TECHNICAL SPECIFICATION

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

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

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

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Foreword

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

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

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

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

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

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order to decide whether it will be confirmed for a further three years, revised to become an International Standard, or withdrawn.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again after a further three years, at which time it must either be transformed into an International Standard or be withdrawn.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

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

Introduction

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

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

NOTE For issues related to the primary mode of action of the vascular device, the reader might find it useful to consider a number of other International Standards (see Bibliography).

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

1 Scope

1.1 This Technical Specification specifies requirements for vascular device-drug combination products (VDDCPs) based upon current technical and medical knowledge. VDDCPs are medical devices with various clinical indications for use in the human vascular blood system. A VDDCP incorporates, as an integral part, substance(s) which, if used separately, can be considered to be a medicinal product (drug product) but the action of the medicinal substance is ancillary to that of the device and supports the primary mode of action of the device. With regard to safety, this Technical Specification outlines requirements for intended performance, design attributes, materials, design evaluation, manufacturing, sterilization packaging, and information supplied by the manufacturer. For implanted products, this Technical Specification should be considered as a supplement to ISO 14630, which specifies general requirements for the performance of non-active surgical implants. This Technical Specification should also be considered as a supplement to relevant device-specific standards, such as the ISO 25539 series specifying requirements for endovascular devices. Requirements listed in this Technical Specification also address VDDCPs that are not necessarily permanent implants.

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

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

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

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

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

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

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

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

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

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

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

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

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

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

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

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

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

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

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

3 Terms and definitions

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

NOTE Potential clinical events are defined in Annex A.

3.1
active pharmaceutical ingredient
API
drug
pharmacologically active (drug or medicinal) substance used as a raw material, which is coated on, bound to or incorporated into the device to achieve an ancillary device function, such as minimizing vascular restenosis

3.2
batch
quantity of VDDCP at the final stage or pre-final stage of manufacture which has undergone the same manufacturing cycle, using the same components (e.g. same coating solution, same device size), and meets the same specifications

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

3.3
clinical event
complication, failure or device-related observation that might be observed with clinical use of a VDDCP

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

3.4
device part of the VDDCP
DP
that part of the VDDCP intended to treat vascular disease by temporary or long-term intervention or implantation that does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but might be assisted in its function by such means

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

3.6
drug-containing part of the VDDCP
DCP
that part of the VDDCP that consists of the active pharmaceutical ingredient or matrix and associated device interfaces intended to assist in the primary mode of action of the device and/or diminish or ameliorate an unintended effect that placement of the device part might stimulate

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

EXAMPLES

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

b) the device surface(s);

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

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

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

3.9
drug delivery
local interaction between the VDDCP drug and the *in vivo* environment, whether the drug is released from, eluted from or remains bound to the VDDCP

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

NOTE There might be other impurities, evaluated separately from the drug-related impurities, that are related to manufacture of the matrix or other components of the VDDCP or come from processing aids, such as monomers, catalysts, residual matrix-related solvents or residual processing solvents.

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

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

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

3.13
evaluate
appraise or analyse qualitatively

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

EXAMPLES Polymers, adhesives.

3.15
matrix
any organic or inorganic material, other than living cells, intentionally applied by a manufacturer to a vascular device and designed for the purpose of drug storage, local drug activity at the surface and/or enabling, retarding, delaying or modifying drug release

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

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

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

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

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

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

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

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

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

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

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

NOTE The VDDCP can be permanently deployed (i.e. it can be an implant like a drug-eluting stent) or temporarily deployed (i.e. it can be a drug-eluting balloon, for instance).

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

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

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

4 General requirements

4.1 Classification

A VDDCP is a product that is considered to be a medical device but which incorporates, as an integral part, substances which, if used separately, can be considered to be a medicinal product. It is classified as a medical device, provided that the action of the medicinal substance is ancillary to that of the device, as reflected in the product claim and as supported by the scientific data provided by the manufacturer of the device.

4.2 Intended clinical location

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

a) abdominal aorta;

b) arterio-venous shunt for vascular access;

c) carotid;

d) coronary;

e) femoral;

f) iliac;

g) popliteal;

h) intracerebral;

i) renal;

j) thoracic aorta;

k) thoraco-abdominal aorta;

l) tibial;

m) other arterial or venous vessels to be specified.

5 Intended performance

The requirements of ISO 14630 shall apply.

6 Design attributes

6.1 General

The requirements of ISO 14630 shall apply.

