Table A.3 continued

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 hemostasis	Evaluate the ability of any seal or valves in the delivery system to maintain an adequate hemostatic seal when used with appropriate accessory devices.	8.5.5 Hemostasis
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 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 RBP.	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 durability	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

Table B.1 continued

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 Hemostasis
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
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 Hemostasis 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

Table B.1 continued

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
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

Table B.1 continued

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 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 days of the procedure.
Atelectasis/pneumonia	Atelectasis or pneumonia documented by chest X-ray within 30 days of the procedure and requiring treatment with antibiotics, inhalation therapy, intubation or suctioning. The type of treatment required should be reported.
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 days 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.
Hematoma	Development of a hematoma 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.

Table C.1 continued

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.
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 days 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 days 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 days 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 30 days or more 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 days of the procedure. Clinical symptoms, EKG changes and/or hemodynamic 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 days of the procedure. Whether the deficit was permanent or transient should also be reported.
Periprocedural mortality	Death from any cause occurring within 30 days 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 days 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.

Table C.1 continued

Respiratory failure	Need for post-procedural mechanical ventilation or the need for re-intubation or ventilator support any time up to 30 days post-operative (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 cord ischemia developing within 30 days of the procedure.
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	Hemodynamically 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 (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 days 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 days 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 recognized that not all of the tests described in this annex are applicable for each stent system design. It is also recognized that testing intended to ensure that the device meets specifications during manufacture might not be conducted in accordance with the details outlined in this annex.

To ensure 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. Use of *in vivo* models may be substituted for *in vitro* methods where reasonable equivalency can be established and clinical relevance is demonstrated.

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 recognized 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 recognized 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 this part of ISO 25539 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 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: