug), if applicable, should be used as control articles. For implanted products, if the matrix is not expected to remain over the implant life, additional testing of the underlying materials shall be considered.

All animals in the study shall be monitored daily and examined as determined necessary by appropriate veterinary staff. All animals, including any that expire prior to scheduled termination, shall undergo a post-mortem examination. The cause of death or illness, and the extent, to which the VDDCP was implicated, shall

be investigated and documentation regarding the findings provided with the final study report. Histological and pathological assessment of explants and appropriate tissues/organs is often necessary.

The design of the preclinical in vivo testing, including the experimental protocol, measurement methods, tissue handling, pathological evaluation plan and data analysis, shall be specified. In addition, the choice of animal model such as species, gender, age and whether or not a lesion is created, shall be justified and shall be consistent with the study objectives. Device use (e.g. implantation, balloon application) shall be consistent with the recommended instructions for clinical use, as far as permitted by the limitations of the animal model, including overlap of stents, if applicable.

When similar products are on the market and safety issues are reported, these shall be taken into account in the design of the animal study (e.g. late stent thrombosis which can result from inadequate endothelial cell coverage of a drug-eluting stent).

Animal welfare requirements per ISO 10993-2 shall be appropriately addressed during the design of the animal study.

NOTE 1 Downstream histopathological assessments can be used to assess potential clinical implications of particulates released from the VDDCP, and/or the response to chemical components and/or metabolites released from the VDDCP.

NOTE 2 Quantitative morphometrics and qualitative morphological assessments can be helpful to the histopathological analysis. Scanning electron microscopy can be helpful to assess completeness of endothelialization along the length and circumference of the vessel. Special staining can be necessary to investigate neointimal composition, fibrin deposition or mineralization. Angiographic assessments can be useful in follow-up observations, depending on the product type.

NOTE 3 The following animal-husbandry-related points, if appropriately addressed, can support optimal animal welfare conditions and potentially prevent differences in data outcomes due to inter-species and intra-species variability or unintended physiologic responses that can be caused by extreme physiologic or mental states in common research animals:

— accurate definition of and minimization of background pathogens (such as the acquisition of animals from closed herds or pathogen-defined herds);

— shipping methods (animals shipped in air-conditioned trucks, in single containers, and whether any national or regional policies or regulations were followed to minimize transportation stress);

— shipping not allowed within the first week following surgery;

— housing conditions ensuring lack of crowding, raised floor surfaces, prevention of sore feet;

— appropriate temperature, humidity, and lighting conditions;

— appropriate diet (such as screening for unacceptable feed additives such as melamine, aflatoxin and other known contaminants of swine food) and water;

— sufficient acclimation period;

— socialization or companionship;

— lack of crowding or isolation in the research facility;

— appropriate bedding and bedding replacement frequency.

NOTE 4 See also any region-specific guidance on preclinical in vivo evaluations, such as the US FDA 21 CFR 58, the Japanese Ministry of Health, Labour and Welfare Ordinance #37 “Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies on Medical Devices,”[102] or the EU GLP Directives: 2004/10/EC[95] and 2004/9/EC[94].

7.2.5.4 Data acquisition

The following minimum data shall be recorded for each animal receiving a VDDCP:

a) identification data:
   1) source of animal;
   2) animal identification;
   3) sex;
   4) age;
   5) weight;

b) pre-operative data:
   1) verification of health status, including appropriate blood testing (haematological and biochemical laboratory parameters);
   2) medications (e.g. prophylactic antibiotics);

c) operative data:
   1) date of procedure;
   2) name of person performing procedure;
   3) description of VDDCP placement, including:
      i) identification of VDDCP and accessory devices;
      ii) VDDCP identification number;
      iii) relevant in situ dimensions of VDDCP;
      iv) relevant dimensions of target anatomic location (e.g. vessel diameter);
      v) use of any kind of medication, e.g. antithrombotic therapy;
      vi) description of route of placement of VDDCP;
      vii) VDDCP location;
      viii) performance issues noted with VDDCP placement and/or accessories;
   4) assessment of parameters specified in the protocol, such as:
      i) safety, accuracy and efficacy of drug delivery;
      ii) safety of VDDCP deployment and withdrawal of the VDDCP delivery system, if applicable;
      iii) appropriateness of size and sizing scheme;
      iv) position, integrity and functionality of the drug-containing part of the VDDCP;
      v) adverse perioperative events;
      vi) appropriate haemodynamic (e.g. heart rate, blood pressure, electrocardiogram) and haematological (e.g. glucose, red blood cell, haemoglobin, haematocrit) parameters;

d) post-operative and follow-up data:
   1) post-operative duration at the time of follow-up;

2) medications, including those that affect coagulation;

3) methods used and results of the assessments specified in the protocol, such as:

i) position, integrity, and functionality of the drug-containing part of the VDDCP;

ii) adverse events, date of occurrence, therapy and outcome;

iii) level of drug in the blood, if required by the protocol;

iv) appropriate haematological and biochemical laboratory parameters;

4) any major deviation from the protocol;

e) termination data:

1) date of death;

2) reason for early termination or death, if applicable;

3) assessments specified in the protocol (e.g. observation of integrity, functionality, patency and position of the VDDCP);

4) gross observation of the withdrawn or explanted VDDCP and surrounding tissue;

5) if required by the protocol, a pathologist's report, including pathological assessment of the local vascular response to the VDDCP and any additional appropriate tissues and/or organs;

6) level of drug in the tissue, if required by the protocol.

