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Cardiovascular implants — Endovascular devices —

Part 2: Vascular stents

Implants cardiovasculaires — Dispositifs endovasculaires —

Partie 2: Endoprothèses vasculaires

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

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

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

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 25539-2 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

ISO 25539 consists of the following parts, under the general title *Cardiovascular implants — Endovascular devices*:

— *Part 1: Endovascular prostheses*

— *Part 2: Vascular stents*

Introduction

This part of ISO 25539 has been prepared in order to provide minimum requirements for endovascular devices and the methods of test that will enable their evaluation. It is the second part of a proposed three-part standard. ISO 25539-1 addresses endovascular prostheses and ISO 25539-3 will address vena cava filters. ISO/TS 15539, from which this part of ISO 25539 is derived, serves as a rationale for the requirements of this document. The Technical Specification ISO/TS 15539 was developed by first identifying the design requirements for these devices and listing the potential device and clinical failure modes. Tests were then identified to address each of the failure modes. The requirements provided in this part of ISO 25539 are based on that assessment.

Cardiovascular implants — Endovascular devices —

Part 2: Vascular stents

1 Scope

1.1 This part of ISO 25539 specifies requirements for vascular stents, based upon current medical knowledge. With regard to safety, it gives requirements for intended performance, design attributes, materials, design evaluation, manufacturing, sterilization, packaging and information supplied by the manufacturer. It should be considered as a supplement to ISO 14630, which specifies general requirements for the performance of non-active surgical implants.

NOTE Due to the variations in the design of implants covered by this part of ISO 25539 and in some cases due to the relatively recent development of some of these implants (e.g. bioabsorbable stents, polymeric stents), acceptable standardized *in vitro* tests and clinical results are not always available. As further scientific and clinical data become available, appropriate revision of this document will be necessary.

1.2 The scope of this part of ISO 25539 includes vascular stents used to treat vascular lesions or stenoses, or other vascular abnormalities. These devices might or might not incorporate surface modifications of the stent such as drug and/or other coatings. Stents covered with materials that significantly modify the permeability of the uncovered stent are within the scope of ISO 25539-1. The stent design might dictate the need to address functional requirements identified in both ISO 25539-1 and this part of ISO 25539.

1.3 Delivery systems are included in this part of ISO 25539 if they comprise an integral component of the deployment of the vascular stent.

1.4 Procedures and devices used prior to the introduction of the vascular stent, such as balloon angioplasty devices, are excluded from the scope of this part of ISO 25539.

1.5 Some pharmacological aspects of drug eluting stents are addressed in this part of ISO 25539, but this document is not comprehensive with respect to the pharmacological evaluation of drug eluting stents.

1.6 Degradation and other time-dependent aspects of bioabsorbable and polymeric stents and coatings are not addressed by this part of ISO 25539.

1.7 With the exception of sterilization, this part of ISO 25539 does not address requirements for the evaluation of animal tissue products.

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 (all parts), *Biological evaluation of medical devices*

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 (both parts), *Packaging for terminally sterilized medical devices*

ISO 14155 (both parts), *Clinical investigation of medical devices for human subjects*

ISO 14160, *Sterilization of single-use medical devices incorporating materials of animal origin — Validation and routine control of sterilization by liquid chemical sterilants*

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*

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*

3 Terms and definitions

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

NOTE Bench and analytical tests are described in Annex B. Reportable clinical events are defined in Annex C.

3.1
balloon-assisted deployment
use of a balloon to facilitate the complete deployment (or expansion) of a self-expanding stent

3.2
balloon winging
cross-sectional shape of the balloon when deflated which can cause problems during withdrawal

NOTE Examples include stent migration, damage to host vessel or balloon, and inability to remove the balloon.

3.3
delivery system
system or mechanism used to deliver the stent to the targeted position and to deploy the stent

NOTE The delivery system is removed after stent placement. Examples of delivery systems include balloon catheters or mechanically activated systems.

3.4
determine
to quantitatively appraise or analyse

NOTE Also see **evaluate (3.8)**.

3.5
dogboning
dumbbell-shaped balloon observed during stent deployment when the unconstrained ends of the balloon expand beyond the dilated stent outer diameter

3.6
coating
organic or inorganic material, other than living cells, intentionally applied by a manufacturer to a substrate

NOTE This coating can be intended to be permanent or temporary, and can be applied to the external and/or internal surface.

3.7
drug content
amount of drug present on the surface(s) of a coating, as part of a coating or within the stent

3.8
evaluate
to qualitatively appraise or analyse

NOTE Also see **determine (3.4)**.

3.9
lumen reduction
reduction of diameter or cross sectional area as observed by imaging

3.10
reportable clinical events
complications, failures or device-related observations, including all adverse events and adverse device effects, that might be observed with clinical use of the stent system

NOTE Examples are listed in Annex C. These events might not have clinical significance and might not be attributable to the device.

3.11
stent configuration
stent shape (e.g. cylindrical, tapered, flared, coiled, segmented, bifurcated)

3.12
stent outer surface area
contact area between the stent and the vessel

3.13
stent-free surface area
percentage of surface area of cylinder formed by the implant frame, which is not covered by implant material

3.14
stent system
vascular stent and its delivery system or a vascular stent mounted on the delivery balloon as specified in the instructions for use (IFU)

3.15
vascular stent
stent
implant
transluminally placed balloon-expandable or self-expanding implant, which is used to treat vascular lesions by providing a mechanical support after deployment to maintain or restore vessel integrity

NOTE 1 Stents can or cannot incorporate surface modifications of the stent such as drug and/or other coatings.

NOTE 2 The following stent types are within the Scope of this part of ISO 25539.

3.15.1
articulated stent
stent constructed of segments with distinct connections

3.15.2
bare stent
stent without a coating or covering

NOTE Bare stents can be constructed of single or multiple materials.

3.15.3
bioabsorbable stent
stent that is designed to be a temporary structure without requiring explantation

3.15.4
balloon-expandable stent
stent where the diameter is increased from its pre-deployed size to its post-deployed size with the aid of a balloon catheter

3.15.5
coated stent
stent with a surface layer of an additional material(s) that does not provide significant (e.g. more than 5 %) structural support or appreciably reduce the permeability or stent-free surface area of the bare stent

3.15.6
composite stent
stent consisting of more than one material or material compound that provides significant (e.g. more than 5 %) overall structural support upon deployment

3.15.7
covered stent
stent covered with an additional material(s) that appreciably reduces the permeability and/or eliminates the stent-free surface area of the bare stent

NOTE Covered stents are within the Scope of ISO 25539-1. The stent design might dictate the need to address functional requirements identified in both parts 1 and 2 of ISO 25539.

3.15.8
drug eluting stent
DES
stent that delivers a drug(s) over time

3.15.9
self-expanding stent
stent where the diameter increases from its pre-deployed size to its post-deployed size when released from the delivery mechanism in absence of balloon inflation or other mechanical assistance

NOTE Self-expanding stents are within the scope of ISO 25539-1. The stent design might dictate the need to address functional requirements identified in both parts 1 and 2 of ISO 25539.

4 General requirements

4.1 Classification

A stent shall be designated by its configuration (see 3.11), type (see 3.15), materials of construction, and any surface modifications, coatings, and/or drugs.

4.2 Size

The size of a stent shall be designated by the following characteristics:

a) external diameter;

   1) self-expanding:

      i) unconstrained external diameter of the device, expressed in millimetres;

      ii) intended vessel lumen diameter range, expressed in millimetres;

   2) balloon expandable: range of intended expanded internal diameters;

b) minimum and maximum usable length, expressed in millimetres or centimetres.

4.3 Intended clinical use designation

The intended clinical use shall be designated by 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) renal;

i) thoracic aorta;

j) thoraco-abdominal aorta;

k) tibial;

l) other arterial vessels to be specified;

m) other venous vessels to be specified.

5 Intended performance

The requirements for intended performance of ISO 14630 shall apply.

6 Design attributes

6.1 General

The requirements for design attributes of ISO 14630 apply. In addition, the following shall be taken into account:

a) oxidation-potential, the possibility of crevice corrosion, passivation over the relevant parts;

b) fretting, galvanic and pitting corrosion;

c) interface between implant and body:

1) fixation hooks if present;

2) relative movement between stent and tissue;

3) forces exerted by the stent on the surrounding tissue;

4) forces required to deform the stent if the deformation is permanent;

d) expected ingrowth, penetration, perforation, tilting and migration; introduction and delivery systems.

NOTE These additional items are adapted from Clause 5 of EN 12006-3:1998[15].

The design attributes for vascular stents (with or without delivery system) are listed in Table A.2 with reference to the test sections for the evaluation of the design (Clause 8). It is recognised that not all tests identified in a category will be necessary or practical for any given stent and/or delivery system. The tests considered and the rationale for selection and/or waiving of tests shall be recorded.

6.2 Delivery system and stent system

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

a) the ability of the system to permit consistent, accurate and safe access to the intended location;

b) the ability of the system to permit consistent, accurate and safe deployment of the stent;

c) the ability of the system to permit consistent and safe withdrawal of the delivery system;

d) the compliance of the system with the requirements of ISO 10993-1 and appropriate other parts of the ISO 10993 series of International Standards (biocompatibility);

e) the ability of the system to minimise blood loss (haemostasis);

f) the visibility of the system under fluoroscopy or other technologies.

6.3 Implant

6.3.1 Stent

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

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

b) the ability of the stent to ensure effective fixation and apposition in the intended location within the vasculature;

c) the ability of the stent to maintain adequate integrity;

d) the consistency of the stent dimensions and its design for compatibility for use in specified vessel diameters;

e) the ability of the stent to maintain adequate blood flow through the lumen (patency);

f) the compatibility of the stent with exposure to magnetic resonance imaging (MRI) fields;

g) the compliance of the stent with the requirements of ISO 10993-1 and appropriate other parts of the ISO 10993 series of International Standards (biocompatibility);

h) the visibility of the stent under fluoroscopy or other technologies.

6.3.2 Coating

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

a) the ability of the coating to maintain adequate integrity over time according to design specifications (e.g. freedom from significant delamination, flaps and bare spots);

b) the appropriate interaction between the coating and the stent (e.g. coating influenced corrosion of the substrate);

c) the ability of the coating to maintain adequate resistance to unintended particulate generation;

d) the conformance of the coating dimensions and other coating parameters (e.g. porosity, density, distribution) to the design requirements;

e) the effect of MRI on the coating of a coated stent (e.g. heating).

6.3.3 Drug

The design attributes to meet the intended performance of the stent if the coating is a drug or if a drug is incorporated into the stent or coating shall additionally take into account at least the following:

a) the ability to reproducibly apply the desired drug type and amount to the stent;

b) the ability to release the desired amount of drug over the specified amount of time;

c) the conformance of the residual drug quantity to design specifications;

d) the freedom of the drug(s) from deleterious impurity and degradant levels at manufacture and with storage;

e) the appropriate interaction between the drug and the coating and/or the stent to which the drug is applied;

f) the effect of MRI on the drug of a drug-eluting stent (e.g. heating).

7 Materials

The requirements for materials of ISO 14630 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. For example, Nitinol materials dependent on shape memory properties shall be subjected to testing in order to assess transformation properties. In addition, for drug-eluting stents drug identity testing shall be performed, including the identification of impurities and degradants. Electro-chemical potentials of differing metals (stents, guidewires, other accessory devices) might require additional types of testing.

8 Design evaluation

8.1 General

The requirements for design evaluation of ISO 14630 apply. A risk assessment shall be carried out and the requirements of ISO 14971 shall apply.

Justification shall be provided for the properties not measured.

NOTE 1 All testing might not be appropriate for all stent system designs.

It is impossible to take into consideration all future and emerging technologies. The stent systems based on these new technologies will need to be evaluated following the basic requirements of this part of ISO 25539. Testing beyond the scope of this part of ISO 25539 might also be necessary in order to characterize these stent systems. Consideration shall be given to the failure modes of the stent systems and their effects on the performance of the implant in identifying the appropriate testing.

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 stent system 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 certain design attributes.

If overlapping of stents can be anticipated in clinical use (e.g. superficial femoral artery, coronary), integrity of the stent under study in overlapping configurations should be evaluated, unless justification can be provided for testing of individual stents. If overlapping with a different device is specifically indicated, testing should include evaluation with the indicated device.

Testing to establish the labelled shelf-life shall be conducted by repeating appropriate tests. Justification for the selection of tests shall be provided. For drug eluting stents, real time and accelerated testing conditions should be used to define drug attributes for product shelf life.

NOTE 2 Additional guidance for stability testing of drug products can be found in ICH[1)] Q1A[35] (R2), ICH Q1B[36], and ICH Q1D[37].

8.2 Sampling

A sampling plan shall be utilized which will ensure that adequate representation of the data has been obtained for each parameter measured. The design characteristics of the stent (including any drugs and/or coatings), delivery system and stent system shall be verified to be representative of the devices to be released for distribution, including all sizes, configurations and components.

The sampling shall fully represent the range of device designs and might not necessarily require the testing of each size. The stent sizes selected for testing shall represent the worst case combination(s) of diameter and length for each test. A rationale shall be provided for sample selection. It might be necessary to conduct an assessment to identify the size(s) of the device with the greatest potential for failure.

Sampling shall ensure adequate representation of the expected variability in the manufacture of devices.

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

1) International Conference on Harmonisation guidelines.

8.3 Conditioning of test samples

All samples shall be subjected to sterilization, including multiple sterilizations, if appropriate, unless justification is provided for use of nonsterilized products.

Samples shall be subjected to conditions that are normally encountered which might affect the test results. Conditioning might include loading the stent on or inside the delivery catheter, preconditioning of the stent system as recommended in the instructions for use (IFU), single or multiple passes through an anatomical model, and deployment of the stent.

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

8.4 Reporting

For the purposes of this part of ISO 25539, reporting relates to requests from a national regulatory authority or from a body responsible for assessing conformity.

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

A summary of results, with acceptance criteria and any potential clinical significance of the results, should be included and can be in tabular form. Consideration shall be given to the anatomical, physiological, and morphological conditions of the intended use in establishing the acceptance criteria. Justification and clinical applicability of acceptance criteria for each test shall 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 part of ISO 25539;

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 and the number of samples tested; selection of test article shall be justified (e.g. sizes, conditioning);

d) acceptance criteria: state the acceptance criteria for 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 on the interpretation of the results;

g) expression of results: describe testing results expressed in units as indicated in the test method;

h) conclusion: state conclusions, based on comparing results to acceptance criteria, including any potential clinical significance of these results.

8.5 Delivery system and stent system

8.5.1 Ability to access

8.5.1.1 General

This covers the ability of the system to permit safe, consistent and accurate access to the intended location.

For estimating risks, the hazards to be considered include, but are not limited to, the following:

a) guidewire not crossing the lesion;

b) introducer and delivery system not matching the access site (i.e., size mismatch);

c) delivery system not advancing to target site;

d) embolism and air embolization;

e) stent dislodgement.

These hazards might result in reportable clinical events, including but not limited to the following:

— access failure;

— vascular trauma;

— neurological deficit;

— ischemia;

— spinal neurological deficit;

— embolization;

— procedural bleeding.

Testing shall include the following items listed in 8.5.1.2 to 8.5.1.13, as appropriate to the design of the stent system.

8.5.1.2 Bond strength

Determine the longitudinal bond strength between parts of the delivery system. All bonds shall remain intact under recommended conditions of use. The results shall be evaluated in relation to the force(s) necessary to access the intended location.

8.5.1.3 Component dimension compatibility

Evaluate the dimensions of the stent system for compatibility with the dimensions of recommended accessories. All components shall be dimensionally compatible. The need for contrast to be able to pass through the lumen of the guide catheter or introducer with the stent system in place should be considered.

8.5.1.4 Dimensional verification

Determine the appropriate dimensions for conformance with design specifications.

8.5.1.5 Dislodgement force (pre-mounted balloon expandable stents)

Determine the force required to dislodge the premounted stent from the crimped position on the non-expanded balloon and to completely separate the stent from the non-expanded balloon during clinical use.

8.5.1.6 Flex/kink

Evaluate the ability of the stent system to bend in order to accommodate the predetermined clinically relevant radius or angle it will be required to negotiate during access and delivery.

8.5.1.7 Profile/diameter test

Determine the maximum diameter along sections of the stent system.

8.5.1.8 Pushability

Evaluate the ability of the stent system to be pushed or positioned by an operator without undesirable bending or buckling.

8.5.1.9 Simulated use

Evaluate the performance of the stent system using a model(s) that simulate(s) the intended use conditions.

8.5.1.10 Torquability

Evaluate the ability of the stent system to provide sufficient rotation to the distal (leading) end to deliver the stent within the anatomy, if appropriate for the intended clinical use.

8.5.1.11 Torsional bond strength

Determine the torque/rotation required to break joints and/or materials in the appropriate delivery system components, if appropriate for the intended clinical use. The results shall be evaluated in relation to the torque necessary to access the system.