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

a) the ability of the device part of the VDDCP (i.e. the device without the active pharmaceutical ingredient and matrix) to fulfil all product-specific requirements for the primary mode of action (e.g. the mechanical function) which are defined in the device-related standards;

b) the ability of the drug-containing part of the VDDCP to fulfil the drug-specific function and requirements of the VDDCP as defined in 6.2.

6.2 Drug-containing part of the VDDCP (DCP)

6.2.1 General

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

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

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

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

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

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

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

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

6.2.2 Matrix

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

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

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

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

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

e) if soluble or degradable, the ability to control the solubility or degradation behaviour and the interaction of the solubilized or degradation products with the body (mechanism of solubility or degradation, biocompatibility of the matrix as well as the degradation products);

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

6.2.3 Active pharmaceutical ingredient (API)

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

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

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

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

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

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

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

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

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

7 Materials

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

8 Design evaluation

8.1 General

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

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

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

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

The use of a control device for comparison should be considered in the evaluation of the design attributes relevant to the performance of the VDDCP.

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

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

For VDDCPs, long-term stability testing augmented by accelerated stability testing, such as defined by ICH guidelines, shall be used to define drug attributes for product shelf life. Additional guidance on stability testing of VDDCPs can be found in ICH Q1A(R2), ICH Q1B(R2), ICH Q1D and ICH Q1E. In addition, ICH Q3B(R2) and ISO 10993 provide guidance on how to test for identification of impurities and/or degradation products. ICH guidelines include specific testing time frames and environmental conditions that might not be appropriate for all product designs, storage conditions and climate zones. Testing intervals for identification of degradation products will depend on the potential degradation characteristics of the API and/or matrix, as well as the shelf life of the medical device.

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

8.2 Sampling

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

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

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

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

NOTE 2 It might be appropriate to assess some properties only at manufacture, if changes are not expected over the shelf life.

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

8.3 Conditioning of test samples

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

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

Samples should be subjected to conditions that are normally encountered that could affect the test results. Conditioning might include preconditioning of the VDDCP as recommended in the instructions for use. If the product is a single-use product, it might be necessary to consider whether multiple attempts with the same product should be included in a simulated-use test. If the product is a multiple-use product, the simulated-use test should incorporate this concept into the test protocol.

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

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

8.4 Reporting

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

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

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

Individual test reports should include the following information:

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

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

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

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

e) 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) 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 might also require submission of raw data and a detailed data analysis.

8.5 Testing of the device part of the VDDCP

Testing of the device part of the VDDCP (the DP) shall be conducted to evaluate the design attributes described in Clause 6, as applicable. The appropriate tests of each design attribute should evaluate potential failure modes and whether the intended product performance is attained.

If the DP is a temporarily placed product, such as a balloon, then testing should also address issues in relevant guidance documents and standards for non-drug-eluting balloons.

If the DP is an implant, such as a stent, coil, valve or graft, then testing should also address issues in relevant guidance documents and standards for these 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 Annex B.

8.6 Testing of the drug-containing part of the VDDCP

Testing of the drug-containing part of the VDDCP (the DCP) shall be conducted to evaluate the design attributes described in Clause 6, as applicable. The appropriate tests for each design attribute should evaluate potential failure modes, VDDCP or clinical effects associated with the potential failure modes, and whether the intended product performance is attained.

NOTE General documentation for the DCP aspects in the Common Technical Document (CTD) format might be helpful for the evaluation of the drug-related aspects by a national regulatory authority due to its internationally accepted format for medicinal products. See Clause B.9 for more information on CTDs.

8.7 Requirements for the drug-containing part of the VDDCP

8.7.1 Ability to access

8.7.1.1 General

This covers the ability of the DCP to permit the safe transport of a sufficient amount of API [i.e. drug(s)] to the target site during VDDCP delivery.

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

a) introducer and DCP not matching the access site (i.e. size mismatch);

b) unintended lack of mechanical (structural) integrity before advancing to target site/tissue (i.e. particle generation by API/matrix);

c) unintended lack of chemical integrity (i.e. lack of stability or purity of API and release of matrix degradation products);

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

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

f) chemical incompatibility with procedural fluids.

These hazards might result in clinical events.

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

Testing shall include the dimensional-compatibility evaluation given in 8.7.1.2.

8.7.1.2 Dimensional compatibility of components

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

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

8.7.2.1 General

This covers the ability of the VDDCP to deploy the DCP safely and deliver the intended amount of API at the target site.

NOTE 1 Drug delivery might not be limited by the intervention or procedure. The drug delivery time can be short (as in the case of burst release from a drug-eluting balloon) or longer (as in the case of sustained drug release by an implanted drug-eluting stent) or continued with local interaction (as in the case of a graft with a bound drug, such as covalently bound heparin).