7.2.5.5 Test report and additional information

The results for all the animals enrolled in the protocol shall be recorded and reported, even if they are excluded from the final analysis.

The test report shall include the following:

a) study protocol;

b) justification for selection of the following:

1) animal species;

2) procedure/implantation site;

3) procedure/implantation durations;

4) methods of data analysis assessment;

5) type of interim assessment and intervals between assessments;

6) sample size (i.e. number of animals and VDDCPs);

7) control, if applicable;

c) justification for not using a control group, if applicable;

d) results:

1) animal accountability, including justification for exclusion of data;

2) summary of adverse events;

3) summary of early deaths or sacrifices, indicating the reason;

4) significant and/or relevant deviations from the protocol;

5) summary of results, discussion and conclusions for each specific aim of the study;

6) pathological assessment of appropriate tissues and/or organs, including representative gross photographs and micrographs, if required by the protocol;

7) summary of quality assurance and data-auditing procedures, including a statement relative to compliance to appropriate standards.

7.3 Clinical evaluation

7.3.1 Purpose

The purpose of the clinical evaluation is to provide reasonable assurance of the safety and to evaluate the performance of the VDDCP. Included in the clinical investigation shall be appropriate testing of any VDDCP incorporating design characteristics for which the safety and effectiveness have not been previously demonstrated. The investigation shall be carried out using the principles given in ISO 14155. The VDDCP shall satisfy all appropriate preclinical in vitro and in vivo testing requirements of this document before starting the clinical investigation.

7.3.2 Specific aims

Specific aims of the study shall be stated and can include, as appropriate:

a) the evaluation of the ability to position the DCP at the target location;

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

c) the evaluation of the acute (less than 24 h), sub-acute (24 h to 7 d), and chronic (more than 7 d) position of the DCP of the VDDCP, if applicable;

d) the evaluation of the acute (less than 24 h), sub-acute (24 h to 7 d), and chronic (more than 7 d) structural integrity and functionality of the VDDCP, if applicable;

e) the monitoring of local and systemic drug effects (over time);

f) the evaluation of any explants;

g) the evaluation of the pathology of any pertinent tissues/organs;

h) the recording of adverse events, VDDCP failure modes and VDDCP effects.

7.3.3 Clinical investigation plan

A multicentre study (at a minimum of three investigation sites) shall be performed. A justification for the number of investigation sites shall be provided. A statistical justification for the number of patients studied shall also be provided, based upon the clinical hypotheses. The calculation of the number of patients to be enrolled shall take into account patients who will be lost to follow-up.

The duration of patient follow-up shall be determined in relation to the objectives of the clinical investigation. The duration of follow-up shall also take into account the effect of comorbidities on the life expectancy of the patient population. All patients treated with either test or control VDDCPs, including those excluded from the final analysis, shall be recorded and reported. The final report shall include all follow-up data as specified by the investigation plan.

Patient follow-up intervals shall include a minimum of a baseline assessment at discharge and at the end of the study. A justification shall be provided for timing of follow-up intervals.

If an appropriate control is not, or cannot be identified, or a concurrent control is unnecessary, a method for evaluating the clinical outcomes shall be prospectively defined and justified. The control should be appropriate to the questions being addressed in the study.

A specific question or set of questions shall be defined prospectively. These questions shall delineate the appropriate end points to be measured. Definitions of success and failure shall also be prospectively defined for all primary and any secondary end points where statistical analyses (other than presentation of descriptive statistics) will be used to support marketing approval.

In addition, the way in which the success of the entire study will be determined shall be prospectively defined. The definitions of success and failure shall incorporate quantitative values specifically applicable to the imaging modalities or other evaluation techniques to be used in the study. If a statistical analysis will be applied to the data to measure study success, an outline of the statistical-analysis plan shall be in place prior to initiating the study and the detailed plan finalized prior to evaluating the study data.

NOTE 1 See ISO 14155 for statistical considerations for the clinical investigation plan.

NOTE 2 Preliminary studies can be necessary to characterize the pharmacokinetics and metabolism of the drug as well as to determine the safety of the drug for human use, prior to initiation of the VDDCP study. These studies are not always necessary for APIs with previous approval for use in humans or with available human-safety study information. However, additional studies can be needed, if the proposed VDDCP use is for vascular delivery of a drug approved for a different route of administration.

Patient selection and exclusion criteria shall be clearly established. The criteria shall specify the target population (i.e. those for whom the VDDCP is intended) and the accessible population (i.e. those who agree to participate fully in the study). An appropriate epidemiological approach shall be utilized for recruiting subjects to minimize bias, unless otherwise justified.

If patients are to be treated with multiple VDDCPs clinically, there can be additive-dose and/or product compatibility issues that may need to be considered for clinical study design.

Prior to study initiation, a study monitoring plan shall be outlined, as appropriate. Detailed case report forms and informed consent documents shall also be prepared for the review of the appropriate oversight committee or regulatory body. See ISO 14155 for additional study monitoring, case report form and informed consent document considerations.