8.5.1.12 Trackability

Evaluate the ability of the stent system to advance through the vessel to the target site using the recommended accessories. Evaluate the potential for displacement of the guidewire from its intended position during the advancement of the stent system, as appropriate for the intended use of the stent (e.g. loss of side-branch access during stenting).

8.5.1.13 Visibility

Evaluate the ability to visualize the delivery system and/ or stent system during access using fluoroscopy. The use of other technologies for visualization shall be justified.

8.5.2 Ability to deploy

8.5.2.1 General

This covers the ability of the system to permit safe, consistent and accurate deployment of the stent.

For estimating risks, the hazards to be considered include, but are not limited to, the following:

a) inability to fully and properly deploy the stent;

b) stent dislodgement;

c) balloon failure (if applicable);

d) stent or delivery system damage;

e) inadequate visualization;

f) embolism and air embolization.

These hazards might result in reportable clinical events, including, but not limited to, the following:

— delivery system failure;

— deployment failure;

— spinal neurological deficit;

— neurological deficit;

— vascular trauma;

— ischemia;

— embolization;

— damage to stent;

— procedural bleeding.

Testing shall include the following items listed in 8.5.2.2 to 8.5.2.13, as appropriate to the design of the stent system.

8.5.2.2 Bond strength

Determine the longitudinal bond strength between parts of the delivery system. All bonds shall remain intact under recommended conditions of use. The results shall be evaluated in relation to the force(s) necessary to deploy the stent.

8.5.2.3 Balloon inflation time (balloon expandable or balloon assisted stents)

Determine the time required to expand the balloon to the maximum recommended inflation pressure, volume or diameter. The stent system should be used for this test if the stent is intended to be mounted on the balloon during inflation.

8.5.2.4 Balloon deflation time (balloon expandable or balloon assisted stents)

Determine the time required to deflate the balloon and evaluate the ability to remove the deflated balloon from within the stent.

8.5.2.5 Balloon rated burst pressure (RBP) (balloon expandable or balloon assisted stents)

Determine the burst pressure with an appropriate safety margin. The stent system should be used for this test if the stent is intended to be mounted on the balloon during inflation.

Designate the maximum recommended inflation pressure. This pressure should not exceed the RBP.

8.5.2.6 Balloon rated fatigue (balloon expandable stents)

Evaluate the ability of the balloon to withstand a clinically justified number of repeated inflation cycles to the rated burst pressure. The stent system should be used for this test if the stent is intended to be mounted on the balloon during inflation.

Designate the maximum recommended number of inflation cycles.

8.5.2.7 Component dimension compatibility

Evaluate the dimensions of the stent delivery system for compatibility with the dimensions of recommended accessories. All components shall be dimensionally compatible. The need for contrast to be able to pass through the lumen of the guide catheter with the stent system in place should be considered.

8.5.2.8 Dimensional verification

Determine the appropriate dimensions for conformance with design specifications.

8.5.2.9 Dislodgement force (pre-mounted balloon expandable stents)

Determine the force required to dislodge the premounted stent from the crimped position on the non-expanded balloon and to completely separate the stent from the non-expanded balloon during clinical use.

8.5.2.10 Dogboning (balloon expandable stents)

Determine the diameter(s) of the balloon extending beyond the ends of the stent that are greater than the stent outer diameter(s) at the maximum recommended inflation pressure.

8.5.2.11 Force to deploy (self-expanding stents)

Determine the force to deploy the stent from the delivery system.

8.5.2.12 Simulated use

Evaluate the performance of the stent-system using a model that simulates the intended use conditions.

8.5.2.13 Visibility

Evaluate the ability to visualize the stent and delivery system during placement and deployment using fluoroscopy. The use of other technologies for visualization shall be justified.

8.5.3 Ability to withdraw

8.5.3.1 General

This covers the ability of the system to permit safe and consistent withdrawal of the delivery system.

For estimating risks, the hazards to be considered include, but are not limited to, the following:

a) improper balloon deflation (balloon expandable);

b) balloon winging (balloon expandable);

c) lack of structural integrity;

d) embolism;

e) diameter mismatch;

f) stent dislodgement;

g) stent or delivery system damage;

h) delivery system snags on, or adheres to the stent;

i) inadequate visualization.

These hazards might result in reportable clinical events, including, but not limited to, the following:

— delivery system failure;

— deployment failure

— neurological deficit;

— vascular trauma;

— ischemia;

— spinal neurological deficit;

— embolization;

— damage to stent;

— procedural bleeding.

Testing shall include the following items in 8.5.3.2 to 8.5.3.9, as appropriate to the design of the stent system.

8.5.3.2 Bond strength

Determine the longitudinal bond strength between parts of the delivery system. All bonds shall remain intact under recommended conditions of use. The results shall be evaluated in relation to the force(s) necessary to withdraw the system.

8.5.3.3 Component dimension compatibility

Evaluate the dimensions of the stent delivery system for compatibility with the dimensions of recommended accessories. All components shall be dimensionally compatible. The need for contrast to be able to pass through the lumen of the guide catheter with the stent system in place should be considered.

8.5.3.4 Dimensional verification

Determine the appropriate dimensions for conformance with design specifications.

8.5.3.5 Flex/kink

Evaluate the ability of the stent system to bend in order to accommodate the predetermined clinically relevant radius or angle it will be required to negotiate during access and delivery.

8.5.3.6 Simulated use

Evaluate the performance of the delivery system using a model that simulates the intended use conditions.

8.5.3.7 Torsional bond strength

Determine the torque/rotation required to break joints and/or materials in the appropriate delivery system components, if appropriate for the intended clinical use. The results shall be evaluated in relation to the torque necessary to withdraw the system.

8.5.3.8 Tubing tensile strength

Determine the strength of the tubing used in the delivery system as appropriate to the material.

8.5.3.9 Visibility

Evaluate the ability to visualize the delivery system during withdrawal using fluoroscopy. The use of other technologies for visualization shall be justified.

8.5.4 Biocompatibility

Biocompatibility shall be tested in accordance with ISO 10993-1 and appropriate other parts of the ISO 10993 series of International Standards. For extraction tests, the stent should be tested separately from the delivery system.

8.5.5 Haemostasis

8.5.5.1 General

This covers the ability of the system to minimise blood loss.

For estimating risks, the hazards to be considered include, but are not limited to, the following:

a) component dimensional incompatibility (size mismatch);

b) seal incompetence;

c) other leakage.

These hazards might result in reportable clinical events, including, but not limited to, the following:

— procedural bleeding;

— haematoma.

Testing shall include the following items listed in 8.5.5.2 to 8.5.5.4, as appropriate to the design of the stent system.

8.5.5.2 Component dimension compatibility

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

8.5.5.3 Dimensional verification

Determine the appropriate dimensions for conformance with design specifications.

8.5.5.4 Assessment of haemostasis

Evaluate the ability of any seal or valves in the delivery system to maintain an adequate haemostatic seal when used with appropriate accessory devices.

8.6 Stent

8.6.1 Ability to accurately deploy

8.6.1.1 General

This covers the ability to permit safe, consistent and accurate deployment of the stent at the intended lesion location.

For estimating risks, the hazards to be considered include, but are not limited to, the following:

a) inaccurate positioning or orientation;

b) improper deployment configuration;

c) incomplete deployment;

d) inadequate visualization.

These hazards might result in reportable clinical events, including, but not limited to, the following:

— branch vessel occlusion;

— delivery system failure;

— deployment failure;

— stent migration;

— intraprocedural vessel occlusion;

— ischemia;

— vascular trauma.

Testing shall include the following items listed in 8.6.1.2 to 8.6.1.5, as appropriate to the design of the stent.

8.6.1.2 Stent length-to-diameter relationship

Determine the relationship between stent length and expanded stent diameter.

8.6.1.3 Profile effect/flaring (balloon expandable stents)

Determine the change in distance between the external diameter of the stent and the external diameter of the balloon after tracking through a tortuous path.

8.6.1.4 Simulated use

Evaluate the performance of the stent using a model that simulates the intended use conditions.

8.6.1.5 Visibility

Evaluate the ability to visualize the stent during deployment and after withdrawal of the delivery system using fluoroscopy. The use of other technologies for visualization shall be justified.

8.6.2 Fixation effectiveness

8.6.2.1 General

This covers the ability of the stent to remain in its deployed position.

For estimating risks, the hazards to be considered include, but are not limited to, the following:

a) incomplete apposition to vessel wall;

b) excessive or inadequate radial outward force.

These hazards might result in reportable clinical events, including, but not limited to, the following:

— stent migration;

— intraprocedural vessel occlusion;

— vascular trauma;

— trauma to adjacent structures;

— branch vessel occlusion.

Testing shall include the following items in 8.6.2.2 to 8.6.2.8, as appropriate to the design of the stent.

NOTE Four tests are listed below, which determine forces related to the deformation of the stent. Although similar, crush resistance with a radially applied load, crush resistance using parallel plates, local compression and radial force tests measure different attributes of the stent, as follows:

— the crush resistance test with a radially applied load measures the ability of a balloon-expandable stent to resist permanent deformation when subjected to a circumferentially uniform radial load;

— the crush resistance test using parallel plates measures the ability of a stent to resist permanent deformation along the entire length of the device when subjected to a load uniformly applied over the length of the device;

— the local compression test measures the ability of a stent to resist permanent deformation under a localized (e.g. point) load;

— the radial force test measures the force exerted by a self-expanding stent on the vessel in the deployed state during expansion and compression.

8.6.2.2 Conformability to vessel wall

Evaluate the ability of the stent to adequately contact the vessel wall upon deployment.

8.6.2.3 Crush resistance with a radially applied load (balloon expandable stents)

Determine the load/deformation characteristics of the stent while a circumferentially uniform radial load is applied.

8.6.2.4 Crush resistance with parallel plates

Determine the load required to cause clinically relevant buckling or a deflection reduction of at least 50 % of the original distance between the plates and the load required to permanently deform or fully collapse the stent. This test is required for stents that can experience direct compression in a clinical setting.

8.6.2.5 Local compression

Determine the load/deformation characteristics of the stent in response to a localized compressive force, perpendicularly applied to the longitudinal axis of the device, and its ability to recover to its original geometry. The plate deflection should be reduced by at least 50 % at the point of contact. This test is required for stents of a design with the potential for a different response to local compression as compared to a radial or flat plate compressive force and for which this test is clinically relevant.

8.6.2.6 Radial force

Determine the force (expansion and compression) exerted by a self-expanding stent as a function of the stent outer diameter.

8.6.2.7 Recoil (balloon expandable stents)

Determine the percent change of the stent outer diameter from the maximum outer diameter obtained with balloon inflation, to the final outer diameter after balloon removal. The sizing scheme recommended for the stent in the IFU should take into consideration this recoil.

8.6.2.8 Simulated use

Evaluate the performance of the stent using a model that simulates the intended use conditions.

8.6.3 Stent integrity

8.6.3.1 General

This covers the ability of the stent to resist structural failure.

For estimating risks, the hazards to be considered include, but are not limited to, the following:

a) structural failure of the stent, including the coating, if applicable;

b) loss of complete apposition to vessel wall;

c) excessive, unintended stent expansion non-uniformity.

These hazards might result in reportable clinical events, including, but not limited to, the following:

— stent fracture;

— residual stenosis;

— in-segment restenosis;

— in-stent restenosis;

— restenosis;

— vessel occlusion, intraprocedural;

— vessel occlusion, periprocedural;

— vessel occlusion, late;

— stent migration;

— vascular trauma;

— ischemia due to emboli or in-stent thrombosis;

— trauma to adjacent structures.

Testing shall include the following items listed in 8.6.3.2 to 8.6.3.6, as appropriate to the design of the stent.

8.6.3.2 Acute coating integrity

Evaluate any damage to the coating due to loading, tracking, deployment and delivery system withdrawal.

8.6.3.3 Coating dimensions and other coating parameters (e.g. porosity, density distribution)

Determine the appropriate dimensions of the stent coating for conformance with design specifications.

8.6.3.4 Corrosion

Evaluate the susceptibility of the stent to corrosion in an actual or simulated environment. These corrosion mechanisms can include pitting, fretting, crevice and galvanic corrosion.

Coating artefacts and coating manufacturing processes might affect corrosion potential of final product and should be considered.

8.6.3.5 Durability

8.6.3.5.1 General

The evaluation of long-term durability under anticipated physiological conditions shall be performed. If not all stent sizes and configurations are evaluated, the size(s) and configurations to be evaluated shall be selected to represent the greatest potential for fatigue failure, so that conclusions regarding the acceptable durability can be reasonably applied to other sizes and configurations not tested. Results from the testing and the analyses to evaluate the durability of the stent are complementary and should be interpreted both independently and in combination.

The following items shall be considered in evaluating stent durability:

— overlapping stents, as appropriate;

— potential failure modes, such as, strut or bridge fracture, wear, permanent deformation, loss of coating integrity (e.g. delamination, particle shedding or dehiscence);

— *in vivo* loads, as appropriate to the specific intended site of implantation (e.g. bending, radial, axial, torsion, crush);

— limitations of the test and associated potential artefacts.

Testing has not yet been standardized for the evaluation of the effects of physiological loads beyond radial loading. Testing and/or analyses in addition to those listed below might be necessary to fully evaluate all physiologic loading and potential failure modes. Anatomic variability and post-implant morphologic changes should be considered in establishing appropriate boundary conditions for test and/or analysis.

8.6.3.5.2 Stress/strain analyses

Determine the critical stresses and/or strains in the stent due to manufacturing, catheter loading, delivery, deployment and *in vivo* loading, using appropriate tools such as finite element analysis (FEA). The material properties shall be selected as those appropriate to the specific stage of manufacturing and deployment being analysed. The results of this stress/strain analysis can be used to determine appropriate design safety margins and can be used to establish the appropriate test conditions and to select the appropriate test articles (e.g. stent sizes) for durability testing.

8.6.3.5.3 Fatigue safety factor determination

Conduct an appropriate fatigue analysis. Evaluation of the stent fatigue safety factor requires an engineering approach such as stress-life, and/or strain-life. In general, all sizes and configurations shall be analysed, unless it can be reasonably demonstrated that a worst-case exists. Stress-life or strain-life fatigue safety analysis requires that the mean and cyclic stresses or strains be determined by stress/strain analysis, and compared to the appropriate material properties (e.g. ultimate and endurance strength or strain). Safety factor can be expressed based on stress, strain or fatigue life.

8.6.3.5.4 Fatigue durability testing

Evaluate the long-term structural integrity of the stent when subjected to simulated worst-case physiologic loads. Durability shall be evaluated for all relevant fatigue loading modes, which shall be justified based on the intended clinical use (implant location) and conditions (e.g. oversizing, overlap). Fatigue testing of the stent

shall include *in vitro* testing until ten-year equivalent cycles have been applied to each stent under test. If the intended stent life is less than ten years, shorter duration fatigue testing might be appropriate and shall be justified. The frequency of the test shall be such that the deformation of the stent under test is no less than the deformation of the stent under the determined physiological conditions. The testing shall be conducted in an appropriate test solution, such as phosphate buffered saline, unless testing in a different environment, such as distilled water, can be justified. The testing shall be conducted at physiological temperature, unless otherwise justified.

Test conditions shall be documented and justified, and shall include the number of samples, stent sizes tested, test frequency, and other parameters used in simulating the physiological conditions. Loading/deformation modes and magnitudes and the requisite number of test cycles shall be justified by appropriate physiological models and analyses. The stent size(s) and configurations to be tested shall be selected to represent the greatest potential for fatigue failure, so that conclusions regarding the acceptable durability can be reasonably applied to other sizes and configurations not tested.

Testing to fracture shall be considered, but is not a requirement. While test methods have not yet been standardized, durability testing to fracture has several potential advantages; including identification of failure modes, verification of device fatigue analysis and appropriateness of factor of safety.

8.6.3.5.5 Coating durability

Evaluate the ability of the coating to resist delamination (e.g. flaps, bare spots) when subjected to simulated worst-case physiologic loads in a manner consistent with 8.6.3.5.4.

Examination of the coating under appropriate magnification shall be conducted. Inspection results shall be compared to baseline characteristics to determine the effective life of the coating. Results shall be analysed with respect to available preclinical *in vivo* and clinical performance.

Examinations at pre-specified intervals should be considered.

8.6.3.5.6 Coating particulate generation

Determine the size and amount of particles generated from the coating when subjected to simulated *in vivo* conditions.

8.6.3.6 Visual inspection

The stent shall conform to the manufacturer's specifications with respect to surface defects and contamination. The stent shall be free of defects that would render the stent unsuitable for its intended use.

8.6.4 Sizing

8.6.4.1 General

This covers the ability of the stent to remain in its placed position within the vasculature, by appropriate sizing.

For estimating risks, the hazards to be considered include, but are not limited to, the following:

a) inappropriate sizing.

These hazards might result in reportable clinical events, including, but not limited to, the following:

— stent migration;

— stent thrombosis;

— branch vessel occlusion;

— vascular trauma;

— trauma to adjacent structures;

— residual stenosis;

— in-segment restenosis;

— in-stent restenosis;

— restenosis;

— vessel occlusion, intraprocedural;

— vessel occlusion, periprocedural;

— vessel occlusion, late;

— ischemia.

Testing shall include the following items listed in 8.6.4.2 to 8.6.4.6, as appropriate to the design of the stent.

8.6.4.2 Dimensional verification

Determine the appropriate dimensions for conformance with design specifications.

8.6.4.3 Stent diameter to balloon inflation pressure (balloon expandable stents)

Determine the relationship between the stent diameter and the balloon inflation pressure for balloon expandable stents.

8.6.4.4 Recoil (balloon expandable stents)

Determine the percent change of the stent outer diameter from the maximum outer diameter obtained with balloon inflation to the final outer diameter after balloon removal. The sizing scheme recommended for the stent in the IFU should take into consideration this recoil.

8.6.4.5 Simulated use

Evaluate the performance of the stent using a model that simulates the intended use conditions.

8.6.4.6 Stent length to diameter relationship

Determine the relationship between stent length and its expanded diameter.

8.6.5 Patency

8.6.5.1 General

This covers the ability of the stent to maintain an open lumen.

For estimating risks, the hazards to be considered include, but are not limited to, the following:

a) kinking;

b) twisting;

c) inaccurate deployment;

d) deformation, including stent closure;

e) thrombogenicity.

These hazards might result in reportable clinical events, including, but not limited to, the following:

— stent thrombosis;

— residual stenosis;

— in-segment restenosis;

— in-stent restenosis;

— restenosis;

— vessel occlusion, intraprocedural;

— vessel occlusion, periprocedural;

— vessel occlusion, late;

— angina;

— recurrence of portal hypertension (for TIPS);

— myocardial infarction;

— ischemia;

— embolism;

— neurological deficit.

Testing shall include the following items listed in 8.6.5.2 to 8.6.5.8, as appropriate to the design of the stent.

NOTE There are four tests listed below that determine forces related to the deformation of the stent. Although similar, crush resistance with a radially applied load, crush resistance using parallel plates, local compression and radial force tests measure different attributes of the stent, as follows:

— the crush resistance test with a radially applied load measures the ability of the stent to resist permanent deformation along the entire length of the device when subjected to a radially applied load;

— the crush resistance test using parallel plates measures the ability of the stent to resist permanent deformation along the entire length of the device when subjected to a load uniformly applied over the length of the device;

— the local compression test measures the ability of the stent to resist permanent deformation under a localized (e.g. point) load;

— the radial force test measures the force exerted by the stent on the vessel in the deployed state.

8.6.5.2 Crush resistance test with a radially applied load (balloon expandable stents)

Determine the load required to cause clinically relevant buckling or a diameter reduction of at least 50 %.

8.6.5.3 Crush resistance with parallel plates

Determine the load required to cause clinically relevant buckling or a deflection equivalent to a diameter reduction (lumen reduction) of at least 50 % and the load required to permanently deform or fully collapse the stent. This test is required for stents that can experience direct compression in a clinical setting.

8.6.5.4 Flex/Kink

Determine the minimum radius of curvature that the stent can accommodate without kinking or exhibiting a diameter reduction (lumen reduction) of greater than 50 % and if the stent recovers its original geometry after testing.

8.6.5.5 Local compression

Determine the deformation of the stent in response to a localized compressive force, perpendicularly applied to the longitudinal axis of the device. This test is required for stents of a design with the potential for a different response to local compression as compared to a radial or flat plate compressive force and for which this test is clinically relevant.

8.6.5.6 Radial force

Determine the force exerted by a self-expanding stent as a function of the stent diameter.

8.6.5.7 Simulated use

Evaluate the performance of the stent using a model that simulates the intended use conditions.

8.6.5.8 Stent-free surface area and stent outer surface area

Determine the free or open surface area of the stent as a function of stent diameter and the contact area between the stent and the vessel.

8.6.6 Magnetic resonance imaging (MRI) safety and compatibility

Evaluate the safety and compatibility of the implant using MRI.

For estimating risks, the hazards to be considered include, but are not limited to, the following:

a) magnetically induced displacement force and torque, and radial force (RF) induced heating of the stent;

b) lack of quality imaging (image artefact).

NOTE 1 Additional guidance for evaluating magnetically induced displacement, torque, RF heating, and imaging artefact can be found in ASTM F2052[21], ASTM F2213[27], ASTM F2182[26] and ASTM F2119[24].

These hazards might result in reportable clinical events, including, but not limited to, the following:

— vascular trauma;

— stent migration.

NOTE 2 The MRI artefact caused by some stents might compromise the effectiveness and limit the use of MRI in patients with these implants.

8.6.7 Biocompatibility

Biocompatibility shall be tested in accordance with ISO 10993-1 and appropriate other parts of the ISO 10993 series of International Standards. For drug-eluting stent (DES) products, additional toxicity testing of the drug and coating components might be necessary. For extraction tests, the stent should be tested separately from the delivery system.

8.6.8 Drug elution

8.6.8.1 General

This covers the ability of the stent to elute the drug per design specifications, both on manufacture and with storage.

For estimating risks, the hazards to be considered include, but are not limited to, the following:

a) excessive drug delivery;

b) inadequate drug delivery;

c) unintended variability in localized drug delivery.

These hazards might result in reportable clinical events, including, but not limited to, the following:

— adverse biological reaction (toxicity);

— aneurysm of vessel wall or necrosis (mal-apposition of stent);

— residual stenosis;

— in-segment restenosis;

— in-stent restenosis;

— restenosis;

— vessel occlusion, intraprocedural;

— vessel occlusion, periprocedural;

— vessel occlusion, late;

— embolization;

— ischemia;

— stent thrombosis.

Testing shall include the following items listed in 8.6.8.2 to 8.6.8.4, as appropriate to the design of the stent.

8.6.8.2 Drug content/amount

Determine the amount of drug on the stent.

8.6.8.3 Elution profile

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

8.6.8.4 Drug identity

Identify the type and determine the purity of the drug and characterize the type and amount of degradants.

8.7 Preclinical *in vivo* evaluation

8.7.1 Purpose

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

8.7.2 Specific aims

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

a) evaluate the ability to access the target location with the delivery system;

b) evaluate the handling and visualization of the delivery system and visualization of the stent;

c) verify the accuracy and efficacy of deployment;

d) characterize the ability to withdraw the delivery system;

e) evaluate the appropriateness of stent sizing;

f) evaluate the functional haemostasis of the delivery system;

g) assess the position, integrity, and functionality of the stent;

h) for drug eluting stents, evaluate the presence of the drug in blood, in the treated vessel and in other relevant tissues over time;

i) assess local biological responses (e.g. thrombus deposition, inflammation, endothelialization, necrosis, aneurysm formation) and downstream and systemic effects (e.g. embolism, infarction) through an evaluation of histology and pathology of explants and pertinent tissues/organs;

j) record adverse events and potential contributing factors (e.g. stent vs. delivery system).

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

8.7.3 Protocol

Each stent system shall be tested by implantation of the stent at the intended, or at an analogous vascular site in a justified number of animals for at least 26 weeks in each animal, unless a justification for a shorter-term study is provided. Type and intervals of interim assessments shall be specified and justified. For novel technologies, interim sacrifices and longer implant durations might be indicated. For drug-eluting stent trials, drug delivery kinetics and residence time in the tissue should be considered in establishing the implant duration. As far as permitted by the limitations of the animal model, all devices used shall be of clinical quality and size, and of the design intended for clinical use.

Safety studies of drug eluting stents should include assessment of dose dependant 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 (down-stream), and systemic toxicities should be assessed.

For drug eluting stents (DES), at least one study should measure drug plasma levels as well as evaluate drug tissue levels, over time.

Interpretation of animal study results can be enhanced by the use of at least a small number of control devices for comparison purposes. A rationale should be provided if a control device is not used in the study. For drug eluting stent (DES) studies, both bare metal and coated stents (without the drug), if applicable, should be used as control articles.

All animals in the study shall be regularly examined. All animals shall undergo post-mortem examination, including those that expire prior to scheduled termination. 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 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 See ISO/IEC 17025[13] for guidance on appropriate laboratory practices.

8.7.4 Data acquisition

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

a) identification data:

   1) source of animals;
   2) animal identification;
   3) sex;
   4) age;
   5) weight;

b) pre-operative data:

   1) verification of health status, including appropriate blood testing;
   2) medications (e.g. prophylactic antibiotics);

c) operative data:

   1) date of procedure;
   2) name of person performing procedure;
   3) description of the implant procedure, including:
      i) identification of stent system and accessory devices;
      ii) stent identification number;
      iii) *in situ* length and diameter of stent;
      iv) diameter(s) of recipient vessel(s);
      v) use of antithrombotic therapy;
      vi) surgical approach;
      vii) implant location;
   4) assessment of parameters specified in the protocol, such as:
      i) accuracy and efficacy of insertion of delivery system and deployment of the stent;
      ii) handling and visualization of the delivery system and visualization of the stent;
      iii) efficacy of withdrawal of delivery system;
      iv) appropriateness of sizing and sizing scheme;
      v) blood loss, including the location;
      vi) position, integrity and functionality of the implant;
      vii) adverse perioperative events;

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) observation of integrity, functionality and position of implant;

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

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

4) any major deviation from 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 implant);

4) gross observation of the explanted stent and surrounding tissue;

5) pathological assessment of appropriate tissues and/or organs, if required per the protocol;

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

8.7.5 Test report and additional information

Results of all animals enrolled in the protocol shall be recorded and reported even if 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) implantation site;

3) implantation durations;

4) methods of assessment;

5) type and intervals of interim assessments;

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

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 for cause;

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

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

8.8 Clinical evaluation

8.8.1 Purpose

The purpose of clinical evaluation is to provide reasonable assurance of the safety and effectiveness of the stent system. A clinical investigation shall be carried out for any stent system incorporating design characteristics for which the safety and effectiveness has not been previously demonstrated. The investigation shall be carried out using ISO 14155-1 and ISO 14155-2, taking account of the specific aspects of vascular stents listed below in the following subclauses. The stent shall have satisfied appropriate preclinical testing requirements of this part of ISO 25539 before starting the clinical investigation.

NOTE The ISO 14155 series of International Standards provides requirements regarding clinical investigations. The following subclauses provide specific details regarding the clinical investigation of vascular stents.

8.8.2 Specific aims

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

a) evaluate the ability to access the target location with the delivery system;

b) evaluate the handling and visualization of the delivery system and visualization of the stent;

c) verify the accuracy and efficacy of deployment;

d) characterize the ability to withdraw the delivery system;

e) evaluate the appropriateness of stent sizing;

f) evaluate the acute and chronic position, structural integrity and effectiveness of the stent;

g) monitor lesion characteristics and stent positioning (over time);

h) evaluate any explants;

i) evaluate pathology of any pertinent tissues/organs;

j) record reportable clinical events.

8.8.3 Clinical investigation plan

A multicentre study (at a minimum of three investigational sites) shall be performed. A justification for the number of investigational 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 account of the effect of comorbidities on the life expectancy of the patient population.

The duration of patient follow-up shall be determined in relation to the objectives of the clinical investigation. All patients implanted with either a test or control stent, including those excluded from the final analysis, shall

be recorded and reported. The final report shall include current follow-up data on all patients with follow-up as specified by the clinical investigation plan for the last patient enrolled. Patient follow-up intervals shall include a minimum of a baseline assessment at discharge and at the end of the clinical evaluation. 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 and include definitions of success and failure for each endpoint. The definitions of success and failure shall incorporate quantitative values specifically applicable for the imaging modalities or other evaluation techniques to be used in the study.

For DES clinical investigations, preliminary studies might be necessary to determine the safety of the drug for human use, prior to initiation of the clinical investigation.

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

8.8.4 Data acquisition during clinical investigations

At a minimum, the following data shall be recorded for each patient in the study. Exceptions for the control population are noted below:

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, hyperlipidemia, tobacco use, obesity, anaesthesia risk and any other cardiovascular risk factors, with some measure of severity and current treatment;

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

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

   4) 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 implanting physician;

   2) date of procedure;

3) identification data for the stent(s) including model number, stent traceability, size and configuration;

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

5) relevant medications;

6) assessment of handling, visualization, deployment and withdrawal;

7) assessment of patency, positioning, and integrity of the stent;

8) reportable clinical events (see Annex C);

   i) severity, management, outcome;

   ii) documentation of stent system involvement (i.e., does the complication involve the stent system?);

   iii) documentation of probable causative factors (i.e., is the complication caused by the stent system, patient factors, technical factors, or other);

9) comparison of intended and actual stent location;

10) luminal diameter of stent;

11) confirmation of stent placement and conformity to vessel;

12) date of hospital discharge;

d) post-operative data:

1) date of each follow-up visit;

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

3) clinical evaluation (assessment protocol might differ between the control group and the treatment group);

   i) clinical assessment;

   ii) objective assessment of stent performance (migration, patency, percentage of diameter stenosis, stent integrity);

   iii) objective assessment of targeted lesion characteristics and stent positioning;

   iv) for DES trials, a subset of patients should be assessed for drug levels in blood over time;

4) stent relevant medications, such as antithrombotic or antibiotics;

5) reportable clinical events;

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

   ii) documentation of stent involvement;

   iii) documentation of probable causative factors (i.e., is the complication caused by stent, patient factors, technical factors or other);

e) patient withdrawal:

1) date;

2) months of study completed;

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

8.8.5 Final report

The final report shall include the following:

a) study protocol;

b) definitions of reportable 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 d following procedure) and late (greater than 30 d following procedure) follow-up data:

   1) patient accountability, including rationale for exclusion of data;

   2) significant and/or relevant deviations from protocol;

   3) summary of patients not completing study (e.g. lost to follow-up or 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 delivery system performance;

   6) summary of stent performance over time (e.g. migration, patency, stent integrity, change in shape);

   7) for drug eluting stents (DES), if required by the protocol, summary of drug levels in blood over time;

   8) summary of lesion characteristics related to stent performance over time;

   9) summary of intraprocedural, adjunctive and subsequent secondary interventions (e.g. atherectomy, post-dilation) needed post-stenting, if any, to optimize 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 and ISO 14971.

10 Manufacturing

Stent systems shall be manufactured in such a way that the specified design attributes are achieved. Requirements are specified in other related International Standards.

NOTE The requirements of ISO 13485[10] might apply.

11 Sterilization

11.1 Products supplied sterile

11.1.1 Stents and/or stent systems that are labelled “Sterile” shall comply with international, national or regional standards. Stents and/or stent systems which are labelled “Sterile” shall have a sterility assurance level (SAL) of 10^{-6}.

11.1.2 Sterilization processes shall be validated and routinely controlled.

a) If stents and/or stent systems are to be sterilized by ethylene oxide, ISO 11135-1 shall apply.

b) If stents and/or stent systems are to be sterilized by moist heat, ISO 17665-1 shall apply.

c) If stents and/or stent systems are to be sterilized by radiation, ISO 11137-1 shall apply.

d) If stents and/or stent systems incorporating animal tissue are to be sterilized using liquid chemical sterilants, ISO 14160 shall apply.

e) If stents and/or stent systems 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 14630 shall apply.

12 Packaging

12.1 Protection from damage in storage and transport

12.1.1 General

The requirements of ISO 14630 shall apply.

12.1.2 Unit container

Each stent and/or stent system shall be packaged in a unit container, providing a sterile barrier, if applicable. It shall be readily apparent if the unit container has been opened.

12.1.3 Outer container

Each unit container shall be packaged in an outer container. This outer container shall be designed so as to protect the unit container from damage due to storage.

12.1.4 Shipping container

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

12.1.5 Maintenance of sterility in transit

For stents and/or stent systems supplied sterile, the unit container shall be designed to maintain the sterility of the stent and/or stent system 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.

12.2 Marking

12.2.1 Container label

Each stent and/or stent system shall be accompanied by a label(s) on an appropriate container(s).

12.2.2 Stents without delivery systems

At least the following information shall be provided in words, phrases, symbols or drawings on the label(s):

— description and/or list of the package contents;

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

— name of the device (if applicable);

— model/reference number;

— lot/serial number;

— sterilization method and the notification “STERILE” if applicable;

— single use;

— expiry/expiration date;

— warnings or reference to read the manual (symbol);

— dimensions: length and outer diameter (unconstrained outer diameter and diameter ranges, as applicable) after expansion;

— manufacturer’s recommendation for storage, if applicable;

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

12.2.3 Stent systems (stents with delivery system)

At least the following information shall be provided in words, phrases, symbols or drawings on the label(s):

a) information as described in 12.2.2;

b) delivery system information, at least:

— dimensions: minimum required size of introducer (internal diameter), maximum size of guidewire and effective length of the catheter;

— rated burst pressure and maximum recommended inflation pressure, if applicable.