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

a) unintended lack of mechanical (structural) integrity due to material degradation (API/matrix particle generation) (see 8.7.4);

b) unintended lack of chemical integrity (i.e. lack of stability or purity of API and unintended degradation of matrix) (see 8.7.4.3);

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

d) excessive API delivery;

e) inadequate (inefficient) API delivery;

f) unintended variability in localized API delivery;

g) chemical incompatibility with procedural fluids;

h) lack of appropriate biocompatibility.

These hazards might result in clinical events.

NOTE 2 Potential clinical events that could be evaluated are given in Annex A.

Testing shall include the items listed in 8.7.2.2 to 8.7.2.5, as appropriate to the design of the DCP.

8.7.2.2 Drug content

Determine the quantity of drug on the DCP (drug 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 and USP 905.

8.7.2.3 Drug distribution

Evaluate the drug distribution along the DCP surfaces.

NOTE This test is commonly done for product characterization.

8.7.2.4 Drug release profile

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

In vitro drug release profile testing could take into consideration the following:

— The rate of drug release and of the amount of drug remaining on the VDDCP at any given time.

NOTE 1 US Food and Drug Administration Draft Guidance, *Coronary drug-eluting stents — Nonclinical and clinical studies*, recommends that the elution profile be complete and cover the release of at least 80 % of the labelled amount of the drug or up to the point when a plateau is reached.

— The relative solubility of the drug (e.g. more lipophilic drugs might exhibit a longer elution time).

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

NOTE 2 Additional guidance on dissolution and release testing can be found in USP 711, USP 724, EP 2.9.3 and EP 2.9.4.

— Method validation information showing that the chosen method is able to detect manufacturing changes (under meaningful testing) that might have an effect on the release of the drug.

— 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.

NOTE 3 If the drug dispersion in the matrix can be characterized and controlled, this can improve the ability to attain the desired release.

The US Food and Drug Administration and the Chinese State Food and Drug Administration have requirements for the setting of drug release/elution acceptance criteria which include the following points:

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

— data from lots used in the clinical trials 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 elution profile should be selected (the acceptance criteria ranges should be based on the overall elution data generated at these times);

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

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

NOTE 4 Establishing an *in vitro*/*in vivo* correlation can be used to validate the clinical relevance of an *in vitro* drug release test, can aid in drug release specification setting and can be used to justify post-approval process changes or manufacturing site changes (see also 8.8.2).

8.7.2.5 Drug identity and purity

Confirm the API-specific identity and determine the purity by characterizing the types and amounts of drug-related impurities and degradant levels.

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

8.7.3 Ability to withdraw

8.7.3.1 General

This 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 include, but are not limited to, the following:

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

b) unintended lack of chemical integrity (i.e. lack of stability or purity of API and release of matrix degradation products);

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

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

e) chemical incompatibility with procedural fluids.

These hazards might result in clinical events.

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

8.7.4 Functionality

8.7.4.1 General

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

Hazards to be evaluated 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 integrity (i.e. lack of stability or purity of API and release of matrix degradation products);

c) excessive API delivery;

d) inadequate (inefficient) 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 might result in clinical events.

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

Testing shall include the items listed in 8.7.4.2 and 8.7.4.3, as appropriate to the design of the DCP.

8.7.4.2 Durability

8.7.4.2.1 General

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

For the device part of the VDDCP, product performance should also be evaluated in accordance with device-specific standards such as ISO 10555-1 and ISO 25539-2 (see also Bibliography).

8.7.4.2.2 DCP integrity

Evaluate the ability of the matrix part of the DCP to resist unintended integrity loss (e.g. delaminations, flaps or bare spots) when subjected to simulated-use testing conditions.

Visual examinations at pre-specified intervals over the expected lifetime of the DCP should be conducted. These inspection results should be compared to results obtained with the manufactured product to determine the effective life of the VDDCP. Results should be analysed with respect to available preclinical *in vivo* and clinical data.

NOTE If there is significant loss of integrity, this could impact drug delivery, and additional drug release testing might be necessary (see 8.7.2.4).

Accelerated test conditions may be employed provided justification is given.

8.7.4.2.3 Particulates

Evaluate any particulate released and/or generated by the VDDCP to determine the embolic risk to the patient during procedural, post-procedural and long-term use, as appropriate.

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

If particle generation occurs with otherwise correct drug delivery, special attention should be paid to characterization of the particles from the DCP. Further characterization of the particles, e.g. their identity and solubility, might be helpful in justifying acceptance of the type of particle, its size and the number generated.