7.3.4 Data acquisition

At a minimum, the following data shall be recorded for each patient in the study:

a) identification data:

   1) patient identification;

   2) gender;

   3) date of birth;

   4) name of investigator;

   5) name of institution;

b) pre-operative data:

   1) risk factors, such as hypertension, diabetes, stroke risk, hyperlipidaemia, tobacco use, obesity, chronic renal failure, anaesthesia risk, myocardial infarction and other relevant vascular risk factors;

   2) summary of previous vascular interventions, including non-surgical interventions, and vascular implants;

   3) relevant medications;

4) urgency of intervention (i.e. emergent, urgent or elective);

5) diagnostic criteria:

i) clinical assessment;

ii) objective assessment of lesion and access vessel characteristics and other relevant factors (such as sizes, degree of calcification, tortuosity and angle of attachment sites);

c) operative data:

1) name of physician;

2) date of procedure;

3) identification data for the VDDCP(s), including product name, model number, traceability information, size and configuration;

4) details of procedure, including any adjunctive vascular procedures performed;

5) assessment of positioning, deployment, placement and withdrawal;

6) reportable clinical events, as defined by the protocol (see Annex A for definitions of potential clinical events):

i) severity, management and outcome;

ii) documentation of the relationship of the clinical event to the VDDCP and/or probable causative factors (i.e. VDDCP properties, individual patient factors, technical factors or other);

7) medications used during the procedure;

d) post-operative data:

1) date of each follow-up visit;

2) summary of vascular interventions since last follow-up;

3) clinical evaluation (assessment plan may differ between the control group and the treatment group):

i) clinical assessment;

ii) objective assessment of VDDCP performance (e.g. VDDCP migration, patency, percentage of diameter stenosis, DCP integrity, unanticipated alterations in shape), if applicable;

iii) objective assessment of target site characteristics and VDDCP positioning, if applicable;

NOTE In addition, data from a subgroup of patients can be necessary to characterize drug levels in blood over time, if pre-clinical in vivo data indicate drug release occurs over time (this assessment can be conducted as a separate study).

4) VDDCP-relevant medications, such as antithrombotics or antibiotics;

5) reportable clinical events as defined by the protocol (see Annex A for definitions of potential clinical events):

i) event, date of occurrence, severity, management and outcome;

ii) documentation of VDDCP involvement;

iii) documentation of the relationship of the clinical event to the VDDCP and/or probable causative factors (i.e. VDDCP properties, individual patient factors, technical factors or other);

6) medications used during the hospital stay (while some hospital/discharge medications may not seem relevant to the procedure/patient outcomes (such as sleeping medications), with VDDCPs

which include an API there can be unanticipated adverse events related to these medications, so consider capturing all medications);

7) medications prescribed at discharge;

8) date of hospital discharge;

e) patient withdrawal:

1) date;

2) months of study completed;

3) reason for withdrawal (lost to follow-up, death).

7.3.5 Final report

The final report shall include, at a minimum, the following:

a) study protocol;

b) definitions of reportable clinical events (see Annex A for definitions of potential clinical events);

c) justification for selection of the following:

1) study size;

2) choice of control;

3) measurement methods;

4) statistical analyses employed;

5) patient follow-up intervals;

d) procedural data and peri-procedural (less than or equal to 30 days after the procedure) and late (more than 30 days after the procedure) follow-up data:

1) patient accountability, including the justification for the exclusion of data;

2) significant and/or relevant deviations from the protocol;

3) summary of patients not completing the study (e.g. lost to follow-up or due to death);

4) summary of reportable clinical events:

i) by type of event, including timing of event relative to procedure (i.e. procedural, peri-procedural and for each follow-up time interval);

ii) by patient, including timing of events;

5) summary of VDDCP performance;

6) summary of VDDCP performance over time (e.g. VDDCP migration, patency, percentage of diameter stenosis, DCP integrity, unanticipated alterations in shape), if applicable;

7) if required by the protocol, summary of drug levels in the blood over time;

8) summary of target site characteristics related to DCP performance over time;

9) summary of any intraprocedural, adjunctive or subsequent secondary interventions (e.g. atherectomy, post-dilation) needed after the VDDCP intervention to optimize the results;

10) summary of conversions to non-endovascular operative surgery;

11) summary of peri-procedural and late deaths;

12) summary of pathology, if appropriate, including representative gross photographs and micrographs;

13) comparison of results for test and control groups;

14) conclusions for each specific aim of the study.

7.4 Post-market surveillance

A systematic procedure to review post-market experience gained from VDDCPs shall be in place, using the principles given in ISO 14630:2012, 7.4, ISO 14971:2019, Clause 9.

8 Manufacturing

8.1 General

A VDDCP shall be manufactured in such a way that the specified design attributes are met and the specifications are maintained. For critical parameters that do not include 100 % in process control inspections, validation testing shall be conducted. This validation testing shall demonstrate that VDDCP manufacturing processes consistently result in product that meets specifications, and thereby such manufacturing tolerances are acceptable.

NOTE The requirements of ISO 13485 for device quality management systems can apply.