12.2.4 Record label

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

— manufacturer's identification;

— 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

The requirements of ISO 14630 shall apply. Further information is contained in tabular form in Annex A that might be included in the information supplied by the manufacturer. Specific information for stents and stent systems follows.

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 stent. The instructions shall include the following:

— indications for use;

— contraindications, cautions and warnings that are applicable;

— for drug eluting stent (DES), the potential for drug interactions with the drug delivered by the stent;

— recommendations for stent sizing, including vessel diameters, lesion lengths, and stent diameter as a function of inflation pressure, as applicable;

— potential adverse events;

— data from clinical studies, if applicable;

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

— recommended methods for vessel preparations, such as pre-dilitation, and methods for access, delivery of the stent and withdrawal of the delivery system;

— the statement STERILE — DO NOT RESTERILIZE — SINGLE USE ONLY in prominent form, if applicable;

— resterilization information, if applicable;

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

— recommendations for storage, if applicable;

— date of or reference relating to the publication of the text, indicating if the text has been revised;

— recommendations for visualization;

— MRI safety and compatibility information;

NOTE Recommendations for MRI labelling can be found in ASTM F2503[30].

— the material of construction of the stent;

— the identity of the coating material(s), if applicable;

— the identity and amount of drug(s), if applicable;

— type of construction (self-expanding or balloon expandable).

Annex A
(informative)

Attributes of endovascular devices — Vascular stents — Technical and clinical considerations

Tables A.1 to A.3 provide a logical method for identifying a set of biocompatibility, bench, pre-clinical *in vivo* and clinical tests to assess device performance. Annex B includes a list of the bench tests identified in the table, with a description of the purpose of each test, and Annex C includes definitions for the reportable clinical events listed in the table. Annexes D and E provide informative methodology for performing bench and analytical testing.

The table headings and explanations are listed in Table A.1 below. In addition, a form is given to help provide the proper context for the information contained within the matrix.

Table A.1 — Table headings and explanations

Column number	Title	Explanation	Context
1	Implant/procedure related attributes	Individual design goals	The implant should have an adequate _____ (column 1).
2	Problem(s)	Difficulties that might be encountered that could result in not meeting the individual design goal	If the implant does not have an adequate _____ (column 1), there could be a problem with _____ (column 2).
3	Reportable clinical events	Complications or failures that might be observed with clinical use if the problems occur	If there is a problem with _____ (column 2), _____ (column 3) could occur and should be documented.
4	Bench and analytical tests	A list of tests, exclusive of animal and clinical studies, that might be conducted to validate the individual design goal	The following tests can be conducted to evaluate the adequacy of the _____ (column 1): _____ (column 4).
5	Preclinical *in vivo* studies	Specific aims of animal studies to validate and verify the individual design goal	In order to evaluate the adequacy of the _____ (column 1) in an *in vivo* environment, the animal study should _____ (column 5).
6	Clinical studies	Specific aims of clinical studies to verify the individual design goal	In order to evaluate the adequacy of the _____ (column 1) in a clinical environment, the clinical study should _____ (column 6).
7	Information supplied by the manufacturer	Information to be supplied by the manufacturer to minimize the potential for failures to occur	To minimize the risk of _____ (column 2) or _____ (column 3), _____ (column 7) should be provided by the manufacturer.

Table A.2 — Attributes of endovascular devices — Vascular stents — Technical and clinical considerations for delivery systems

Delivery system						
1) Device/ procedure related attributes	**2) Problem(s)**	**3) Reportable clinical events**	**4) Bench and analytical tests**	**5) Preclinical *in vivo* studies**	**6) Clinical studies**	**7) Information supplied by the manufacturer**
Ability to access	Wire not crossing the lesion Introducer and delivery system not matching the access site (i.e., size mismatch) Delivery system not advancing to target site Embolism Stent dislodgement	Access failure Vascular trauma Neurological deficit Ischemia Spinal neurological deficit Embolization	Component dimension compatibility Flex/kink Torsional bond strength Bond strength Torquability Pushability Trackability Simulated use Dimensional verification Profile/diameter Visibility Dislodgement force	Evaluate ability to access Assess handling and visualization Evaluate adverse events with particular attention to events listed in column 3	Evaluate ability to access Assess handling and visualization Evaluate reportable clinical events	Implant profile, wire dimensions compatible with delivery system Sizing recommendations For user-mounted implants, manufacturer supplied information should include recommendations or specifications for delivery components Information should include recommendations or specifications for accessory devices
Ability to deploy: balloon expandable	Inability to activate deployment mechanism Disproportionate dimensions and properties, such as balloon compliance and burst pressure, of balloon relative to vessel Stent dislodgement Balloon failure Damage of stent or delivery system (e.g. by other components) Inadequate visualization Embolism	Deployment system failure Spinal neurological deficit Neurological deficit Vascular trauma Embolization Damage to stent	Component dimension compatibility Bond strength Simulated use Dimensional verification Balloon deflation Balloon rated burst Balloon rated fatigue Balloon inflation time Visibility Dogboning Dislodgement force	Verify efficacy of deployment Assess handling and visualization Evaluate adverse events with particular attention to events listed in column 3	Verify efficacy of deployment Assess handling and visualization Evaluate reportable clinical events	For user-mounted implants, manufacturer supplied information should include recommendations or specifications for delivery components. Information should include recommendations or specifications for accessory devices

Table A.2 (*continued*)

Delivery system						
1) Device/ procedure related attributes	**2) Problem(s)**	**3) Reportable clinical events**	**4) Bench and analytical tests**	**5) Preclinical *in vivo* studies**	**6) Clinical studies**	**7) Information supplied by the manufacturer**
Ability to deploy: self expanding	Inability to activate deployment mechanism Disproportionate dimensions of 'modelling' balloon relative to implant/vessel Damage of stent or delivery system (e.g. by other components) Inadequate visualization Embolism Stent dislodgement	Deployment system failure Neurological deficit Vascular trauma Spinal neurological deficit Embolization Damage to stent	Component dimension compatibility Bond strength Simulated use Dimensional verification Visibility Deployment force	Verify efficacy of deployment Assess handling and visualization Evaluate adverse events with particular attention to events listed in column 3	Verify efficacy of deployment Assess handling and visualization Evaluate reportable clinical events	For user-mounted implants, manufacturer supplied information should include recommendations or specifications for delivery components. Information should include recommendations or specifications for accessory devices
Ability to withdraw: balloon expandable	Improper balloon deflation Balloon winging Lack of structural integrity Embolism Diameter mismatch Implant dislodgement Damage of stent or delivery system (e.g. by other components) Delivery system snagging or adhering to the stent Inadequate visualization	Delivery system failure Neurological deficit Vascular trauma Ischemia Spinal neurological deficit Embolization Damage to stent	Tubing tensile strength Component dimension compatibility Torsional bond strength Bond strength Simulated use Dimensional verification Flex/kink Visibility	Verify efficacy of withdrawal Assess handling and visualization Evaluate adverse events with particular attention to events listed in column 3	Verify efficacy of withdrawal Assess handling and visualization Evaluate reportable clinical events	Information should include recommendations or specifications for accessory devices

Table A.2 (*continued*)

Delivery system						
1) Device/ procedure related attributes	**2) Problem(s)**	**3) Reportable clinical events**	**4) Bench and analytical tests**	**5) Preclinical *in vivo* studies**	**6) Clinical studies**	**7) Information supplied by the manufacturer**
Ability to withdraw: self expanding	Diameter mismatch Lack of structural integrity Embolism Stent dislodgement Damage of stent or delivery system (e.g. by other components) Delivery system snagging on or adhering to the stent Inadequate visualization	Delivery system failure Neurological deficit Vascular trauma Ischemia Spinal neurological deficit Embolization Damage to stent	Tubing tensile strength Component dimension compatibility Torsional bond strength Bond strength Simulated use Dimensional verification Flex/kink Visibility	Verify efficacy of withdrawal Assess handling and visualization Evaluate adverse events with particular attention to events listed in column 3	Verify efficacy of withdrawal Assess handling and visualization Evaluate reportable clinical events	Information should include recommendations or specifications for accessory devices
Biocompatibility	Lack of appropriate biocompatibility	Complications attributable to a lack of appropriate biocompatibility	ISO 10993 series	ISO 10993 series Appropriate histological and pathological investigations of explants Evaluate adverse events with particular attention to events listed in column 3	Evaluate reportable clinical events	N/A
Sterility	Non-sterile product	Infection	Sterilization assurance	N/A	Evaluate reportable clinical events	Appropriate handling instructions Whether single or multiple use
Haemostasis	Component dimensional incompatibility (size mismatch) Haemostasis valve incompetency Leaking	Haematoma Procedural bleeding Post procedure bleeding	Assessment of haemostasis Dimensional verification Component dimensional compatibility	Evaluate appropriateness of sizing Assess blood loss Evaluate adverse events with particular attention to events listed in column 3	Evaluate appropriateness of sizing Assess blood loss Evaluate reportable clinical events	Sizing recommendations Specifications for accessory devices

Table A.3 — Attributes of endovascular devices — Vascular stents — Technical and clinical considerations for stent

Stent						
1) Device/ procedure related attributes	**2) Problem(s)**	**3) Reportable clinical events**	**4) Bench tests**	**5) Preclinical *in vivo* studies**	**6) Clinical studies**	**7) Information supplied by the manufacturer**
Ability to accurately deploy	Inaccurate positioning or orientation Improper deployment configuration Incomplete deployment Inadequate visualization	Branch vessel occlusion Delivery system failure Stent migration Lumen obstruction Vascular trauma Ischemia	Simulated use Stent length to diameter relationship Visibility Profile effect/flaring	Assess visualization Verify accuracy and efficacy of deployment Evaluate adverse events with particular attention to events listed in column 3	Assess visualization Verify accuracy and efficacy of deployment Evaluate reportable clinical events	Location and description of radio-opaque landmarks whenever present
Fixation effectiveness	Incomplete apposition to vessel wall Excessive or inadequate radial force	Stent migration Lumen obstruction Vascular trauma Trauma to adjacent structures Branch vessel occlusion	Radial force Crush resistance Recoil Local compression Conformability to vessel wall Simulated use	Assess position, integrity and functionality Appropriate histological and pathological investigation of explants Evaluate adverse events with particular attention to events listed in column 3	Assess position, integrity and functionality Monitor lesion morphology Appropriate histological and pathological investigation of explants if occurring Evaluate reportable clinical events	Directions regarding restrictions and requirements to assure proper fixation
Stent integrity	Structural failure of stent including coating, if applicable Loss of complete apposition to vessel wall	Stent fracture Stent thrombosis Stent migration Vascular trauma Lumen obstruction Trauma to adjacent structures Ischemia Embolization	Fatigue and durability Stress/strain analysis Corrosion Longitudinal tensile strength Visual inspection Coating delamination Coating dimensions Coating integrity	Assess position, integrity and functionality Appropriate histological and pathological investigation of explants Evaluate adverse events with particular attention to events listed in column 3	Assess position, integrity and functionality Appropriate histological and pathological investigation of explants if occurring Evaluate reportable clinical events	N/A
Appropriate sizing	Inappropriate sizing	Stent migration Stent thrombosis Branch vessel occlusion Vessel trauma Trauma to adjacent structures Lumen obstruction Ischemia	Simulated use Stent length to diameter relationship Recoil Dimensional verification Stent diameter to balloon inflation pressure	Verify sizing scheme Evaluate adverse events with particular attention to events listed in column 3	Evaluate reportable clinical events	Sizing recommendations

Table A.3 (*continued*)

Stent						
1) Device/ procedure related attributes	**2) Problem(s)**	**3) Reportable clinical events**	**4) Bench tests**	**5) Preclinical *in vivo* studies**	**6) Clinical studies**	**7) Information supplied by the manufacturer**
Patency	Kinking Twisting Inaccurate deployment Deformation Thrombogenecity	Stent thrombosis Lumen obstruction Restenosis Abrupt reclosure Angina Recurrence of portal hypertension Myocardial infarction Ischemia Embolization Neurological deficit	Radial force Crush resistance Simulated use Stent free surface area Local Compression Flex/Kink Stent free surface area	Assess position, integrity and functionality Appropriate histological and pathological investigation of explants Evaluate adverse events with particular attention to events listed in column 3	Assess position, integrity and functionality Monitor lesion morphology Appropriate histological and pathological investigation of explants if occurring Evaluate reportable clinical events	N/A
Magnetic resonance imaging (MRI) compatibility	Lack of quality imaging (artefact) Movement or heating of the stent	Vascular trauma Stent migration	MRI compatibility	N/A	Evaluate reportable clinical events	Describe MRI safety and compatibility of the device
Biocompatibility	Lack of appropriate biocompatibility	Adverse biological reaction (toxicity)	ISO 10993 series	ISO 10993 series Appropriate histological and pathological investigations of explants	Evaluate reportable clinical events	List of materials utilized
Sterility	Non-sterile product	Infection	Sterilization assurance	N/A	Evaluate reportable clinical events	Appropriate handling instructions Whether single or multiple use
Drug elution	Excessive drug delivery Inadequate drug delivery Unintended variability in localized drug delivery	Adverse biological reaction (toxicity) Aneurysm of vessel wall or necrosis (mal-apposition of stent) Restenosis Embolization Ischemia Lumen obstruction Stent thrombosis	Drug content/amount Elution profile	Evaluate adverse events with particular attention to events listed in column 3 Appropriate histological and pathological investigations of explants Evaluate the presence of the drug in the blood and tissue over time Pathological assessment of appropriate tissues and/or organs	Evaluate reportable clinical events Evaluate the presence of the drug in the blood over time	Name of therapeutic agent Drug specific handling and storage requirements (e.g. temperature range for storage) The chemical or biological nature of the drug (mechanism of action) Any appropriate hazard warning Total drug content/amount Dose per unit area

Annex B
(informative)

Bench and analytical tests

Table B.1 — Bench and analytical tests

Tests	Description of test and requirements	Relevant design evaluation subclause(s)
Acute coating integrity	Evaluate the ability of the coating to resist damage due to loading, tracking, deployment and delivery system withdrawal.	8.6.3 Stent integrity
Assessment of biocompatibility	Biocompatibility should be tested in accordance with ISO 10993-1 and appropriate other parts of the ISO 10993 series of International Standards.	8.5.4 Biocompatibility
Assessment of haemostasis	Evaluate the ability of any seal or valves in the delivery system to maintain an adequate haemostatic seal when used with appropriate accessory devices.	8.5.5 Haemostasis
Balloon deflation time	Determine time required to deflate balloon and evaluate ability to remove deflated balloon.	8.5.2 Ability to deploy
Balloon inflation time	Determine the time required to expand the balloon to the maximum recommended inflation pressure, volume or diameter.	8.5.2 Ability to deploy
Balloon rated burst pressure (RBP)	Determine the rated burst pressure (RBP) with an appropriate safety margin including reliability parameters of the balloon when used with the stent.	8.5.2 Ability to deploy
Balloon rated fatigue	Evaluate the ability of the balloon to withstand a clinically justified number of repeated inflation cycles to the rated burst pressure.	8.5.2 Ability to deploy
Bond strength	Determine the longitudinal bond strength between parts of the delivery system. All bonds shall remain intact under recommended conditions of use.	8.5.1 Ability to access 8.5.2 Ability to deploy 8.5.3 Ability to withdraw
Coating dimensions	Determine the appropriate dimensions of the stent coating for conformance with design specifications.	8.6.3 Stent integrity
Coating durabilty	Evaluate the ability of the coating to resist delamination (e.g. flaps, bare spots) when subjected to simulated worst-case physiologic loads.	8.6.3 Stent integrity
Coating particulate generation	Determine the size and amount of particles generated from the coating when subjected to simulated *in vivo* conditions.	8.6.3 Stent integrity
Component dimension compatibility	Evaluate the dimensions of the stent delivery system for compatibility with the dimensions of recommended accessories. All components shall be dimensionally compatible.	8.5.1 Ability to access 8.5.2 Ability to deploy 8.5.3 Ability to withdraw 8.5.5 Haemostasis
Conformability to vessel wall	Evaluate the ability of the implant to maintain adequate contact with the vessel wall.	8.6.2 Fixation effectiveness
Corrosion	Evaluate the susceptibility of the stent to corrosion in a simulated physiological environment.	8.6.3 Stent integrity
Crush resistance with parallel plates	Determine the load required to cause clinically relevant buckling or a deflection equivalent to a diameter reduction of at least 50 % and the load required to permanently deform or fully collapse the stent.	8.6.2 Fixation effectiveness 8.6.5 Patency

Table B.1 (*continued*)