8.7.4.3 Degradable matrix

If the matrix is intended to be degradable, the degradation behaviour, including the intermediate and final degradation products, should be described and evaluated.

When describing the degradation behaviour, it should be borne in mind that degradation defines the mechanism of breakdown, decomposition and dissolution of materials in a physiological environment.

NOTE Additional guidance on degradation testing can be found in ISO 15814 and ISO 13781.

8.7.5 Compatibility with procedural fluids

Evaluate the ability of the VDDCP to resist unintended chemical changes in the DCP (e.g. API decomposition and matrix degradation) when exposed to procedural fluids. Bench tests, such as API stability and drug release tests or preclinical *in vivo* tests to assess the compatibility with procedural fluids, might be appropriate.

8.7.6 Corrosion

Evaluate the influence of the DCP regarding the susceptibility of the VDDCP to corrosion in an actual or simulated environment, if applicable. Possible corrosion mechanisms include pitting, fretting, crevice corrosion and galvanic corrosion.

DCP (coating) artefacts and coating manufacturing processes can affect the corrosion potential of the final product and should be considered.

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.

8.7.7 Magnetic resonance imaging (MRI) safety and compatibility

Evaluate the safety and compatibility of the VDDCP with MRI.

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

a) magnetically induced displacement force and torque;

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

c) lack of sufficient quality imaging (image artefacts).

These hazards may result in clinical events.

NOTE 1 Potential clinical events that could 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 The MRI artefacts caused by some VDDCPs can compromise the effectiveness and limit the use of MRI in patients with these VDDCPs.

NOTE 4 Additional guidance on evaluating the marking of medical devices for safety in the magnetic resonance environment can be found in ASTM F2503.

8.7.8 Biocompatibility

Biocompatibility of the manufactured VDDCP should be tested in accordance with ISO 10993-1 and other relevant parts of ISO 10993. For extraction tests, the drug-containing part of a VDDCP should be tested separately from the device part of the VDDCP.

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 might 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 toxicity testing on the individual materials might be necessary, if not already carried out by the material supplier.

NOTE 3 Additional guidance on drug toxicology issues can be found in ICH S3A, ICH S7A, ICH E4 and ICH S4.

NOTE 4 If VDDCP testing is conducted and it results in toxic responses that could be attributed to the drug, it might be appropriate to also test products without the drug to confirm that the toxicity is a result of the drug itself.

8.8 Preclinical *in vivo* evaluation

8.8.1 Purpose

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

8.8.2 Specific aims

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

a) evaluation of the ability to access the target location with the drug-containing part of the VDDCP;

b) verification of the safety and accuracy of deployment of the drug-containing part of the VDDCP;

c) evaluation of the position, integrity and functionality of the drug-containing part of the VDDCP after placement, and withdrawal if applicable (e.g. if interventionally placed);

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

e) evaluation of appropriate haematological and biochemical laboratory parameters;

f) 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;

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

NOTE More than one study could be used to address the specific aims.

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 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 might not be 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, if the animal studies demonstrate delays in healing or other minor adverse effects of drug delivery using a VDDCP, the animal studies should also demonstrate some relative effectiveness so that a risk-benefit determination can be made as to whether or not to initiate a clinical trial.

8.8.3 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 and vascular anatomy. The number of animals used for testing shall also be justified.

At study follow-up time points, consideration should be given to how long the device and drug-containing parts of the VDDCP should remain [e.g. for a very short period (<24 h), for a short period (<30 days) or permanently]. Long-term in-dwelling VDDCPs, or VDDCPs with absorbable components, might require additional study follow-up time points.

Long-term studies for VDDCP implants lasting at least 26 weeks in each animal might 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 might be indicated.

For VDDCP trials of both implanted and non-implanted products, at least one study (in multiple animals) should evaluate the complete *in vivo* elution profile (*in vivo* pharmacokinetics), including drug plasma levels, drug tissue levels and the amount of drug left on the VDDCP, over time.

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.

Safety studies of VDDCPs should include assessment of dose-dependent effects, including the effect of overdosing (e.g. no drug, nominal drug dose and 3× overdose) unless justification can be provided for omission of this type of testing. Local, regional (downstream) and systemic toxicities should be assessed.

NOTE 1 Downstream histopathological assessments can be used to assess potential clinical implications of particulates released from the VDDCP.

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

Interpretation of animal study results might be enhanced by the use of at least a small number of control devices for comparison purposes. The rationale should 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 should 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 implant was implicated, shall be documented. Histological and pathological assessment of explants and appropriate tissues/organs shall be provided.

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. Implantation 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.