The finished VDDCP shall be evaluated to determine the initial performance characteristics. However, if there are differences between the VDDCP from the initial evaluation, clinical models (VDDCPs used in human studies), and the VDDCP to be commercialized (due to scale-up of the manufacturing process), the changes shall be clearly documented and appropriate additional testing shall be conducted or scientific justification provided to demonstrate that these modifications will not affect the safety or effectiveness of the VDDCP. Changes to the manufacturing specifications used during clinical evaluation as compared to commercialization shall also be evaluated and justified.

Manufacturing controls to minimize unintended particulates shall manage three areas of concern: components and raw materials, the manufacturing process, and the manufacturing environment. The potential impact of any changes in these areas on unintended device particulates shall be evaluated and documented. Monitoring may include identification of unintended particulates present on a VDDCP and in the manufacturing processes.

8.2 Raw material reporting and analysis of the API

8.2.1 For submissions to national or regional regulatory authorities, the following information shall be provided for each API raw material included in a pharmacopoeia as a monograph:

a) name and address of the supplier;

b) certificate of analysis (COA) from the supplier;

c) results from incoming qualification procedures;

d) results from any additional testing (e.g. good manufacturing process (GMP) certificates, drug master files for various national or regional regulatory authorities).

8.2.2 For submissions to national or regional regulatory authorities, the following information shall be provided for each API raw material not included in a pharmacopoeia as a monograph:

a) name and address of the supplier;

b) specifications;

c) COA from the supplier;

d) results from incoming qualification procedures;

e) additional information as appropriate (e.g. GMP certificates, drug master files for various national or regional regulatory authorities).

NOTE Regional regulatory authorities can request information on the analytical procedure's validation to verify whether incoming API specifications have been met.

8.2.3 In order to permit continued use of an API that has been stored beyond its retest (expiry) date, retesting in accordance with the stability specifications shall be conducted to allow continued use (see ICH Q7).

8.3 Raw material analysis and reporting for excipients

8.3.1 For submissions to national or regional regulatory authorities, the following information shall be provided for each excipient raw material included in a pharmacopoeia as a monograph:

a) name and address of the supplier;

b) COA from the supplier;

c) results from incoming qualification procedures;

d) results from any additional testing.

8.3.2 For submissions to national or regional regulatory authorities, the following information shall be provided for each excipient raw material not included in a pharmacopoeia as a monograph:

a) name and address of the supplier;

b) specifications;

c) COA from the supplier;

d) results from incoming qualification procedures;

e) additional information as appropriate (e.g. safety data for novel excipients).

Information can also be requested on the analytical procedure's validation to verify whether incoming excipient specifications have been met.

8.4 VDDCP batch release testing

The batch release reports for the VDDCP shall include the following:

a) batch identity (e.g. batch number, dose, product size);

b) date of manufacture;

c) site of manufacture;

d) date of sterilization;

e) acceptance criteria and results for each parameter tested (e.g. drug identity, impurities, drug content and drug release rate).

NOTE For submissions to national or regional regulatory authorities, the following batch release information can also be requested for the VDDCP:

— clarification as to whether the batches reported on were used for clinical testing, non-clinical testing (e.g. in vitro, in vivo preclinical or stability studies) or qualification of the commercial product;

— validation of the analytical procedures used to verify that the acceptance criteria have been met.

9 Sterilization

9.1 Products supplied sterile — Testing to support "Sterile" labelling

VDDCPs that are labelled "STERILE" shall comply with international, national, and regional sterilization standards appropriate to the country of distribution. VDDCPs that are labelled "STERILE" shall have a sterility assurance level (SAL) of 10^{-6}.

NOTE For examples of sterilization requirements, see EN 556 and ANSI/AAMI ST67.

Sterilization processes shall be validated and routinely controlled.

VDDCP sterilization processes shall be characterized in accordance with ISO 14937.

9.2 Products supplied non-sterile

VDDCPs that are provided non-sterile, shall be sterilized prior to clinical use. The requirements of ISO 14630:2012, 9.3.1 shall apply.

9.3 Sterilization residuals

If VDDCPs are sterilized using ethylene oxide sterilization, the requirements of ISO 10993-7 for ethylene oxide and ethylene chlorohydrin (ECH) residuals shall apply.

NOTE See Clause B.2 for information on the history of sterilization residuals for devices and drug or medicinal products.

10 Packaging

10.1 General

The requirements of ISO 11607-1, and for non-active devices ISO 14630:2012, Clause 10, shall apply.

10.2 Considerations for VDDCPs

The impact of environmental variables such as oxygen, light, temperature, and humidity on packaging shall be considered, to maintain the appropriate physical, chemical, pharmaceutical, and mechanical specifications of the VDDCP.

Packaging materials that have direct contact with the DCP shall be included in the VDDCP evaluation.

10.3 Impact of changes in storage and shipping temperatures on VDDCP

The affect of extreme temperatures during storage and shipping on the VDDCP should be considered. Table 1 gives examples of possible thermal-cycling conditions.