Tests	Description of test and requirements	Relevant design evaluation subclause(s)
Crush resistance with radially applied load	Determine the load/deformation characteristics of the stent while a circumferentially uniform radial load is applied.	8.6.2 Fixation effectiveness 8.6.5 Patency
Dimensional verification	Determine the appropriate dimensions for conformance with design specifications.	8.5.1 Ability to access 8.5.2 Ability to deploy 8.5.3 Ability to withdraw 8.5.5 Haemostasis 8.6.4 Sizing
Dislodgment force	Determine the force required to dislodge the stent from the original crimped position and to completely separate the stent from the non-expanded balloon while simulating clinical use conditions.	8.5.1 Ability to access 8.5.2 Ability to deploy 8.5.3 Ability to withdraw
Dogboning	Determine the diameter of balloon extending beyond the ends of the stent, which are greater than the stent outer diameter at the maximum recommended inflation pressure.	8.5.2 Ability to deploy
Drug content/amount	Determine the amount of drug on the stent.	8.6.8 Drug elution
Drug identity	Determine the type and purity of the drug and characterize the type and amount of degradants at manufacture and with storage.	8.6.8 Drug elution
Elution profile	Determine the amount of drug that elutes over the desired time period.	8.6.8 Drug elution
Fatigue durability testing	Evaluate the long-term dimensional and structural integrity of the stent and any coating.	8.6.3 Stent integrity
Flex/kink	Evaluate the ability of the implant and stent system to bend in order to accommodate the predetermined clinically relevant radius or angle it will be required to negotiate during access and delivery. Determine clinically relevant radius of curvature that the implant can accommodate without kinking.	8.5.1 Ability to access 8.5.3 Ability to withdraw 8.6.5 Patency
Force to deploy	Determine the force to deploy the stent from the delivery system.	8.5.2 Ability to deploy
Local compression	Determine the deformation of the stent in response to a localized compressive force, perpendicularly applied to the longitudinal axis of the device, and if the stent recovers its original geometry after testing.	8.6.2 Fixation effectiveness 8.6.5 Patency
MRI safety and compatibility	Evaluate MRI safety and compatibility.	8.6.6 MRI safety and compatibility
Profile/diameter	Determine the maximum diameter along sections of the stent system.	8.5.1 Ability to access
Profile effect/flaring	Determine the distance between the external diameter of the stent and the external diameter of the balloon while tracking through a tortuous path.	8.6.1 Ability to accurately deploy
Pushability	Evaluate the ability of the stent system to be pushed or positioned by an operator without undesirable bending or buckling.	8.5.1 Ability to access
Radial force	Determine the force exerted by a self-expanding stent as a function of the stent diameter.	8.6.2 Fixation effectiveness 8.6.5 Patency
Recoil	Determine the percent change of the stent outer diameter from the maximum outer diameter obtained with balloon inflation to the final outer diameter after balloon removal. The sizing scheme recommended for the stent in the IFU should take into consideration this recoil.	8.6.2 Fixation effectiveness 8.6.4 Sizing

Table B.1 (*continued*)

Tests	Description of test and requirements	Relevant design evaluation subclause(s)
Simulated use	Evaluate the performance of the stent system using a model(s) that simulate(s) the intended use conditions.	8.5.1 Ability to access 8.5.2 Ability to deploy 8.5.3 Ability to withdraw 8.6.1 Ability to accurately deploy 8.6.2 Fixation effectiveness 8.6.4 Sizing 8.6.5 Patency
Stent diameter to balloon inflation pressure	Determine the relationship between the stent diameter and the balloon inflation pressure for balloon expandable stents.	8.6.4 Sizing
Stent-free surface area and stent outer surface area	Determine the free or open surface area of the stent as a function of stent diameter and the contact area between the stent and the vessel.	8.6.5 Patency
Stent length to diameter relationship	Determine the relationship between stent length and expanded stent diameter.	8.6.1 Ability to accurately deploy 8.6.4 Sizing
Stress/strain analyses (e.g. finite element analysis)	Determine the critical stresses and/or strains within the stent due to manufacturing, catheter loading, delivery, deployment and *in vivo* loading using appropriate tools such as finite element analysis (FEA).	8.6.3 Stent integrity
Torquability	Evaluate the ability of the stent system to provide sufficient rotation to the distal (leading) end to deliver the stent within the anatomy.	8.5.1 Ability to access
Torsional bond strength	Determine the torque/rotation required to break joints and/or materials in the appropriate delivery system components.	8.5.1 Ability to access 8.5.2 Ability to deploy 8.5.3 Ability to withdraw
Trackability	Evaluate the ability of the stent system to advance through the vessel to the target site using the recommended accessories. Evaluate the potential for displacement of the guidewire from its intended position during the advancement of the stent system, as appropriate for the intended use of the stent.	8.5.1 Ability to access
Tubing tensile strength	Determine the strength of the tubing used in the delivery system as appropriate to the material (ISO 10555-1 or similar).	8.5.3 Ability to withdraw
Visibility	Evaluate the ability to visualize the delivery system and/or stent system during access using fluoroscopy or using the imaging techniques specified in the instructions for use (IFU). The use of other technologies for visualization shall be justified.	8.5.1 Ability to access 8.5.2 Ability to deploy 8.5.3 Ability to withdraw 8.6.1 Ability to accurately deploy
Visual inspection	Evaluate the ability of the stent to conform to the manufacturer's specifications with respect to surface defects and contamination that would render the stent unsuitable for its intended use.	8.6.3 Stent integrity

Annex C
(informative)

Definitions of reportable clinical events

This annex contains examples of clinically reportable events and might not be all inclusive.

Table C.1 — Definitions of reportable clinical events

Event	Definition
Access failure	Failure to reach the intended site with the stent due to mechanical failure or patient anatomy.
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 stent deployment should be documented.
Adverse biological response (toxicity) to stent coating or drug elution (if applicable)	Local, regional and/or systemic toxic reaction due to stent coating or drug elution. The type of reaction should be documented.
Aneurysm	For true aneurysms: dilatation of all or part of the treated vessel to twice its post-procedural diameter; dilatation to less than twice the post-procedural diameter should also be reported. For false (pseudo) aneurysms: an outpouching of any size should be reported. The aneurysm size and imaging modality should be specified in all cases.
Angina	Chest, neck, arm or other pain related to decreased coronary blood flow.
Arrhythmia	Development of a new atrial or ventricular arrhythmia or exacerbation of a prior arrhythmia requiring treatment (i.e., medical therapy, cardioversion, pacemaker) within 30 d of the procedure.
Atelectasis/pneumonia	Atelectasis or pneumonia documented by chest X-ray within 30 d of the procedure and requiring treatment with antibiotics, inhalation therapy, intubation or suctioning. The type of treatment required should be reported.
Branch vessel occlusion	Clinically significant, unplanned occlusion or obstruction of a major branch vessel.
Coagulopathy	Development of a bleeding disorder documented by appropriate laboratory studies within 30 d of the procedure. The specific syndrome or factor deficiency(ies) should also be noted.
Congestive heart failure	Development of an acute episode or exacerbation of existing low cardiac output accompanied by peripheral and/or pulmonary edema.
Damage to stent	Damage to the stent by any cause, such as by an accessory device or the delivery system.
Deep vein thrombosis	Thrombus in a deep vein documented by duplex scanning, venography, or other imaging technique.
Deployment failure (delivery system failure)	Inability to fully deploy the stent at the intended site and/or withdraw the delivery system intact due to mechanical failure or patient anatomy. Whether or not successful stent deployment was achieved should be documented.
Embolization	Embolization of intraluminal debris or thrombus with clinical sequelae.
Haematoma	Development of a haematoma related to the endovascular procedure requiring surgical intervention, evacuation and/or transfusion.
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 to resume the degree of sexual function registered preoperatively, within 6 months of the procedure.

Table C.1 (*continued*)

Event	Definition
In-segment restenosis	Significant reduction in luminal diameter at any point along the length of the stent in addition to any reduction in luminal diameter within the non-stented adjacent sections of the vessel, when compared to the post-procedural reference diameter. The degree of narrowing and imaging modality should be specified.
Insertion site infection, deep	Infection at percutaneous or surgical access site requiring surgical debridement or vascular repair, and occurring within 30 d of the procedure.
Insertion site infection, superficial	Infection at percutaneous or surgical access site not involving the access vessel or deep muscle, and occurring within 30 d of the procedure.
In-stent restenosis	Significant reduction in luminal diameter at any point along the length of the stent when compared to the post-procedural reference diameter. The degree of narrowing and imaging modality should be specified.
Ischemia	Development of acute or chronic ischemia within 30 d of the procedure. The cause of the ischemia should be diagnosed and reported (i.e., embolism, thrombosis or dissection). Examples include, but are not limited to, extremity, mesenteric and renal ischemia.
Late mortality	Death occurring at greater than 30 d following the procedure attributable to the stent.
Lymphocele/lymphatic fistula	Cystic accumulation of lymph or groin wound drainage occurring at an incision site (if used for access).
Malaposition of stent	Appreciable portion of stent not in direct contact with the vessel wall. Note timing in relation to procedure.
Myocardial infarction	Myocardial infarction documented by the presence of raised cardiac enzymes within 30 d of the procedure. Clinical symptoms, EKG changes and/or haemodynamic instability associated with the event should also be reported.
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 d of the procedure. Whether the deficit was permanent or transient should also be reported.
Peri-procedural mortality	Death from any cause occurring within 30 d of the procedure.
Post procedure bleeding	Procedure related bleeding which occurs after the patient leaves the procedure room resulting in the need for blood transfusion. The volume of replaced blood, the source of the bleeding and whether or not surgical intervention was required to stop the bleeding should also be reported.
Procedural bleeding	Any blood loss requiring intervention (i.e., blood transfusion, 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 also be reported.
Pulmonary embolism	Clinical evidence of pulmonary embolism confirmed by high probability VQ scan, CT scan or pulmonary angiography occurring within 30 d of the procedure.
Recurrence of portal hypertension	Recurrent high blood pressure in the portal venous system.
Renal insufficiency	Rise in creatinine greater than 25 % or 0,5 mg/dl above the pre-procedure level that does not resolve. The need for and the duration of dialysis, if required, should also be reported.
Residual stenosis	> 30 % luminal narrowing compared to the normal vessel diameter immediately after completing the stent procedure. The degree of narrowing and imaging modality should be specified.
Respiratory failure	Need for post-procedural mechanical ventilation or the need for re-intubation or ventilator support any time up to 30 d postoperative (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 reference diameter. The degree of narrowing and imaging modality should be specified.
Spinal neurological deficit	Neurological deficit related to spinal chord ischemia developing within 30 d of the procedure.

Table C.1 (*continued*)

Event	Definition
Stent fracture	Fracture or breakage of any portion of the stent.
Stent infection	Development of a confirmed stent infection occurring at any time following stent placement. The etiology (i.e., device sterility, endocarditis, etc.) should be reported if known.
Stent migration	Longitudinal movement of all or part of a stent resulting in clinical symptoms.
Stent thrombosis	Haemodynamically significant thrombus formation within the lumen of the stent occurring at any time following stent placement. The degree of narrowing, the timing of the thrombosis in relation to the procedure, and imaging modality should be specified.
Trauma to adjacent structures	Injury to adjacent structures associated with vascular trauma (see definition below).
Vascular trauma	Injuries to vessels as a result of an endovascular procedure, including dissections or perforations, false or true aneurysms. The specific site (e.g., access site, treatment site, proximal or distal vessel, etc.) and source of the injury as well as the clinical sequelae should be reported.
Vessel occlusion, intraprocedural	Occlusion of flow within the target or other vessel which was previously documented to be patent with antegrade flow. Might be due to twisting or kinking of the stent, failure of the stent to fully open, dissection or any other 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 greater than 30 d following the procedure. Might be due to twisting or kinking of the stent, intimal hyperplasia, dissection or any other cause. Time of occlusion and imaging modality should be specified.
Vessel occlusion, periprocedural	Occlusion of flow within the target or other vessel which was previously documented to be patent with antegrade flow within 30 d of the procedure. Might be due to twisting or kinking of the stent, dissection, or any other cause. Time of occlusion and imaging modality should be specified.

Annex D
(informative)

Test methods

D.1 General

The information included in this annex is intended to provide guidance for preclinical *in vitro* testing performed in order to verify the design of the stent system and provide guidance for reporting. It is recognised that not all of the tests described in this annex are applicable for each stent system design. It is also recognised that testing intended to assure that the device meets specifications during manufacture might not be conducted in accordance with the details outlined in this annex.

To assure consistency in the testing of devices, use of the methods in this annex is recommended. If alternative methods are employed, these methods should be justified.

In some cases in this annex, one or more of the methods for the tests identified in the body of this part of ISO 25539 were combined into a single method. It was recognised during the drafting of these test methods that they should be combined to reflect the manner in which this testing is often conducted. It is also recognised that additional methods might be combined when testing is conducted for a specific device. For those tests performed simultaneously, the report should provide the individual test results for each of the tests listed in the body of this part of ISO 25539.

Some requirements in the body of the document do not have associated test method guidance in this annex, as either the methodologies have not been standardized or are better addressed by other standards (e.g. MRI compatibility, pharmacokinetics for drug eluting stents).

The use of “shall” indicates requirements strictly to be followed in order to conform to the recommended test.

D.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 design characteristics of the test article should be verified to be representative of the devices 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 testing of each size. The stent sizes selected for testing should represent the worst case combination(s) of diameter and length 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 device with the greatest potential for failure.

Sampling should ensure adequate representation of the expected variability in the manufacture of devices.

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

Additional recommendations regarding sampling are included with each test method as appropriate.

D.3 Conditioning of test samples

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

Samples should be subjected to conditions that are normally encountered and that might affect the test results. Conditioning might include loading the stent on or inside the delivery catheter, preconditioning of the stent system as recommended in the instructions for use (IFU), single or multiple passes through an anatomical model, and deployment of the stent.

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

D.4 Reporting

For the purposes of this annex, 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 identification of tests, with the rationale for the omission of any tests identified in Annex B or the selection of alternative tests. The information provided in each test report should be based upon a prospectively defined test protocol.

A summary of results, with acceptance criteria and any potential clinical significance of the results, should be included and can be in tabular form. Consideration shall be given to the anatomical, physiological and morphological conditions of the intended use in establishing the acceptance criteria. Justification and clinical applicability of acceptance criteria for each test shall 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 part of ISO 25539;

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 and the number of samples tested; selection of test article shall be justified (e.g. sizes, conditioning);

d) acceptance criteria: state the acceptance criteria for 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 on the interpretation of the results;

g) expression of results: describe testing results expressed in units as indicated in the test method;

h) conclusion: state conclusions, based on comparing results to acceptance criteria, including any potential clinical significance of these results.

D.5 Test methods

NOTE As used within the context of D.5, "shall" indicates requirements strictly to be followed in order to conform to the recommended test method.

D.5.1 Stent system

D.5.1.1 Dimensional verification and component dimension compatibility

D.5.1.1.1 Purpose

The purpose of this test is to determine the stent system dimensions, including, but not limited to, the outer diameter, guidewire lumen diameter and useable length, for verification to design specifications, and to evaluate the dimensional compatibility between the stent system and the recommended accessory devices listed in the product IFU. The relevant design evaluation sections of this part of ISO 25539 include 8.5.1, 8.5.2, 8.5.3 and 8.5.5.

D.5.1.1.2 Materials

D.5.1.1.2.1 Stent system.

D.5.1.1.2.2 Accessory devices necessary to accomplish deployment in accordance with the IFU.

D.5.1.1.2.3 Measuring equipment for diameters (e.g. micrometer, optical profile projector, laser-micrometer, appropriate profile hole gauges), capable of measuring to 10 % of the specified tolerance or 1 % of the measured value. If a tolerance is specified, the lesser value of the respective percentage shall be used.

D.5.1.1.2.4 Measuring equipment for length, capable of measuring to 10 % of the specified tolerance or 1 % of the measured value. If a tolerance is specified, the lesser value of the respective percentage shall be used.

D.5.1.1.2.5 Wire mandrels/pin gauges/guidewires (for the delivery system inner lumen), capable of measuring to 10 % of the specified tolerance or 1 % of the measured value. If a tolerance is specified, the lesser value of the respective percentage shall be used.

D.5.1.1.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.1.1.4 Conditioning

Conditioning shall be in accordance with Clause D.3.

D.5.1.1.5 Test method

Develop a test method based on the following:

a) insert an appropriate guidewire or mandrel into the stent system lumen to verify the lumen dimension and guidewire compatibility;

b) measure the maximum outer diameter of the stent system or verify that the outer diameter fits through the appropriately sized profile hole gauge; it is only necessary to measure the region of the stent system intended to be passed through the specified introducer sheath and consideration should be given to the potential for asymmetry;

c) measure the length of the stent system; it is only necessary to measure the region of the stent system intended to be passed through the introducer sheath;

d) measure all other appropriate dimensions;

e) verify compatibility with all types of recommended accessory components.