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

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

NOTE 3 The following animal-husbandry-related points, if appropriately addressed, might prevent data confounders that could contribute to poor outcomes:

— 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 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;

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

— a sufficient acclimation period;

— socialization or companionship;

— lack of crowding or isolation in the research facility;

— appropriate bedding and bedding changes.

NOTE 4 See ISO/IEC 17025 for guidance on appropriate laboratory practices.

8.8.4 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 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 haematological and biochemical laboratory 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) the 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.

8.8.5 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) rationale for selection of the following:

   1) animal species,

   2) procedure/implantation site,

   3) procedure/implantation durations,

   4) methods of 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) rationale for not using a control group, if applicable;

d) results:

   1) animal accountability, including rationale 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.

8.9 Clinical evaluation

8.9.1 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 testing requirements of this Technical Specification before starting the clinical investigation.

8.9.2 Specific aims

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

a) evaluation of the ability to access the target location with the drug-containing part of the VDDCP;

b) verification of the safety, accuracy and efficacy of deployment of the drug-containing part of the VDDCP;

c) evaluation of the acute (less than 24 h), sub-acute (24 h to 7 days) and chronic (more than 7 days) position, structural integrity and functionality of the drug-containing part of the VDDCP, after placement and withdrawal, if applicable (e.g. if interventionally placed);

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

e) evaluation of any explants;

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

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

8.9.3 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 implanted 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 trial. A justification will be required for 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 endpoints to be measured. Definitions of success and failure should also be prospectively defined for all primary and any secondary endpoints 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 should 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. An outline of a statistical-analysis plan should 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 might 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 trial. These studies might not be necessary for molecular entities (APIs) with previous approval for use in humans or with available human-safety study information.

Patient selection and exclusion criteria shall be clearly established. The criteria shall specify the target population (i.e. those for whom the DCP 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.

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

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

8.9.4 Data acquisition

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

a) identification data:

   1) patient identification,

   2) sex,

   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 deployment, positioning, placement and withdrawal,

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

   i) severity, management, 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 might differ between the control group and the treatment group):

   i) clinical assessment,

   ii) objective assessment of VDDCP performance (VDDCP migration, patency, percentage of diameter stenosis, DCP integrity), if applicable,

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

   iv) in addition, a subgroup of patients should be assessed for drug levels in blood over time (this assessment could 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 might not seem relevant to the procedure/patient outcomes (such as sleeping medications), with VDDCPs which include an API there could be some 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).

8.9.5 Final report

The final report shall include the following:

a) study protocol;

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

c) rationale 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 rationale 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, DCP integrity, change 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.

9 Post-market surveillance

A systematic procedure to review post-market experience gained from implants shall be in place, using the principles given in ISO 14630, ISO 14971 or an equivalent publication.

10 Manufacturing

10.1 General

A VDDCP shall be manufactured in such a way that the specified design attributes are achieved. Requirements are specified in related International Standards.

NOTE The requirements of ISO 13485 for good manufacturing practice might apply.

The finished VDDCP should 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 should be clearly documented and appropriate additional testing should be conducted or scientific rationale provided to demonstrate that these modifications will not affect the safety and effectiveness of the VDDCP. Changes to the manufacturing specifications used during clinical evaluation should also be evaluated in an appropriate way.

Products used in development studies (e.g. preclinical or clinical studies) should be considered when establishing production specifications for the DCP.

Manufacturing controls to minimize unintended particulate matter 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 device particulate matter should be evaluated. Monitoring might include identification of particulate matter present on a VDDCP and in the manufacturing processes.

10.2 Raw-material analysis and reporting for the API

The batch analysis reports for the API should include:

— batch identity (i.e. batch number) and size;

— date of manufacture;

— site of manufacture;

— manufacturing-process identification (e.g. synthesis route A), if there are different synthesis routes;

— results for each parameter tested (e.g. identity, solubility, hydrophobicity).

NOTE For submissions to a national regulatory authority, the following batch analysis information might also be needed for the API:

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

— results from testing of API compatibility with excipients in the VDDCP;

— API stability information (e.g. a summary of the results, if available, the retest date and recommended storage and handling conditions).

For an API that has been stored beyond its retest date, retesting (in accordance with the stability specifications) should be conducted to allow continued use (see ICH Q7A).

10.3 Raw-material analysis and reporting for excipients

For submissions to a national regulatory authority, the following information should be provided for each excipient included in a pharmacopoeia as a monograph:

— name and address of the supplier;

— certificate of analysis (COA) from the supplier;

— results from incoming qualification procedures;

— results from any additional testing.