Table 1 — Examples of thermal-cycling tests

Thermal test description	Number of cycles	Cycle conditions
Test A: Freeze/thaw	3	2 d at –20 °C then 2 d at 5 °C
Test B: Warm/cold	3	2 d at 40 °C (75 % RH) then 2 d at 5 °C

11 Information supplied by the manufacturer

11.1 General

The requirements of ISO 14630:2012, Clause 11 and ISO 15223-1 shall apply to VDDCPs.

11.2 Labelling

11.2.1 VDDCP label(s)

Each VDDCP shall be accompanied by one or more labels, one on each of the containers.

At a minimum, the following information shall be supplied on each label:

a) description of the contents;

b) name and/or trade name and address of the manufacturer or authorized representative, including at least the city and country;

c) name of the VDDCP;

d) model/reference number;

e) batch number or serial number, if applicable, as described in ISO 14630:2012, 11.2 c);

f) sterilization method and the indication “STERILE”, if applicable;

g) single-use, if applicable;

h) expiration date, expressed as year and month (YYYY-MM), with the VDDCP expiring at the end of the labelled month;

i) warnings or references to read the instructions for use manual;

j) applicable dimensions of the VDDCP, such as diameter, and length of a stent or catheter, in accordance with ISO 25539-2 or ISO 11070;

k) recommendations for storage, taking into consideration the drug-containing part of the VDDCP;

NOTE CPMP/QWP/609/96/Rev 2 contains information for labelling statements for storage conditions for medicinal products in the European Union.

l) chemical nature of any storage medium in the unit container, with an appropriate hazard warning, if applicable;

m) UDI information, as applicable;

n) if using electronic labelling, include the appropriate symbol in accordance with ISO 15223-1.

11.2.2 Record label

Each VDDCP should be supplied with transferable record labels suitable for attachment to the records of the patient receiving the VDDCP. The record label should include the following information:

a) product name;

b) manufacturer's batch and/or sterile-lot number;

c) part or model number (manufacturer's catalogue number).

11.3 Instructions for use

The VDDCP shall be supplied with instructions for the use. The instructions shall include the following:

a) description of the drug-containing part of the VDDCP:
   1) identification and description of the drug;
   2) identification and description of the matrix;
b) location of the drug-containing part of the VDDCP;
c) nominal drug content of the VDDCP;
d) indications for use;
e) contraindications, cautions and warnings that are applicable:
f) relevant drug information;
g) potential for drug interactions associated with the drug-containing part of the VDDCP;
h) potential for drug interaction between VDDCPs in the case of direct contact;
i) VDDCP handling and contact with fluid prior to placement;
j) MRI safety and compatibility information, including any impact of an RF-induced temperature rise on the drug part of the VDDCP (recommendations for MR labelling can be found in ASTM F2503);
k) potential adverse events;
l) data from clinical studies, if applicable;
m) recommended methods for the aseptic presentation and the preparation of the product system;
n) the statement “STERILE” in prominent form, if applicable;
o) the statement “DO NOT RESTERILIZE” in prominent form, if applicable;
p) the statement “SINGLE USE ONLY” in prominent form, if applicable;
q) resterilization information, if applicable;
r) notification of additives and/or leachable components, if applicable;
s) recommendations for storage, handling and disposal, if applicable;
t) date of publication of the text (or some other indication making it clear whether the text has been revised or not).

Annex A
(informative)

Description of potential clinical and technical events

This annex provides an alphabetical listing of potential clinical events (see Table A.1) and potential technical events (see Table A.2) that can occur with use of a VDDCP. For the purposes of this annex, the term "device" below refers to the VDDCP. Potential technical events are those events which can be relevant to the DCP of the VDDCP.

Other types of product-specific potential clinical events and technical events can be found in relevant device-specific standards such as ISO 25539-1 for endovascular prostheses, ISO 25539-2 for vascular stents and the ISO 5840 series for cardiac valve prostheses. There can be differences between the descriptions in Table A.1.

Where differences between the descriptions of potential clinical events given in Table A.1 and other references occur, one should choose the description that is most appropriate for the particular product under consideration, and in consultation with the local regulatory authority.

Table A.1 — Listing of potential clinical events

Potential clinical event	Description
Adverse biological response (toxic reaction) to device	Local, regional and/or systemic toxic reaction to the device. The type of reaction should be documented.
Aneurysm	For true aneurysms: localized abnormal dilatation of all or part of the treated vessel. For false (pseudo) aneurysms: an extravascular haematoma that communicates with the intravascular space. The aneurysm size and imaging modality should be specified in all cases.
Aneurysm enlargement	Any enlargement of the diameter or volume of the aneurysm greater than documented measurement error. the aneurysm size and imaging modality should be specified.
Aneurysm rupture	Rupture of the native aneurysm.
Angina pectoris	Chest, neck, arm or other pain related to decreased coronary blood flow.
Arrhythmia	Development of a new atrial or ventricular rhythm disturbance or exacerbation of a prior arrhythmia requiring treatment (i.e. medical therapy, cardioversion, pacemaker) from procedure until 30 days after final drug release.
Atelectasis/pneumonia	Atelectasis or pneumonia documented by chest X-ray within 30 days of the procedure and requiring treatment with antibiotics, inhalation therapy, intubation or suctioning. The type of treatment required should be reported.
Cardiac tamponade	Mechanical compression of the heart by large amounts of fluid or blood within the pericardial space that limits the normal range of motion and function of the heart.
Coagulopathy	Development of a bleeding disorder which can lead to an increased propensity for thrombosis or bleeding, documented by appropriate laboratory studies from procedure until 30 days after final drug release. The specific syndrome or factor deficiency(ies) should be noted.
Congestive heart failure	Peripheral or pulmonary oedema as a result of: a) haemodynamic decompensation from an acute episode or exacerbation of existing low cardiac output, or b) decompensation of a high cardiac output state.
Damage to adjacent structures	Damage to adjacent organs by device.