D.5.1.1.6 Expression of results

Length shall be expressed in centimetres. Other dimensions shall be expressed in millimetres. Results regarding the compatibility of the recommended accessory devices and the verification of the lumen and outer diameters, if applicable, shall be documented.

D.5.1.1.7 Test report

The test report shall be in accordance with D.4. The test report shall include the maximum, minimum, mean and standard deviation of all measured dimensions, the results of any verified dimensions, and the results of the observations of the accessory compatibility.

NOTE Additional guidance can be found in ASTM F2081[23].

D.5.1.2 Profile/diameter test

D.5.1.2.1 Purpose

The purpose of this test is to determine the maximum diameter along sections of the stent system in order to evaluate the dimensional compatibility between the stent system and the vasculature, including the lesion to be treated. The relevant design evaluation section of this part of ISO 25539 includes 8.5.1.

D.5.1.2.2 Materials

D.5.1.2.2.1 Stent system.

D.5.1.2.2.2 Measuring equipment for diameters (e.g. micrometer, optical profile projector, laser-micrometer), capable of measuring to 10 % of the specified tolerance or 1 % of the measured value. If a tolerance is specified, the lesser value of the respective percentage shall be used.

D.5.1.2.2.3 Recommended guidewire or equivalent, as appropriate.

D.5.1.2.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.1.2.4 Conditioning

Conditioning shall be in accordance with Clause D.3.

D.5.1.2.5 Test method

Develop a test method based on the following:

a) if applicable, insert an appropriate guidewire into the stent system such that it extends past the end of the stent system;

b) measure the maximum outer diameter of the stent system. Consideration should be given to the potential for asymmetry; it is necessary to measure the region that is intended to pass through a vessel and/or vessel lesion, and the region that contains the stent.

D.5.1.2.6 Expression of results

Diameters measured shall be expressed in millimetres.

D.5.1.2.7 Test report

The test report shall be in accordance with Clause D.4 and shall include the maximum, minimum, mean and standard deviation of the measured outer diameter of the stent system and the diameter of the region containing the stent for each size tested.

NOTE Additional guidance can be found in ASTM F2081[23].

D.5.1.3 Simulated use

D.5.1.3.1 Purpose

The purpose of this test is to evaluate the performance of the stent system using a model(s) that simulate(s) the intended use conditions. This test addresses the requirements for qualitative evaluation of simulated use, flex/kink, pushability, torquability and trackability of the stent system. Conformability of the deployed stent to the vessel wall is also to be evaluated. The relevant design evaluation sections of this part of ISO 25539 include 8.5.1, 8.5.2, 8.5.3, 8.6.1, 8.6.2, 8.6.4 and 8.6.5.

D.5.1.3.2 Materials

D.5.1.3.2.1 **Stent system**.

D.5.1.3.2.2 **Accessory devices**, necessary to accomplish deployment in accordance with the IFU.

D.5.1.3.2.3 **Anatomical model**, that includes a delivery pathway and a deployment location. The angulation and tortuosity of the intended stent location and delivery pathway should be considered in the design of the model. Use of a compliant model should be considered.

D.5.1.3.2.4 **Fluid fixture**, capable of delivering water or appropriate fluid, at physiological temperature (37 ± 2) °C, pulsatile pressures, and antegrade or retrograde flow, as appropriate.

D.5.1.3.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.1.3.4 Conditioning

Conditioning shall be in accordance with Clause D.3.

D.5.1.3.5 Test method

Develop a test method based on the following:

a) connect the anatomical model to the fluid fixture and allow the test system to stabilize (e.g, temperature, pressure);

b) insert the appropriate accessory devices (e.g. guidewire, introducer sheath) in the fixture;

c) following the IFU, insert, deliver and deploy the stent in the model and withdraw the delivery system;

d) evaluate the ease of advancing the delivery system into the model (pushability), the ability to transmit torque from the proximal end to the distal end of the catheter (torquability) if applicable, and the ability of the delivery system to track over a guidewire during insertion around bends in the model (trackability);

e) note any anomalies, such as kinking or buckling of the system, the inability to fully and accurately deploy the stent, stent dislodgment while withdrawing the delivery system and any other appropriate observations;

f) visually inspect the deployed stent in the anatomical model, note the conformance to the model vessel wall, the placement accuracy, kinks, undesirable bends, twisting, excessive unintended stent expansion non-uniformity, component separation, any damage and any other critical observations;

g) inspect the delivery system, note any damage and any other critical observations;

h) to evaluate delivery and deployment for multiple stents, repeat steps c) to g) with additional stent systems.

D.5.1.3.6 Expression of results

For each test, all critical observations and aspects of the ability to access, deploy, and withdraw the stent system should be documented.

D.5.1.3.7 Test report

The test report shall be in accordance with Clause D.4 and shall include all critical observations and aspects of the ability to access, deploy and withdraw the stent system. Critical observations regarding multiple or overlapping stents shall be reported, where appropriate. The test fluid shall be identified. The results for flex/kink, pushability, torquability (if applicable) and trackability of the stent system should be individually documented as well as the conformity of the stent(s) to the vessel wall. The report shall include a description of the anatomical model used, including the geometry and material of construction.

D.5.1.4 Visibility

D.5.1.4.1 Purpose

The purpose of this test is to evaluate the ability to visualize the stent system and/or stent using the imaging techniques specified in the IFU. The relevant design evaluation sections of this part of ISO 25539 include 8.5.1, 8.5.2, 8.5.3 and 8.6.1.

D.5.1.4.2 Materials

D.5.1.4.2.1 Stent system.

D.5.1.4.2.2 Phantom tissue model, or equivalent, with appropriate accessories, such as radiopaque markers and a ruler.

D.5.1.4.2.3 Imaging system, capable of operating at clinically relevant power levels.

NOTE Visibility is significantly affected by variations in equipment and parameter settings. In the selection of the equipment used for this evaluation, consideration should be given to this variability.

D.5.1.4.2.4 Accessory devices, necessary to accomplish deployment in accordance with the IFU.

D.5.1.4.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.1.4.4 Conditioning

Conditioning shall be in accordance with Clause D.3.

D.5.1.4.5 Test method

Develop a test method based on the following:

a) position the stent system and the phantom tissue model to simulate clinical conditions;

b) use the imaging system to visualize the stent system and any radiopaque markers;

c) qualitatively examine the images for ease of visibility, e.g., the degree of visibility can be assessed by locating the exact ends, orientation of critical points and/or parts of the stent system; alternatively, the degree of visibility can be compared to a specified control device;

d) repeat a) to c) for the stent during deployment and after withdrawal of the delivery system.

D.5.1.4.6 Expression of results

This is a qualitative assessment. Record the degree of visibility for all applicable components at the various stages of the testing and any comparison to a specified control.

D.5.1.4.7 Test report

The test report shall be in accordance with Clause D.4 and shall include the assessment of visibility and visual results (e.g. representative fluoroscopic images). The test report shall also include the make and model of the imaging equipment, the parameter settings and details of the phantom tissue model.

D.5.1.5 Force to deploy

D.5.1.5.1 Purpose

The purpose of this test is to determine the force to deploy the self expanding stent. All applicable steps of the deployment process will be evaluated. The relevant design evaluation section of this part of ISO 25539 includes 8.5.2.

D.5.1.5.2 Materials

D.5.1.5.2.1 **Stent system**.

D.5.1.5.2.2 **Accessory devices**, necessary to accomplish deployment in accordance with the IFU.

D.5.1.5.2.3 **Anatomical model**, that includes a delivery pathway and a deployment location. The angulation and tortuosity of the intended stent location and delivery pathway should be considered in the design of the model.

D.5.1.5.2.4 **Force measuring mechanism**, (e.g. force gauge, universal mechanical testing system), capable of measuring force to an accuracy of ± 5 % of the reported value.

D.5.1.5.2.5 **Gripping fixture**.

D.5.1.5.2.6 **Temperature controlled environment** (37 ± 2) °C.

D.5.1.5.3 Sampling

Sampling shall be in accordance with Clause D.2. Devices to be tested should represent worst-case deployment force conditions (e.g. greatest bulk within the sheath or cover, highest compression ratio). The effect of device diameter and length should be taken into consideration in the selection of devices for testing.

D.5.1.5.4 Conditioning

Conditioning shall be in accordance with Clause D.3.

D.5.1.5.5 Test Method

Develop a test method based on the following:

a) prepare the stent system in accordance with the IFU;

b) insert the stent system into the anatomical model;

c) secure the hub or proximal end of the stent system such that it remains stationary during testing;

d) attach the deployment mechanism to the load measuring equipment;

e) allow the device to stabilize at physiological temperatures;

f) initiate and complete the deployment per the IFU at a rate that simulates clinical use while measuring the force to deploy (e.g. uncover) the self-expanding stent;

g) record any anomalous observations (e.g. buckling) for each test sample.

D.5.1.5.6 Expression of results

The maximum force of each step required to deploy (e.g. uncover) the stent is recorded in newtons. Also record any anomalous observations (e.g. buckling) for each test sample.

D.5.1.5.7 Test report

Test report shall be in accordance with Clause D.4 and shall include the maximum, minimum, mean and standard deviation of the deployment forces and any anomalous observations.

D.5.1.6 Balloon inflation and deflation time (balloon expandable or balloon assisted stents)

D.5.1.6.1 Purpose

The purpose of this test is to determine the time required to inflate the balloon to the maximum recommended inflation pressure, volume or diameter and to measure the time required to deflate the balloon. This test provides information that might be clinically useful for treatment planning (e.g. potential occlusion time). The relevant design evaluation section of this part of ISO 25539 includes 8.5.2.

NOTE This test might also be of importance in evaluating the ability to withdraw.

D.5.1.6.2 Materials

D.5.1.6.2.1 Stent system.

D.5.1.6.2.2 Recommended guidewire or equivalent.

D.5.1.6.2.3 Temperature controlled water bath (37 ± 2) °C.

D.5.1.6.2.4 Contrast medium, in accordance with the IFU.

D.5.1.6.2.5 Inflation device, syringe or equivalent, fitted with a means of measuring pressure or volume with accuracy of ± 5 % of the reported value, and of maintaining the inflation pressure or volume.

D.5.1.6.2.6 **Rigid tube**, of a diameter that represents the largest recommended stent or vessel diameter for the compliant balloon under test. No tube is necessary for semi- and non-compliant balloon testing.

D.5.1.6.2.7 **Timer**, with an accuracy of ± 0,2 s.

D.5.1.6.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.1.6.4 Conditioning

Conditioning shall be in accordance with Clause D.3.

D.5.1.6.5 Test method

Develop a test method based on the following:

a) prepare the stent system;

b) insert the appropriate guidewire in the device;

c) submerge the device in the water bath and insert into the rigid tube, if appropriate;

d) allow to equilibrate to test temperature;

e) inflate the balloon in accordance with the IFU, simulating clinical use, at a specified rate;

f) time the balloon inflation period to the maximum inflation pressure, volume or diameter as indicated in the IFU;

g) deflate the balloon in accordance with the IFU and time the balloon deflation period.

D.5.1.6.6 Expression of results

The inflation and deflation times should be expressed in seconds.

D.5.1.6.7 Test report

The test report shall be in accordance with Clause D.4 and include the maximum, minimum, mean and standard deviation of the balloon inflation and deflation times. The definition of the inflation and deflation endpoints shall also be reported. The fluid used for inflation and the inflation pressure and rate shall be reported. Any anomalies observed shall be reported.

D.5.1.7 Balloon rated burst pressure (RBP) (balloon expandable or balloon assisted stents)

D.5.1.7.1 Purpose

The purpose of this test is to determine the rated burst pressure (RBP) of the balloon when used with the stent. The relevant design evaluation section of this part of ISO 25539 includes 8.5.2.

NOTE This test might also be of importance in evaluating the ability to withdraw.

D.5.1.7.2 Materials

D.5.1.7.2.1 **Stent system**.

D.5.1.7.2.2 **Temperature-controlled water bath** (37 ± 2) °C.

D.5.1.7.2.3 **Fluid for inflation**, e.g. room temperature water.

D.5.1.7.2.4 **Leak detection mechanism**, e.g. dye in the test fluid, pressure drop monitor, flow rate monitor.

D.5.1.7.2.5 **Inflation device, syringe or equivalent**, fitted with a means of measuring pressure to an accuracy of ± 5 % of the reported value, and capable of maintaining the inflation pressure.

D.5.1.7.2.6 **Timer**, with an accuracy of ± 1 s.

D.5.1.7.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.1.7.4 Conditioning

Conditioning shall be in accordance with Clause D.3.

D.5.1.7.5 Test method

Develop a test method based on the following:

a) prepare the stent system;

b) submerge the device in the water bath;

c) allow to equilibrate to test temperature;

d) inflate the balloon with the mounted stent or within an appropriate stent for balloon-assisted deployment to a value less than the estimated rated burst pressure; hold the inflation pressure constant for a minimum of 10 s and inspect the balloon for leakage or burst;

e) if no leakage is noted, with the balloon inside the stent, increase the pressure by an increment appropriate to the balloon being tested and hold the pressure for a minimum of 10 s;

f) repeat step e) until the balloon leaks or bursts; any persistent leak or decrease in pressure, whether due to failure of the balloon, shaft, or proximal or distal seals, should be considered a failure (“bursting”) in this test; record the burst pressure and describe the location and failure mode (e.g. seal leaks, balloon rupture, fragmentation);

g) repeat this test with a sufficient number of samples;

h) calculate the rated burst pressure; for balloon expandable stents, the rated burst pressure (RBP) is based upon the results of this testing that shows statistically with at least a 95 % confidence that 99,9 % of the balloons will not burst at or below this pressure.

The RBP can be calculated in the following manner.

Using a one-sided tolerance limit for a normal distribution:

$$\text{RBP} = X - K(SD)$$

where

K is the factor of a one-sided tolerance limit for a normal distribution (K is found in statistical tables and is dependent on P, C and N);

P = 0,999 (99,9 %);

C = 0,95 (95 % confidence);

N is the number of balloons tested;

X is the mean balloon burst pressure;

SD is the standard deviation of balloon burst pressure.

For balloons used for balloon-assisted deployment, a lesser reliability might be appropriate.

D.5.1.7.6 Expression of results

The individual burst pressures and the RBP should be expressed in atmospheres or kilopascals. Calculate the mean and standard deviation of the burst pressure. Appropriate confidence and reliability parameters should be used for determining RBP.

D.5.1.7.7 Test report

The test report shall be in accordance with Clause D.4 and shall include the mean burst pressure (MBP), the calculated RBP, the maximum, minimum and standard deviation of the burst data and any observed failure modes. If lesser reliability parameters are specified, justification shall be provided for the selection of these parameters.

NOTE Additional guidance can be found in ISO 10555-4[5].

D.5.1.8 Balloon rated fatigue (balloon expandable or balloon-assisted stents)

D.5.1.8.1 Purpose

The purpose of this test is to evaluate the ability of the balloon to withstand repeated inflation cycles. The relevant design evaluation section of this part of ISO 25539 includes 8.5.2.

NOTE This test might also be of importance in evaluating the ability to withdraw.

D.5.1.8.2 Materials

D.5.1.8.2.1 **Stent system**.

D.5.1.8.2.2 **Temperature controlled water bath** (37 ± 2) °C.

D.5.1.8.2.3 **Fluid for inflation**, e.g. room temperature water.

D.5.1.8.2.4 **Leak detection mechanism**, e.g. dye in the test fluid, pressure drop monitor, flow rate monitor.

D.5.1.8.2.5 **Inflation device, syringe or equivalent**, fitted with a means of measuring pressure to an accuracy of ± 5 % of the reported value, and capable of maintaining the inflation pressure or volume.

D.5.1.8.2.6 **Compliant tube**, (with a clinically relevant compliance) of a diameter that represents the largest recommended vessel diameter for the stent system under test in order to keep the stent from moving excessively during the inflation cycles.

D.5.1.8.2.7 **Timer**, with an accuracy of ± 1 s.

D.5.1.8.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.1.8.4 Conditioning

Conditioning shall be in accordance with Clause D.3.

D.5.1.8.5 Test method

Develop a test method based on the following:

a) prepare the stent system;

b) submerge the device in the water bath and insert the compliant tube;

c) allow to equilibrate to test temperature;

d) inflate the balloon, using clinically relevant rates, to the rated burst pressure or maximum diameter as indicated in the IFU, for a minimum of 30 s or for the length of time stated in the IFU;

NOTE If the length of time stated in the IFU is longer than 30 s, the specified length of time should be used for this test, unless adequate justification is provided for using the shorter duration.

e) deflate balloon using clinically relevant rates;

f) repeat steps d) and e), with the balloon inside the stent, for a minimum of 10 cycles;

g) if any persistent leak or decrease of pressure or volume occurs during testing, record the number of cycles and the mode of failure; any such leak or decrease in pressure due to failure of the balloon, shaft, or proximal or distal seals, should be considered a failure in this test.