For submissions to a national regulatory authority, the following information should be provided for each excipient not included in a pharmacopoeia as a monograph:

— name and address of the supplier;

— specifications;

— COA from the supplier;

— results from incoming qualification procedures;

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

NOTE For submissions to a national regulatory authority for excipients not included in a pharmacopoeia as a monograph, information might also be needed on the validation of the analytical procedures used to verify that the specifications have been met.

10.4 VDDCP batch release testing

The batch release reports for the VDDCP should include:

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

— date of manufacture;

— site of manufacture;

— date of sterilization;

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

NOTE For submissions to a national regulatory authority, the following batch release information might also be needed 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* or stability studies) or qualification of the commercial product;

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

11 Sterilization

11.1 Products supplied sterile

11.1.1 Labelling

11.1.1.1 VDDCPs that are labelled “STERILE” shall comply with international, national or regional standards. 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.

11.1.1.2 Sterilization processes shall be validated and routinely controlled.

11.1.1.3 If VDDCPs are to be sterilized by ethylene oxide, ISO 11135-1 shall apply.

11.1.1.4 If VDDCPs are to be sterilized by moist heat, ISO 17665-1 shall apply.

11.1.1.5 If VDDCPs are to be sterilized by radiation, ISO 11137-1 shall apply.

11.1.1.6 If VDDCPs incorporating animal tissue are to be sterilized using liquid chemical sterilants, ISO 14160 shall apply.

NOTE For VDDCPs sterilized using aseptic techniques, it might not be possible to achieve an SAL of 10^{-6}.

11.1.1.7 If VDDCPs are to be sterilized by other sterilization processes, ISO 14937 shall apply.

11.2 Products supplied non-sterile

The requirements of ISO 14630 shall apply.

11.3 Sterilization residuals

The requirements of ISO 10993-7 shall apply.

12 Packaging

12.1 Protection from damage during storage and transport

12.1.1 General

It is understood that this Technical Specification may be applied to both non-implantable products and implants. The requirements of ISO 14630 shall apply.

12.1.2 Unit container

Each VDDCP shall be packaged in a packaging system, which shall provide a sterile barrier, if applicable.

NOTE Other package attributes might be needed to eliminate the effects of light, moisture or other environmental factors in order to maintain the specification of the VDDCP throughout the labelled shelf life.

Each packaging system shall be placed in an outer container. This outer container shall be designed so as to protect, preserve and contain the unit container during storage.

12.1.3 Shipping container

Each outer container, or a number of outer containers, not necessarily of the same type, may be packaged in a shipping container designed to protect, preserve and contain the contents under normal conditions of handling, transit and storage.

12.1.4 Maintenance of sterility in transit

For VDDCPs that are supplied sterile, the unit container shall be designed to maintain the sterility of the VDDCP under normal conditions of handling, transit and storage and to permit the contents to be presented for use in an aseptic manner.

The packaging shall conform to ISO 11607-1.

Perform shipping challenge tests to verify the stability of the VDDCP.

Examples of thermal-cycling tests:

Test A (= 3 cycles): 1 cycle = 2 days at –20 °C then 2 days at 5 °C
Test B (= 3 cycles): 1 cycle = 2 days at 40 °C (75 % RH) then 2 days at 5 °C

12.2 Marking

12.2.1 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:

— description of the contents;

— name and/or trademark and contact information of the manufacturer;

— name of the VDDCP;

— model/reference number;

— lot/serial number;

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

— single-use, if applicable;

— expiration date;

— warnings or references to read the instructions for use manual (symbol);

— applicable dimensions of the VDDCP;

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

— chemical nature of any storage medium in the unit container, with an appropriate hazard warning, if applicable.

NOTE 1 Consider CPMP/QWP/609/96/Rev 2 for contained drug substances.

NOTE 2 Consider ISO 15223 for symbols to be used with medical-device labels.

12.2.2 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:

— product name;

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

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

12.3 Information supplied by the manufacturer

12.3.1 General

It is understood that this Technical Specification may be applied to both non-implantable products and implants. The requirements of ISO 14630 shall apply to VDDCPs.