Table A.1 *(continued)*

Potential clinical event	Description
Damage to end organ	Injury to any organs distal to the device or target organs related to device component embolization.
Damage, systemic	Injury to any organs that can be related to device (e.g. systemic drug release).
Damage, vascular (vascular trauma)	Injuries to vessels as a result of a procedure, including dissections or perforations, or false or true aneurysms. The specific site (e.g. access site, treatment site, proximal or distal vessel) and the source of the injury, as well as the clinical sequelae, should be reported. All surgical or interventional procedures required to repair the injury should be reported.
Oedema	An abnormal accumulation of excess serous fluid in connective tissue.
Embolism, pulmonary	Clinical evidence of pulmonary embolism, confirmed by high-probability ventilation/perfusion scan, computed tomography scan, or pulmonary angiography, occurring within 30 days of the procedure.
Embolization	Movement of intraluminal debris (e.g. from delamination, or particle generation) or thrombus into the distal bloodstream, detected by clinical sequelae or captured on imaging.
Extravasation of contrast	Extravascular leaking of contrast material, noted at the time of imaging.
Haematoma, major	Development of a haematoma related to the procedure and requiring medical intervention, such as a blood transfusion, ultrasound guided compression, or thrombin injection, or surgical repair. Documentation of the haematoma size should be included in the case report forms.
Haematoma, minor	Development of a haematoma related to the procedure but not requiring medical intervention other than manual compression.
Hepatic encephalopathy	Neurological dysfunction due to inadequate detoxification of the blood by the liver.
Hypotension	Low blood pressure.
Impotence, vasculogenic	Subjective report or documentation of failure, due to vasculogenic causes, to resume, within six months of the procedure, the degree of sexual function registered preoperatively.
Inadequate contrast flow	Inability to inject sufficient volumes of contrast media to visualize properly the deployment site, the patient anatomy and/or the device itself.
Inadequate haemostasis	Inability to avoid excessive bleeding from the insertion site.
Inadequate VDDCP visibility	Inability to image the VDDCP or a necessary portion of the VDDCP in accordance with the requirements of the IFU.
Inadequate vessel imaging	Inability to adequately visualize the vascular anatomy caused by the VDDCP in situ.
Insertion site infection	Confirmed wound infection at insertion site.
Ischemia	Acute (less than 24 h), sub-acute (24 h to 7 d) or chronic (more than 7 d) development of inadequate blood supply to an end organ within 30 d of the procedure. The cause, location and severity of the ischemia should be diagnosed and reported (e.g. embolism, thrombosis, flow-limiting stenosis, restenosis or dissection).
Lumen obstruction	Unintended obstruction of flow through the vascular lumen due to twisting or kinking of the device, inappropriate device sizing, failure of the device to fully deploy, or any other cause.
Lymphocele/lymphatic fistula	Cystic accumulation of lymph or insufficient wound drainage occurring at an incision site. Any intervention required to resolve the event should be reported.
Malapposition, VDDCP	Appreciable portion of the device not in direct contact with the vessel wall. Note timing in relation to procedure.
Misplacement	Deployment of the VDDCP in an unintended location.
Mortality, late	Death attributable to the device occurring more than 30 days after the procedure.
Mortality, periprocedural	Death from any cause occurring up to 30 days after the procedure.