D.5.1.8.6 Expression of results

The maximum inflation diameter or pressure used shall be expressed with diameter in millimetres, pressure in kilopascals or atmospheres.

D.5.1.8.7 Test report

The test report shall be in accordance with Clause D.4 and shall include the number of cycles successfully completed, the maximum number of cycles expected clinically, any observed failure modes and the maximum inflation diameter or pressure.

NOTE Additional guidance can be found in ISO 10555-4[5].

D.5.2 Delivery system

D.5.2.1 Bond strength

D.5.2.1.1 Purpose

The purpose of this test is to determine the bond strength of the joints and/or fixed connections of the delivery system. The relevant design evaluation sections of this part of ISO 25539 include 8.5.1, 8.5.2 and 8.5.3.

D.5.2.1.2 Materials

D.5.2.1.2.1 **Delivery system**, or appropriate component joints and/or fixed connections.

D.5.2.1.2.2 **Universal mechanical testing system**, equipped with a suitable load cell capable of measuring force to an accuracy of ± 5 % of the reported value, a constant rate of traverse and appropriate gripping fixtures.

D.5.2.1.2.3 Temperature controlled environment (37 ± 2) °C, as appropriate.

D.5.2.1.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.2.1.4 Conditioning

Conditioning shall be in accordance with Clause D.3.

D.5.2.1.5 Test method

For bonds that will be subjected to physiological temperatures, testing should be performed at (37 ± 2) °C or immediately after conditioning at this temperature.

Develop a test method based on the following:

a) using a mechanical testing system with an appropriate crosshead speed (e.g. 200 mm/min), apply tension to each bonded joint or to a series of bonded joints until a bond breaks or loses functional integrity;

b) record the force at which failure occurs and describe the type and location of the failure.

D.5.2.1.6 Expression of results

Bond strength shall be expressed in newtons.

D.5.2.1.7 Test report

The test report shall be in accordance with Clause D.4 and shall include the type and location of the failure, and the maximum, minimum, mean and standard deviation of the bond strength.

NOTE Additional guidance can be found in ISO 10555-1[2].

D.5.2.2 Torsional bond strength

D.5.2.2.1 Purpose

The purpose of this test is to determine the torsional bond strength of the joints and/or fixed connections of the delivery system. The relevant design evaluation sections of this part of ISO 25539 include 8.5.1 and 8.5.3.

D.5.2.2.2 Materials

D.5.2.2.2.1 Delivery system, or appropriate component joints and/or fixed connections.

D.5.2.2.2.2 Recommended guidewire, or equivalent, if appropriate.

D.5.2.2.2.3 Torque testing system, equipped with a suitable gauge capable of measuring to an accuracy of ± 5 % of the reported value.

D.5.2.2.2.4 Temperature controlled environment (37 ± 2) °C, as appropriate.

D.5.2.2.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.2.2.4 Conditioning

Conditioning shall be in accordance with Clause D.3.

D.5.2.2.5 Test method

For bonds that will be subjected to physiological temperatures, testing should be performed at (37 ± 2) °C.

Develop a test method based on the following:

a) insert the delivery system or component over the guidewire, if appropriate;

b) affix one end of the test sample in a clamping apparatus;

c) attach other end of the test sample to the torque gauge;

d) apply a torque (twisting force), at a rate characteristic of that used in a typical clinical deployment, to one end of the sample until the joint and/or delivery system breaks or loses functional integrity;

e) record the torque value at which failure occurs and the failure mode and location.

D.5.2.2.6 Expression of results

Torsional bond strength shall be expressed in newton metres.

D.5.2.2.7 Test report

Test report shall be in accordance with Clause D.4 and shall include the mode and location of the failure, and the maximum, minimum, mean and standard deviation of the torsional bond strength.

D.5.3 Stent

D.5.3.1 Stent diameter to balloon inflation pressure

D.5.3.1.1 Purpose

The purpose of this test is to determine the relationship between the stent diameter and the balloon inflation pressure for balloon expandable stents. The relevant design evaluation section of this part of ISO 25539 includes 8.6.4.

D.5.3.1.2 Materials

D.5.3.1.2.1 Stent system.

NOTE This test is not designed to evaluate the entire system; however, the system is required to deploy the stent that is under test.

D.5.3.1.2.2 Inflation device, syringe or equivalent, fitted with a means of measuring pressure to an accuracy of ± 5 % of the reported value, and capable of maintaining the inflation pressure.

D.5.3.1.2.3 Fluid for inflation, e.g. room temperature water.

D.5.3.1.2.4 Measuring equipment for diameters (e.g. micrometer, optical profile projector, laser-micrometer) capable of measuring to 10 % of the specified tolerance or 1 % of the measured value. If a tolerance is specified, the lesser value of the respective percentages shall be used.

D.5.3.1.2.5 Temperature controlled environment (37 ± 2) °C, as appropriate.

D.5.3.1.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.3.1.4 Conditioning

Conditioning shall be in accordance with Clause D.3 and shall include loading and preconditioning.

D.5.3.1.5 Test method

Develop a test method based on the following:

a) inflate the balloon incrementally, allowing the system to stabilize between intervals; pressures should be chosen to determine the stent diameter at appropriate intervals (e.g. 1 atm or 1 bar) over the indicated range of diameters;

b) determine the average diameter of the stent at each pressure interval at appropriate locations along the length of the stent; these measurements should be taken immediately after stabilization;

c) inflation should not be terminated until the balloon reaches the rated burst pressure.

The entire test should be completed rapidly to minimise the effects of viscoelastic behaviour and to better simulate the inflation method used clinically.

D.5.3.1.6 Expression of results

The stent diameters should be expressed in millimetres and the associated pressures in kilopascals and/or atmospheres.

D.5.3.1.7 Test report

The test report shall be in accordance with Clause D.4 and shall include the maximum, minimum, mean and standard deviation of the stent diameter (inner or outer) measurements and associated pressures. These data can be reported in tabular or graphical format.

D.5.3.2 Dimensional verification and stent length to diameter relationship

D.5.3.2.1 Purpose

The purpose of this test is to determine the length to diameter relationship of the stent, the unconstrained length of a self-expanding stent and the wall thickness(es) of the stent. The relevant design evaluation section of this part of ISO 25539 includes 8.6.1 and 8.6.4.

Other measurements might be needed to completely verify the dimensions of a particular stent.

D.5.3.2.2 Materials

D.5.3.2.2.1 **Stent system**.

NOTE This test is not designed to evaluate the entire system; however, the system is required to deploy the stent that is under test.

D.5.3.2.2.2 Measuring equipment for diameters (e.g. micrometer, optical profile projector, laser-micrometer, calipers) capable of measuring to 10 % of the specified tolerance or 1 % of the measured value. If a tolerance is specified, the lesser value of the respective percentages shall be used.

D.5.3.2.2.3 Measuring equipment for wall thickness(es) (e.g. microscope with calibrated eyepiece, constant load thickness gauge, optical profile projector, laser-micrometer) capable of measuring to an accuracy of ± 5 % of the reported value.

D.5.3.2.2.4 Measuring equipment, for lengths capable of measuring to 10 % of the specified tolerance or 1 % of the measured value. If a tolerance is specified, the lesser value of the respective percentage shall be used.

D.5.3.2.2.5 Clear rigid tube, with inner diameters corresponding to the minimum and maximum vessel diameters indicated in the IFU for each stent size under test.

D.5.3.2.2.6 Accessory devices, necessary to accomplish deployment in accordance with the IFU.

D.5.3.2.2.7 Temperature controlled environment (37 ± 2) °C for stents with dimensions that are sensitive to changes between ambient and physiological temperatures.

D.5.3.2.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.3.2.4 Conditioning

Conditioning shall be in accordance with Clause D.3.

D.5.3.2.5 Test method

Develop a test method based on the following:

NOTE 1 For a balloon expandable stent with significant recoil, there might be difficulty in obtaining appropriate apposition of the stent to the wall of the tube. Alternative methodology might need to be developed to appropriately evaluate this attribute for such devices.

a) measure the mounted length of the stent;

b) deploy the stent in accordance with the IFU into the rigid tube that represents the minimum nominal diameter for each stent configuration following the IFU;

c) measure the stent length within the tube;

NOTE 2 It might be appropriate to measure the length of a balloon expandable stent with the balloon inflated.

d) repeat steps b) and c) using the rigid tube that represents the maximum nominal diameter for each stent configuration; for self expanding stents, also deploy the stent without diameter constraint and measure the outer diameter(s) and length; outer diameter(s) shall be measured at both ends of the stent and in the middle of the stent in two perpendicular directions, after deployment in accordance with the IFU;

NOTE 3 For non-circular cross-sections it might be appropriate to measure and report the maximum and minimum values.

e) for balloon expandable stents remove the stent from the maximum diameter rigid tube;

f) for both stent types, measure the wall thickness(es) of the unconstrained stent at multiple axial and circumferential locations; if the wall thickness of the stent is non-uniform by design, the wall thickness of each representative stent region shall be measured and the results for each region shall be reported separately.

NOTE 4 Devices can be re-used, if appropriate and justified.

The stent length to diameter relationship might be affected by angulation. Additional testing or analyses should be considered to evaluate the effect of angulation on this parameter, as appropriate.

D.5.3.2.6 Expression of results

Stent length, diameter and wall thickness shall be reported in millimetres. In addition, any and all changes in length measured after deployment shall be reported as percentages of the undeployed length.

D.5.3.2.7 Test report

The test report shall be in accordance with Clause D.4 and include the maximum, minimum, mean and standard deviation of all measured and calculated values. The length to diameter relationship should be reported in a tabular format, including both absolute values and percentages.

NOTE Additional guidance can be found in ASTM F2081[23].

D.5.3.3 Recoil

D.5.3.3.1 Purpose

The purpose of this test is to determine the amount of elastic recoil after the deployment of a balloon-expandable stent in the absence of external loading to determine the diameter of the stent in its deployed state. The relevant design evaluation section of this part of ISO 25539 includes 8.6.2 and 8.6.4.

D.5.3.3.2 Materials

D.5.3.3.2.1 Stent system.

NOTE This test is not designed to evaluate the entire system; however, the system is required to deploy the stent that is under test.

D.5.3.3.2.2 Accessory devices, necessary to allow for appropriate expansion of the stent.

D.5.3.3.2.3 Inflation device, syringe or equivalent, fitted with a means of measuring pressure to an accuracy of ± 5 % of the reported value, and capable of maintaining the inflation pressure.

D.5.3.3.2.4 Fluid for inflation, e.g. room temperature water.

D.5.3.3.2.5 Measuring equipment for diameters (e.g. micrometer, optical profile projector, laser-micrometer) capable of measuring to 10 % of the specified tolerance or 1 % of the measured value. If a tolerance is specified, the lesser value of the respective percentages shall be used.

D.5.3.3.2.6 Temperature controlled environment (37 ± 2) °C for stents with material properties that are sensitive to changes between ambient and physiological temperatures.

D.5.3.3.2.7 Timer, with an accuracy of ± 1 s.

D.5.3.3.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.3.3.4 Conditioning

Conditioning shall be in accordance with Clause D.3 and shall include loading and preconditioning.

D.5.3.3.5 Test method

Develop a test method based on the following:

a) inflate the balloon to expand the stent using the recommended inflation pressure and hold the pressure to allow the balloon and stent to stabilize (approximately 30 s);

b) determine the average outer diameter of the stent at appropriate locations along the length; outer diameter(s) shall be measured at both ends of the stent and in the middle of the stent in two perpendicular directions after deployment, in accordance with the IFU;

c) deflate and remove the balloon catheter;

d) allow the stent to stabilize (approximately 30 s);

e) repeat step c) at the same locations;

f) calculate the average percent recoil at each longitudinal location and/or for the entire length of the stent, as appropriate, using the following equation:

$$\%\ \text{stent recoil} = \frac{\text{outer diameter (inflated)} - \text{outer diameter (final)}}{\text{outer diameter (inflated)}} \times 100$$

D.5.3.3.6 Expression of results

The stent recoil shall be expressed in percent.

D.5.3.3.7 Test report

The test report shall be in accordance with Clause D.4 and shall include the maximum, minimum, mean and standard deviation of the recoil percentages at each longitudinal location and/or for the entire length of the stent, as appropriate.

NOTE Additional guidance can be found in ASTM F2079[22].

D.5.3.4 Crush resistance with radially applied load

D.5.3.4.1 Purpose

The purpose of the test is to determine the load/deformation characteristics of the stent while a circumferentially uniform radial load is applied. The relevant design evaluation section of this part of ISO 25539 includes 8.6.2 and 8.6.5.

NOTE Although similar, crush resistance with a radially applied load, crush resistance using parallel plates, local compression and radial force tests measure different attributes of the stent, as follows:

— the crush resistance test with a radially applied load measures the ability of a balloon-expandable stent to resist permanent deformation when subjected to a circumferentially uniform radial load;

— the crush resistance test using parallel plates measures the ability of a stent to resist permanent deformation along the entire length of the device when subjected to a load uniformly applied over the length of the device;

— the local compression test measures the ability of a stent to resist permanent deformation under a localized (e.g. point) load;

— the radial force test measures the force exerted by a self-expanding stent on the vessel in the deployed state during expansion and compression.

D.5.3.4.2 Materials

D.5.3.4.2.1 **Stent system**.

NOTE This test is not designed to evaluate the entire system; however, the system is required to deploy the stent that is under test.

D.5.3.4.2.2 Universal mechanical testing system, equipped with a suitable load cell capable of measuring force to an accuracy of ± 5 % of the reported value and a constant rate of traverse, and appropriate gripping fixtures and circumferential tension devices (e.g. loop, snare).

D.5.3.4.2.3 Mechanical radial force testing system (e.g. iris tester) equipped with a suitable load cell capable of measuring force or pressure to an accuracy of ± 5 % of the reported value and a constant rate of traverse.

D.5.3.4.2.4 Temperature controlled environment (37 ± 2) °C for stents with material properties that are sensitive to changes between ambient and physiological temperatures.

D.5.3.4.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.3.4.4 Conditioning

Conditioning shall be in accordance with Clause D.3 and shall include loading, preconditioning and deployment.

D.5.3.4.5 Test method

Develop a test method based on the following:

a) place the stent in the test fixture;

b) compress the stent using a uniform rate of compression; start with a diameter equal to the maximum indicated vessel diameter;

c) record the load and the associated diameter while compressing the stent until an appreciable reduction in force occurs or a diameter reduction of at least 50 % is reached;

d) repeat this test using the minimum nominal indicated vessel diameter for each stent configuration.

D.5.3.4.6 Expression of results

Express load (pressure or force) per unit axial length in kilopascals per millimetre or newtons per millimetre, as appropriate, and diameters in millimetres.

D.5.3.4.7 Test report

The test report shall be in accordance with Clause D.4 and shall include a description of the method used for determining the force and diameter. Report the maximum, minimum, mean and standard deviation of the peak force and the diameter at the peak force. Report the length of the stent segment under test. Data should also be reported as a curve of load versus diameter for the range of diameters tested.

D.5.3.5 Crush resistance with parallel plates

D.5.3.5.1 Purpose

The purpose of the test is to determine the load required to cause clinically relevant buckling or a deflection equivalent to a diameter reduction of at least 50 %, and the load required to permanently deform or fully collapse the stent. The purpose of the test is to also determine if the stent recovers its original geometry after testing. The relevant design evaluation section of this part of ISO 25539 includes 8.6.2 and 8.6.5.

NOTE Although similar, crush resistance with a radially applied load, crush resistance using parallel plates, local compression and radial force tests measure different attributes of the stent, as follows:

— the crush resistance test with a radially applied load measures the ability of a balloon-expandable stent to resist permanent deformation when subjected to a circumferentially uniform radial load;

— the crush resistance test using parallel plates measures the ability of a stent to resist permanent deformation along the entire length of the device when subjected to a load uniformly applied over the length of the device;

— the local compression test measures the ability of a stent to resist permanent deformation under a localized (e.g. point) load;

— the radial force test measures the force exerted by a self-expanding stent on the vessel in the deployed state during expansion and compression.

D.5.3.5.2 Materials

D.5.3.5.2.1 **Stent system**.

NOTE This test is not designed to evaluate the entire system; however, the system is required to deploy the stent that is under test.

D.5.3.5.2.2 Universal mechanical testing system, equipped with a suitable load cell capable of measuring force to an accuracy of ± 5 % of the reported value and a constant rate of traverse and appropriate parallel plate fixtures (i.e., of length longer than the test article).

D.5.3.5.2.3 Temperature controlled environment (37 ± 2) °C for stents with material properties that are sensitive to changes between ambient and physiological temperatures.