12.3.2 Information and instructions for use (IFU)

Each unit container or outer container of which the contents are identical shall be supplied with instructions for the use of the VDDCP. The instructions shall include the following:

— description of the drug-containing part of the VDDCP:

  — identification and description of the drug,

  — identification and description of the matrix;

— location of the drug-containing part of the VDDCP;

— nominal drug content of the VDDCP;

— indications for use;

— contraindications, cautions and warnings that are applicable:

  — relevant drug information,

  — potential for drug interactions associated with the drug-containing part of the VDDCP,

  — potential for drug interaction between VDDCPs in the case of direct contact,

  — VDDCP handling and contact with fluid prior to placement,

  — 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);

— potential adverse events;

— data from clinical studies, if applicable;

— recommended methods for the aseptic presentation and the preparation of the product system;

— the statement “STERILE” in prominent form, if applicable;

— the statement “DO NOT RESTERILIZE” in prominent form, if applicable;

— the statement “SINGLE USE ONLY” in prominent form, if applicable;

— resterilization information, if applicable;

— notification of additives and/or leachable components, if applicable;

— recommendations for storage, handling and disposal, if applicable;

— date of publication of the text (or some other indication making it clear whether the text has been revised or not).

Annex A
(informative)

Definitions of potential clinical events

This annex provides an alphabetical listing of potential clinical events that could be evaluated in a clinical investigation of a VDDCP. Other types of product-specific potential clinical events can be found in relevant device-specific standards such as ISO 25539-1 for endovascular prostheses, ISO 25539-2 for vascular stents and ISO 5840 for cardiac valve prostheses.

Table A.1 — Definitions of potential clinical events

Potential clinical event	Definition
Accessory device failure	Inability to use an accessory device as intended due to mechanical failure or patient anatomy. Whether or not the failure contributed to an unsuccessful VDDCP deployment should be documented.
Adverse biological response (toxic reaction) to VDDCP	Local, regional and/or systemic toxic reaction to VDDCP. 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 artrial 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 edema as a result of: 1) haemodynamic decompensation from an acute episode or exacerbation of existing low cardiac output or 2) a decompensation of a high cardiac output state.
Corrosion	Deterioration of exposed metal surface and/or reduction of its strength and/or structural integrity due to electrochemical reactions with surrounding body fluids.
Damage to adjacent structures	Damage to adjacent organs by VDDCP.
Damage to end organ	Injury to any organs distal to the VDDCP or target organs related to VDDCP component embolization.
Damage, systemic	Injury to any organs related to VDDCP systemic drug release.

Table A.1 (*continued*)

Potential clinical event	Definition
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.
Damage to VDDCP	Damage to the VDDCP by any cause, such as by an accessory device or a transport device such as a catheter.
Delamination	Unintended physical separation of the VDDCP coating.
Device delivery failure	Failure to reach the intended site of action with the VDDCP due to mechanical failure or patient or procedural factors. Whether or not successful VDDCP deployment was achieved should be documented.
Device deployment failure	Inability to fully deploy the VDDCP at the intended site due to mechanical failure, patient or procedural factors.The amount of partial deployment, if any, should be documented.
Drug delivery failure	Inability to deliver the drug from the VDDCP.
Edema	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 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.
Generation of particles by system	Unintended generation of particles through abrasion, where particles become detached from their source and can migrate into the blood stream.
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.
Heating of VDDCP	Rise in temperature of a VDDCP, induced during magnetic resonance imaging.
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 6 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 days) or chronic (more than 7 days) development of inadequate blood supply to an end organ within 30 days 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).

Table A.1 (*continued*)

Potential clinical event	Definition
Lumen obstruction	Unintended obstruction of flow through the vascular lumen due to twisting or kinking of the VDDCP, inappropriate VDDCP sizing, failure of the VDDCP 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 VDDCP 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 VDDCP occurring more than 30 days after the procedure.
Mortality, periprocedural	Death from any cause occurring up to 30 days after the procedure.
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)[a], together with evidence of myocardial ischemia with at least one of the following: — symptoms of ischemia; — ECG changes 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. [a] 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-chord ischemia developing within 30 days of the procedure.
Non-sterile product	Ineffective sterilization of the VDDCP.
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, autotransfused) 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.

Table A.1 (*continued*)

Potential clinical event	Definition
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 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.
Restenosis, in-segment	Significant reduction in luminal diameter at any point along the length of the VDDCP, 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 VDDCP placement. 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 of the VDDCP, occurring at any time following VDDCP placement. 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.
VDDCP damage	Damage to the VDDCP by any cause, such as by an accessory device or by the deployment or delivery system.
VDDCP infection	Development of a confirmed VDDCP infection occurring at any time following VDDCP placement. The aetiology (i.e. device sterility, endocarditis) should be reported, if known.
VDDCP migration	A change in VDDCP position compared to its deployed position.
VDDCP realignment	Clinical symptoms associated with movement of the vessel relative to the VDDCP as a result of post-procedural morphological changes. The clinical symptoms should be specified (from ISO 25539-1).