Table A.1 *(continued)*

Potential clinical event	Description
Myocardial infarction	Detection of rise and/or fall of cardiac biomarkers (CK-MB or troponin) with at least one value above the 99th percentile of the upper reference limit (URL), together with evidence of myocardial ischemia with at least one of the following: — symptoms of ischemia; — ECG observations indicative of new ischemia (new ST-T changes or new left bundle branch block); — development in the ECG of pathological Q-waves ≥ 0,03 s in duration and ≥1 mm in depth in ≥2 contiguous precordial leads or ≥2 adjacent limb leads; — imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. If the 99th percentile of the URL from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the myocardial-infarction decision limit for the particular laboratory should be used as the URL. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. CK may be used in the absence of CK-MB.
Neurological deficit	Development of a new transient or permanent neurological deficit or exacerbation of a prior deficit as determined by CT/MRI scan and/or clinical examination that occurs within 30 days of the procedure whether the deficit was permanent or transient should be reported.
Neurological deficit, spinal	Neurological deficit related to spinal-cord ischemia developing within 30 days of the procedure.
Occlusion, branch vessel	Clinically significant, unplanned occlusion or obstruction of a major branch vessel.
Portal hypertension, recurrence of	Recurrent high blood pressure in the portal venous system.
Post-procedure bleeding	Procedure-related bleeding which occurs after the patient leaves the procedure room, up to 48 h after the procedure, resulting in the need for a blood transfusion. The volume of blood replaced, the source of the bleeding, and whether or not surgical intervention was required to stop the bleeding should be reported.
Procedural bleeding	Any blood loss requiring intervention (i.e. blood transfusion or medical therapy). The volume of blood lost during the procedure should be determined from the procedure report. The need for blood transfusion and the volume and source (banked, autologous, auto-transfused) of transfused blood should be reported.
Renal failure	Rise in creatinine level to more than 50 % above the pre-procedure level or an absolute increase of 0,5 mg/dl to 1,0 mg/dl, that does not spontaneously resolve itself. The need for, and duration of, dialysis, if required, should be reported.
Renal insufficiency	Rise in creatinine level to more than 25 % above the pre-procedure level or an absolute increase of 0,5 mg/dl that does not spontaneously resolve itself. The need for, and duration of, dialysis, if required, should be reported.
Respiratory failure	Need for post-procedural mechanical ventilation or the need for re-intubation or ventilator support, any time up to 30 days after the procedure (unless the patient was ventilator-dependent when he/she entered the study). The duration of ventilator support should be reported.
Restenosis	Significant reduction in luminal diameter when compared to the post-procedural vessel reference diameter. The degree of narrowing and the imaging modality should be specified.
Restenosis, binary	A >50 % narrowing of the lumen at the VDDCP site, with or without haemodynamic significance, confirmed by imaging.

Table A.1 *(continued)*

Potential clinical event	Description
Restenosis, in-segment	Significant reduction in luminal diameter at any point along the length of the VDDCP site, in addition to any reduction in luminal diameter within the adjacent sections of the vessel, when compared to the post-procedural vessel reference diameter. The degree of narrowing and the imaging modality should be specified.
Restenosis within the VDDCP	Significant reduction in luminal diameter at any point along the length of the VDDCP when compared to the post-procedural vessel reference diameter. The degree of narrowing and the imaging modality should be specified.
Sepsis	Development of a confirmed systemic infection occurring at any time following procedure. The aetiology (i.e. device sterility, endocarditis) should be reported, if known.
Stenosis, flow-limiting	Narrowing of the lumen at the VDDCP site or haemodynamically significant obstruction confirmed by imaging or another modality. The degree of stenosis associated with a threshold for intervention will depend on the specific vascular bed where the VDDCP is placed.
Stenosis, residual	A > 30 % narrowing of the lumen compared to the normal vessel diameter immediately after placing the VDDCP. The degree of narrowing and the imaging modality should be specified.
Subabrupt vessel closure	Severely reduced flow, within the target or other vessel, which was previously documented to be patent, occurring after the procedure is completed (and the patient has left the procedure room), but before 30 days.
Thrombosis	Haemodynamically significant clot formation within the lumen at the application site, occurring at any time following procedure. The degree of narrowing, the timing of the thrombosis in relation to the procedure and the imaging modality should be specified.
Thrombosis, deep-vein	Thrombus in a deep vein documented by duplex scanning, venography or another imaging technique.
Tissue necrosis	Cell death typically demonstrated by histology. In the absence of histological evaluation of tissue specimens, validated clinical imaging studies and/or validated serum biomarkers may be utilized. The timing of necrosis in relation to the procedure, the imaging modality utilized (if applicable), and biomarker measurements (if applicable) should be specified.
Infection localized to the device	Development of a confirmed infection localized to the device occurring at any time following device placement. The aetiology (e.g. device sterility, endocarditis) should be reported, if known.
Device realignment	Clinical symptoms associated with movement of the vessel relative to the device as a result of post-procedural morphological alterations (e.g. IVC filter tilt, blood flow alterations that result in tissue remodelling). The clinical symptoms, if any, should be specified.
Vessel occlusion, intraprocedural	Occlusion of flow, within the target or other vessel, which was previously documented to be patent with antegrade flow. This might be due to twisting or kinking of the VDDCP, failure of the VDDCP to fully deploy, dissection, or another cause. The imaging modality should be specified.
Vessel occlusion, late	Occlusion of flow, within the target or other vessel, which was previously documented to be patent with antegrade flow occurring more than 30 days after the procedure. This can be due to twisting or kinking of the VDDCP, intimal hyperplasia, dissection or another cause. The time of occlusion and the imaging modality should be specified.
Vessel occlusion, periprocedural	Occlusion of flow, within 30 days of the procedure, of the target or other vessel, which was documented to be patent with antegrade flow at the conclusion of the procedure. This can be due to twisting or kinking of the VDDCP, dissection or another cause. The time of occlusion and the imaging modality should be specified.