D.5.3.5.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.3.5.4 Conditioning

Conditioning shall be in accordance with Clause D.3 and shall include loading, preconditioning and deployment.

D.5.3.5.5 Test method

Develop a test method based on the following:

a) place the stent in the test fixture in the orientation anticipated to have the least amount of crush resistance;

b) compress the stent using a uniform rate of compression; for balloon-expandable stents, start with a diameter equal to the maximum indicated vessel diameter; for self-expanding stents, start at the free expanded diameter of the stent;

c) record the load and the associated displacement while compressing the stent until clinically relevant buckling or a deflection equivalent to a diameter reduction of at least 50 % occurs; determine the load required to permanently deform or fully collapse the stent;

d) release the force applied to the stent and record whether the stent recovers its original geometry;

e) for balloon expandable stents, deploy a stent to the minimum nominal indicated vessel diameter for each stent configuration and repeat steps a) to d).

NOTE The method for determining the force and deflection at which plastic deformation begins is not defined in this part of ISO 25539 since this method will be specific to the device design under evaluation.

D.5.3.5.6 Expression of results

Express load (force) per unit axial length in newtons per millimetre, as appropriate, and displacement (including diameter equivalent) in millimetres.

D.5.3.5.7 Test report

The test report shall be in accordance with Clause D.4 and shall include a description of the method used for determining the force and displacement (diameter). Report the maximum, minimum, mean and standard deviation of the load and displacement required to cause clinically relevant buckling or the load at a deflection equivalent to a diameter reduction of at least 50 % and the load and displacement required to permanently deform or fully collapse the stent. Report whether or not the stent recovers its original geometry after testing. Data should also be reported as curves of load versus displacement. The orientation of the stent during load application shall be justified.

D.5.3.6 Flex/kink

D.5.3.6.1 Purpose

The purpose of this test is to determine the minimum radius at which the deployed stent can be flexed without kinking or exhibiting a diameter reduction of greater than 50 % and if the stent recovers its original geometry after testing. If overlapping of stents can be anticipated in clinical use (e.g. superficial femoral artery), the kink radius of the stent under study in overlapping configurations should also be determined. This section provides two alternative test methods (method A and method B) which might be applied as appropriate to the device design. The relevant design evaluation sections of this part of ISO 25539 include 8.6.5.

NOTE For permanently deformed stents (e.g. a balloon-expandable stainless steel stent) recovery to the original geometry is not expected to occur.

D.5.3.6.2 Materials

D.5.3.6.2.1 Stent system.

NOTE This test is not designed to evaluate the entire system; however, the system is required to deploy the stent that is under test.

D.5.3.6.2.2 Accessory devices, necessary to accomplish deployment in accordance with the IFU.

D.5.3.6.2.3 Elastomeric tubes, of diameters that represent the smallest and largest recommended vessel diameters, as appropriate, for the stent under test. **For test method A only**.

D.5.3.6.2.4 Cylindrical gauges, of progressively decreasing radii. **For test method A only**.

D.5.3.6.2.5 Rigid bend model, that represents the smallest and largest recommended vessel diameters, as appropriate, for the stent under test with progressively decreasing bending radii. **For test method B only**.

The bend model should be manufactured from translucent material to allow observation of stent buckling/strut protrusion and should consist of two half plates or half shells, which can be unmounted for stent removal after deployment to allow assessment of stent recovery to original shape and size.

D.5.3.6.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.3.6.4 Conditioning

Conditioning shall be in accordance with Clause D.3 and shall include loading and preconditioning.

D.5.3.6.5 Test method A

a) Deploy a single stent in a straight tube of the minimum nominal indicated vessel diameters for each stent configuration, in accordance with the IFU;

b) position stent loaded tubing on the cylindrical gauge; test worst case stent orientation;

c) bend stent loaded tubing around the gauge so that the entire length of the stent is in contact with the gauge or to a maximum of 180°;

d) record the radius and whether kink or significant narrowing is observed;

NOTE The radius is calculated by adding the tubing wall thickness to the gauge radius.

e) release the force applied to the stent and record whether the stent recovers its original geometry;

f) repeat steps c) and d) using progressively smaller radius fixtures until a kink or a stent diameter reduction of at least 50 % is observed;

g) repeat steps a) to f) for different positions along the length of the stent, if applicable;

h) repeat steps a) to g) using a compliant tubing of the maximum indicated vessel diameter;

i) repeat steps a) to h) using stents in overlapped configuration, if applicable.

D.5.3.6.6 Test method B

a) Deploy a single stent in the bend model of the minimum nominal indicated vessel diameters, for each stent configuration in accordance with the IFU; test worst case stent orientation;

b) record the bend radius and whether a kink or significant narrowing is observed;

c) release the stent from the bend model and record whether the stent recovers its original geometry;

d) repeat steps a) to c) using progressively smaller bend radii until a kink or a stent diameter reduction of at least 50 % is observed;

e) repeat steps a) to d) for different positions along the length of the stent, if applicable;

f) repeat steps a) to e) using the bend model of the maximum indicated vessel diameter;

g) repeat steps a) to f) using stents in overlapped configuration, if applicable.

D.5.3.6.7 Expression of results

The kink radius shall be expressed in millimeters.

D.5.3.6.8 Test report

The test report shall be in accordance with Clause D.4 and shall include the maximum, minimum, mean and standard deviation of the smallest radius at which neither kink nor a reduction of stent diameter of 50 % is observed for each test condition (i.e., minimum and maximum tubing diameters, with and without overlap). Record the largest radius and location at which a kink or stent diameter reduction is observed. Report whether permanent deformation is observed and the radius at which permanent deformation is observed. Note any anomalous findings (e.g. separation of overlapped stents, fractures, strut protrusion into the lumen). Justify the type of elastomeric tubing used, if applicable.

D.5.3.7 Local compression

D.5.3.7.1 Purpose

The purpose of this test is to determine the deformation of the device in response to a localized compressive force perpendicularly applied to the longitudinal axis of the device, and to determine if the stent recovers its original geometry after testing. This test is required for stents of a design with the potential for a different response to local compression as compared to a radial or flat plate compressive force and for which this test is clinically relevant.

The relevant design evaluation section of this part of ISO 25539 includes 8.6.2 and 8.6.5.

NOTE Although similar, crush resistance with a radially applied load, crush resistance using parallel plates, local compression and radial force tests measure different attributes of the stent, as follows:

— the crush resistance test with a radially applied load measures the ability of a balloon-expandable stent to resist permanent deformation when subjected to a circumferentially uniform radial load;

— the crush resistance test using parallel plates measures the ability of a stent to resist permanent deformation along the entire length of the device when subjected to a load uniformly applied over the length of the device;

— the local compression test measures the ability of a stent to resist permanent deformation under a localized (e.g. point) load;

— the radial force test measures the force exerted by a self-expanding stent on the vessel in the deployed state during expansion and compression.

D.5.3.7.2 Materials

D.5.3.7.2.1 **Stent system**.

NOTE This test is not designed to evaluate the entire system; however, the system is required to deploy the stent that is under test.

D.5.3.7.2.2 **Universal mechanical testing system**, with compressive capability, equipped with a suitable load cell capable of measuring force to an accuracy of ± 5 % of the reported value, a constant rate of traverse and appropriate load application fixtures.

D.5.3.7.2.3 **Probe**, for applying compressive force. The design of the probe (e.g. shape, cross-sectional area) shall be appropriate for the stent design and potential *in vivo* local compressive forces.

D.5.3.7.2.4 **Temperature controlled environment** (37 ± 2) °C for stent with material properties that are sensitive to changes between ambient and physiological temperatures.

D.5.3.7.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.3.7.4 Conditioning

Conditioning shall be in accordance with Clause D.3 and shall include loading, preconditioning and deployment.

D.5.3.7.5 Test method

Develop a test method based on the following:

a) measure the outer diameter of the stent;

b) compress the stent with a locally applied load using a uniform rate of compression until a displacement equivalent to a diameter reduction of at least 50 % is achieved; application of the load shall be within an area of the stent considered to be most susceptible to deformation as a result of the application of a focal load;

c) release the force applied to the stent and measure the minimum diameter of the stent after the test.

D.5.3.7.6 Expression of results

Diameters shall be reported in millimetres.

D.5.3.7.7 Test report

The test report shall be in accordance with Clause D.4 and shall include the initial and final measured diameters and a justification for the area of the stent tested.

D.5.3.8 Radial force

D.5.3.8.1 Purpose

The purpose of this test is to determine the force exerted by a self-expanding stent as a function of the stent diameter, under the conditions of expansion and compression. The relevant design evaluation sections of this part of ISO 25539 include 8.6.2 and 8.6.5.

NOTE Although similar, crush resistance with a radially applied load, crush resistance using parallel plates, local compression and radial force tests measure different attributes of the stent, as follows:

— the crush resistance test with a radially applied load measures the ability of a balloon-expandable stent to resist permanent deformation when subjected to a circumferentially uniform radial load;

— the crush resistance test using parallel plates measures the ability of a stent to resist permanent deformation along the entire length of the device when subjected to a load uniformly applied over the length of the device;

— the local compression test measures the ability of a stent to resist permanent deformation under a localized (e.g. point) load;

— the radial force test measures the force exerted by a self-expanding stent on the vessel in the deployed state during expansion and compression.

D.5.3.8.2 Materials

D.5.3.8.2.1 Stent system.

NOTE This test is not designed to evaluate the entire system; however, the system is required to deploy the stent that is under test.

D.5.3.8.2.2 Universal mechanical testing system, equipped with a suitable load cell capable of measuring force to an accuracy of ± 5 % of the reported value, a constant rate of traverse and appropriate gripping fixtures.

D.5.3.8.2.3 Expansion and compression clamps/fixtures, such as “Clamshell”, “V” Block or a circumferential tension device such as a loop or snare. The fixture diameter/dimensions should be appropriate for the stent being tested.

D.5.3.8.2.4 Temperature controlled environment (37 ± 2) °C for stents with material properties that are sensitive to changes between ambient and physiological temperatures.

NOTE When selecting the test fixture, consideration should be given to the width or area under study, the effects of friction and the influence of the fixture geometry on the measured loads.

D.5.3.8.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.3.8.4 Conditioning

Conditioning shall be in accordance with Clause D.3 and shall include loading and preconditioning.

D.5.3.8.5 Test method

Develop a test method based on the following:

a) deploy the stent within the fixture such that the initial diameter is less than or equal to the minimum vessel diameter indicated in the IFU;

b) measure the radial force as a function of diameter as the stent is expanded to the maximum indicated vessel diameter; the speed of testing should be such that the results represent static conditions;

c) measure the radial force as a function of diameter as the stent is compressed to the minimum nominal indicated vessel diameter for each stent configuration; the speed of testing should be such that the results represent static conditions;

d) calculate the radial pressure based on the measured force and the cylindrical area under test.

D.5.3.8.6 Expression of results

Radial force shall be expressed in newtons per unit length in millimetres. The length shall be defined as the length of the stent within the fixture. Radial pressure shall be expressed in kilopascals.

D.5.3.8.7 Test report

The test report shall be in accordance with Clause D.4 and shall include a description of the stent location(s) tested, the minimum, maximum, mean and standard deviation of the radial force and radial pressure at the minimum and maximum diameters for each device size tested. Results from both expansion and compression shall be reported, with the respective speeds used during testing.

D.5.3.9 Corrosion assessment

D.5.3.9.1 Purpose

The purpose of this assessment is to evaluate the susceptibility of the metallic components of the stent to corrosion in a simulated physiological environment for the intended stent duration. The relevant design evaluation section of this part of ISO 25539 includes 8.6.3.

D.5.3.9.2 Materials

D.5.3.9.2.1 Stent or appropriate test samples of the stent (e.g. segments, sections, components, subassemblies). Test samples shall be appropriate to the type of corrosion under evaluation (e.g. crevice, pitting, fretting, galvanic).

D.5.3.9.2.2 Materials, apparatus and test conditions, as specified in the test methods selected for this evaluation.

D.5.3.9.2.3 Suitable, standard reference samples.

D.5.3.9.3 Sampling

Sampling shall be in accordance with Clause D.2.

D.5.3.9.4 Conditioning

Conditioning shall be in accordance with Clause D.3 and shall include loading, preconditioning and deployment. The materials under evaluation shall undergo all manufacturing, fabrication and finish processing, as well as all post processing steps such as cleaning. For coated stents, a portion of the underlying substrate should be exposed prior to testing to simulate potential clinical exposure over time. Care should be taken not to damage the underlying substrate during conditioning. Additional preconditioning steps might be appropriate for coated stents.

D.5.3.9.5 Test Method

a) All metallic components of the stent should be evaluated using appropriate corrosion test methods and assessment. In cases where different metals might be in contact by virtue of the device design or IFU, they shall be in similar contact during evaluation (e.g. radiopaque markers). In cases where the stent design allows for relative micromotion between components such as woven wires or when overlapping of stents can be anticipated in clinical use (e.g. superficial femoral artery, coronary), fretting corrosion shall be assessed.

b) Corrosion assessment includes, but is not limited to, evaluation of test results, review of literature and consideration of the historical clinical performance of the material(s) under assessment. Guidance on corrosion assessment can be found from a variety of sources (e.g. literature, text books, standards, regulatory guidance documents). The Bibliography includes a partial list of references regarding corrosion terminology, equipment, test procedures and methods.

NOTE Additional guidance can be found in: ISO 17475[14]; ASTM B117[18], ASTM F746[20], ASTM F2129[25], ASTM G5[31], ASTM G15[32], ASTM G61[33] and ASTM G102[34].

D.5.3.9.6 Expression of results

Test data shall be expressed in units appropriate to the methods selected.

D.5.3.9.7 Test report

The test report shall be in accordance with Clause D.4 and shall include the complete corrosion assessment, including a summary of all test data, analyses and referenced information, comparisons to applicable controls, any appropriate comparison between *in vivo* and *in vitro* performance and conclusions regarding the anticipated corrosion resistance of the stent. For quantitative data, the maximum, minimum, mean and standard deviation shall be included. Applicable requirements indicated in the guidance documents used for testing should also be included.

D.5.3.10 Fatigue durability test

D.5.3.10.1 Purpose

The purpose of this test is to evaluate aspects of the long-term integrity of the stent and any coating under cyclic radial loading conditions. If overlapping of stents can be anticipated in clinical use (e.g. superficial femoral artery, coronary), integrity of the stent under study in overlapping configurations should be evaluated, unless justification can be provided for testing of individual stents. The relevant design evaluation sections of this part of ISO 25539 include 8.6.3, 8.6.3.5, 8.6.3.5.4 and 8.6.3.5.5.

Potential failure modes that might be identified by this test include, but are not limited to, stent fracture due to fatigue and wear or abrasion between stents. The potential coating failure mode that might be identified by this test includes disruption of the coating, such as delamination, creation of flaps or bare spots and cracking. This test is not intended to fully evaluate the potential for failures related to corrosion, abrasion between the stent and the recipient artery, or stent migration. It is acknowledged that these types of potential failure mode might be observed during testing and consideration should be given as to whether such observations indicate an increased potential for these failure modes to appear clinically.

This test might be modified to include evaluation of failure modes induced by flexion, extension, torsion, tension, compression or deployment in an angulated recipient artery. In addition, this test might be modified to evaluate coating particulate generation. Other types of testing or evaluation of devices or components will be necessary to fully evaluate all potential failure modes.

Results of component and preliminary testing should be considered in development of this test method.

D.5.3.10.2 Materials

D.5.3.10.2.1 Stent system.

NOTE This test is not designed to evaluate the entire system; however, the system is required to deploy the stent that is under test.

D.5.3.10.2.2 Accessory devices, necessary to accomplish deployment in accordance with the IFU.

D.5.3.10.2.3 Mock arteries, with geometries, diameters and properties appropriate to allow simulation of worst case forces or diametric displacements expected on the device at the intended site of implantation. To ensure that the mock artery has the appropriate diameter during testing, operating pressures should be considered when specifying the diameter of the mock artery. If appropriate, the compliance of the mock artery should be defined and measured by a method similar to that described in ISO 7198. The compliance of the native artery should be considered when designing the mock artery. For coating evaluation, the artefacts due to friction should be considered.

D.5.3.10.2.4 Pulsatile fatigue tester, capable of applying cyclic displacement to the mock artery with the stent deployed. The test equipment shall include provisions for either direct or indirect measurement of the mock artery inner diameter, D_i, at the test frequency, maintaining physiological temperature (37 ± 2) °C of the test assembly, and counting the cycles.

D.5.3.10.2.5 Appropriate inspection equipment, (e.g. light microscope, lighted magnifying glass, SEM).

D.5.3.10.3 Sampling

Sampling shall be in accordance with Clause D.2. The device size(s) shall be selected to represent the greatest potential for each failure mode being evaluated based upon appropriate engineering analyses such as stress/strain analyses.

For coating durability testing, different samples might be necessary for different inspection time points.