Table A.1 (*continued*)

Potential clinical event	Definition
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 might 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 might be due to twisting or kinking of the VDDCP, dissection or another cause. The time of occlusion and the imaging modality should be specified.
Withdrawal failure	Inability to remove the VDDCP or deployment system as intended due to mechanical failure or patient anatomy or other patient factors.

Annex B
(informative)

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

NOTE Region-specific requirements might deviate from harmonized International Standards.

B.1 Australia

VDDCPs must be approved by the Department of Health and Ageing.

NOTE For more information, see http://www.tga.gov.au/.

B.2 Canada

VDDCPs must be approved by Health Canada.

NOTE For more information, see http://www.hc-sc.gc.ca/dhp-mps/md-im/index-eng.php.

B.3 China

VDDCPs must be approved by the China State Food and Drug Administration (SFDA).

VDDCPs have to comply with applicable local YY-series medical industrial standards.

Pharmaceuticals have to comply with the Pharmacopoeia of the People's Republic of China (CP). Pharmaceuticals not included in the CP have to be pre-approved for Chinese marketing by the SFDA.

NOTE 1 Table B.1 gives an overview of regional-standard codes and abbreviations.

Table B.1 — Chinese standard codes and abbreviations

Code	Type of standard	Institution
GB	Mandatory national standard	SAC
GB/T	Optional national standard	SAC
GB/Z	National standardization, technical document	SAC
YY	Mandatory medical industrial standard	SFDA
YY/T	Optional medical industrial standard	SFDA
SAC Standardization Administration of the People's Republic of China. SFDA State Food and Drug Administration of the People's Republic of China, Division of Standards, Technical Committee for medical-device standardization.		

NOTE 2 For more information, see http://eng.sfda.gov.cn/eng/.

NOTE 3 See also the Bibliography for local guidelines.

B.4 Europe

VDDCPs must be approved by a notified body as medical devices. The notified body has to consult a competent authority (national regulatory authority). VDDCP documentation must comply with MEDDEV 2.1/3, a guideline explaining the approval process for VDDCPs as well as the necessary content of documentation for product approval.

Pharmaceuticals have to be in compliance with the European Pharmacopoeia (EP).

NOTE 1 The notified bodies are listed at http://ec.europa.eu/enterprise/newapproach/nando/index.cfm?fuseaction=country.main.

NOTE 2 The competent authorities are listed at http://ec.europa.eu/enterprise/sectors/medical-devices/links/index_en.htm.

NOTE 3 MEDDEV 2.1/3-related information can be found at http://ec.europa.eu/enterprise/sectors/medical-devices/documents/guidelines/index_en.htm.

NOTE 4 Information concerning the council resolution on the so-called New Approach to technical harmonization and standards can be found at http://ec.europa.eu/enterprise/newapproach/index_en.htm#directives.

NOTE 5 See also the Bibliography for local guidelines, such as the Medical Device Directive.

B.5 Japan

VDDCPs must be approved by the Ministry of Health, Labour and Welfare (MHLW) as medical devices.

VDDCPs have to comply with applicable local approval guidelines and medical industrial standards.

Pharmaceuticals have to be in compliance with the Japanese Pharmacopoeia (JP).

NOTE See also the Bibliography for local guidelines.

B.6 USA

VDDCPs must be approved or cleared for market by the US Food and Drug Administration (FDA). For VDDCPs in which the primary mode of action is from the device (e.g. stents and balloons), FDA's Center for Devices and Radiological Health (CDRH) has primary review responsibility and consults with the Center for Drug Evaluation and Research (CDER) regarding drug-related issues.

NOTE 1 Information on general FDA policies and procedures can be found at http://www.fda.gov/.

NOTE 2 Information on FDA review of combination products can be found at http://www.fda.gov/CombinationProducts/default.htm.

NOTE 3 There are many FDA guidance documents applicable to submissions for VDDCPs. These guidance documents can be found at http://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If APIs are in compliance with the United States Pharmacopoeia (USP), this has to be noted in submissions to the FDA.

NOTE See also the Bibliography for local guidelines.

B.7 History of sterilization residuals

For a VDDCP, device limits apply.

NOTE Ethylene oxide (EO) is not commonly used for the sterilization of drugs. Drugs generally require tighter EO or ethylene chlorohydrin (ECH) limits than devices. Like devices, VDDCPs often have complex geometries, with many chemical compounds. It is often difficult to achieve the tight EO or ECH limits that are commonly required for drugs. Separate EO and ECH residual tests might be necessary for implanted and for non-implanted components of the VDDCP.

Table B.2 gives an overview of region-specific requirements for sterilization residuals.