Table A.2 — Listing of potential technical events

Potential technical event	Description
Access failure	Failure to reach the intended site with the device due to mechanical failure of the device or patient or procedural factors.
Accessory device failure	Inability to use an accessory device as intended due to mechanical failure of the device or patient or procedural factors.
Corrosion	Deterioration of exposed metal surface and/or reduction of its strength and/or structural integrity due to electrochemical reactions with surrounding body or procedural fluids.
Damage to VDDCP	Damage to the device by any cause, such as by an accessory device or a transport device such as a catheter.
Interface failure	Complete or partial unintended separation of discrete structural or material elements of the VDDCP at the common boundary or interconnection within the DCP or between components of the DCP and other various components of the VDDCP (e.g. delamination of a coating from the underlying device).
Treatment delay	Preprocedural issues with VDDCP lead to postponement of procedure after patient is prepared for treatment. Impact on patient of unnecessary procedures e.g. fluoroscopy leading to radiation exposure.
VDDCP deployment failure	Inability to fully deploy the VDDCP at the intended site due to mechanical failure of the VDDCP, or patient or procedural factors.
VDDCP migration	Post-procedural movement of the VDDCP from its intended position.
Withdrawal failure	Inability to safely remove any product components not intended to remain in the body due to mechanical failure of the device or patient or procedural factors.

Annex B
(informative)

Local information regarding submission issues for VDDCPs

B.1 Information for local regulatory authorities

Table B.1 provides contact information for local regulatory authorities.

Table B.1 — Contact information for local regulatory authorities

Country	Responsible authority	Website
Australia	Therapeutics Goods Administration website (TGA)	https://www.tga.gov.au/
Brazil	National Health Surveillance Agency (ANVISA)	https://www.gov.br/anvisa/pt-br/english
Canada	Health Canada	https://www.canada.ca/en/health-canada.html
China	National Medical Product Administration (NMPA)	http://english.nmpa.gov.cn/
European Union	One Notified Body (NB) of the European member states The NB will consult a competent authority (CA) for drug related questions.	list of all NB: https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=notifiedbody.main list of all CA: https://www.ema.europa.eu/en/partners-networks/eu-partners/eu-member-states/national-competent-authorities-human
India	Director Controller General of India (DCGI)	https://cdsco.gov.in/opencms/opencms/en/About-us/who/
Japan	Ministry of Health, Labour and Welfare (MHLW) The application for approval of VDDCPs is to be submitted to Pharmaceuticals and Medical Devices Agency (PMDA).	MHLW: https://www.mhlw.go.jp/english/ PMDA: https://cdsco.gov.in/opencms/opencms/en/About-us/who/
Russia	Ministry of Health A NB is to be consulted to ensure compliance with local standards and provide a license of approval for marketing in Russia.	http://government.ru/en/department/23/events/
USA	US Food and Drug Administration (FDA)	https://www.fda.gov/

B.2 History of ethylene oxide sterilization residuals

Ethylene oxide (EO) is currently used for sterilization of many medical devices. The defined EO limits are sufficient for these medical devices. Since 2002, these EO limits have been applied to VDDCPs. For VDDCPs with multiple components such as an implant and a separate delivery system, separate EO residual testing can be necessary.

Although EO is not commonly used for the sterilization of drugs, national or regional regulatory authorities generally consider it necessary for drug products that are EO sterilized to meet tighter EO or ECH limits than devices, but these tighter drug limits are not necessary for VDDCPs.

Table B.2 gives an overview of the region-specific requirements for EO sterilization residuals for device limits, and drug or medicinal product limits for some national or regional regulatory authorities.

Table B.2 — Region-specific requirements for sterilization residuals

			Requirements for							
			EO				ECH (or any other halogenated ethylene hydrine)			
Device limits in ISO 10993-7	Short exposure		≤4 mg/d				≤9 mg/d			
	Long-lasting exposure		≤2 mg per mean daily dose	4 mg for the first 24 h	60 mg for the first 30 d		≤2 mg per mean daily dose	9 mg for the first 24 h	60 mg for the first 30 d	
	Continuous or permanent exposure		≤0,1 mg per mean daily dose	4 mg for the first 24 h	60 mg for the first 30 d	2,5 g per lifetime	≤0,4 mg per mean daily dose	9 mg for the first 24 h	60 mg for the first 30 d	10 g per lifetime
Device limits for Australia			see ISO 10993-7				see ISO 10993-7			
Device limits for Brazil			see ISO 10993-7				see ISO 10993-7			
Device limits for Canada			see ISO 10993-7				see ISO 10993-7			
Device limits for China			The Chinese limits are aligned with ISO 10993-7.							
Device limits for Europe			see ISO 10993-7				see ISO 10993-7			
Drug limits for raw materials for Europe[92]			1 µg/g				50 µg/g			
Device limits for India			see ISO 10993-7				see ISO 10993-7			
Device limits for Japan			see ISO 10993-7				see ISO 10993-7			
Device limits for the US			see ISO 10993-7				see ISO 10993-7			
Drugs limits in US FDA CDER[82] (for EO residuals recommendations for drug products, see Reference [83][a])	Blood-contacting		25 µg/g				25 µg/g			
	Implant	<10 g	250 µg/g				250 µg/g			
		>10 to <100 g	100 µg/g				100 µg/g			
		>100 g	25 µg/g				25 µg/g			
	Finished product		1 µg/g				50 µg/g			
	Packaging material		1 µg/ml of container volume				50 µg/ml			

NOTE 1 The values for EO are based on the limitation of EO residuals to 1 µg/g (i.e. the limit of detection).

NOTE 2 Information in this table is accurate at the time of its publication and is provided for guidance only. More recent documents can apply.

[a] The requirements proposed in 1978 in the US FDA rule[83] are no longer required.