

Endovascular Device Testing

A Survey of Requirements for Product Validation

There is a very large range of minimally invasive medical devices, which access the vasculature percutaneously.

Rigorous testing is required for CE Marking design verification and also for FDA submissions. We take an intravascular stent and its delivery system as examples here.

FDA Guidance ref 1 describes intravascular stents as Class III devices requiring premarket approval (PMA). This would usually require a clinical study prior to marketing and a post marketing surveillance study. Here we consider only the non-clinical test requirements. Specific FDA Guidance is published for drug eluting stents ref 2, this is not discussed here.

Non-clinical testing can be broadly divided into biological evaluation and functional testing. Functional testing includes how the device works, its durability and packaging and sterility studies.

Biological Evaluation

The guidance provided in the ISO 10993 ^{ref 3} series (Biological Evaluation of Medical Devices) is broadly accepted worldwide. ISO 10993 Part 1 details the types of test that should be considered, but manufacturers intending to market in the USA (where requirements can be more stringent) should also be aware of the useful guidance provided in ASTM F748-04 ^{ref 4}.

Biological evaluation should be considered in terms of the toxicological risk to patients, drawing on the nature of the materials, the literature, the biological data and the clinical purpose and environment. Toxicological risk assessment should be performed in accordance with the guidance provided in ISO 14971 ^{ref 5}. This can be applied to reduce the amount of biological testing required if a predicate device exists or the material(s) have a documented history of use in other medical devices.

Parts 18 and 19 are relative newcomers to ISO 10993. They address the chemical and physicochemical characterisation of medical device materials, including potentially hazardous extractables and leachables. It is recommended that manufacturers using new or novel materials or manufacturing processes perform a thorough characterisation at an early stage and use the information in a first toxicological risk assessment.

Biological evaluation plans for two devices are presented: a (European) Class III intravascular stent and its Class IIa delivery system. Manufacturers should be aware that if the two products are marketed in Europe as a single device then the whole system becomes Class III, meaning that the delivery system must also be treated as a Class III device with more stringent testing.

ISO 10993 Part 1 recommends that a Class IIa device be subjected to cytotoxicity, acute systemic toxicity and irritation testing. These address the short term biocompatibility of the materials as the stent delivery system is in contact with the patient only for a short period of time. Additionally, because the delivery system comes into contact with circulating blood a haemocompatibility test is recommended. The test data can then be fed into a further round of toxicological risk assessment. Part 4, regarding haemocompatibility, lists 25 different categories of test and therefore manufacturers should consider the IR strategy carefully and are advised to discuss it first with the appropriate regulatory agency. A typical set of tests for a stent delivery system might include thrombosis, coagulation, platelet count, haematology (two tests) and a complement activation panel for immunology.

As a Class III long term implant device that contacts circulating blood the intravascular stent should be subjected to additional tests that address the potential longer term effects: sensitisation, genotoxicity, chronic toxicity, local and systemic toxicity and carcinogenicity. Note that: in Europe two *in vitro* genotoxicity tests (Part 3) are usually performed, whilst in the USA, FDA also require an *in vivo* study to assess the mutagenic potential of stent extracts.

It should not be necessary to perform both subchronic and chronic studies but the more appropriate one should be chosen and justified. Local effects after implantation should also be evaluated.

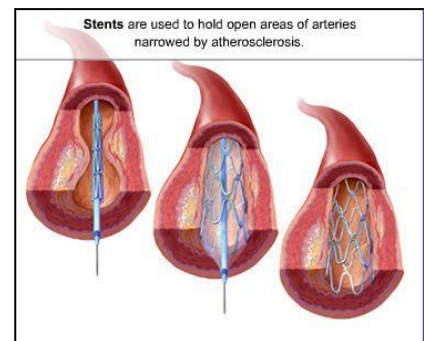


Image 1: Diagram showing the insertion of the stent on the delivery catheter, expansion of the stent, and lastly appearance after withdrawal of the delivery catheter.

Functional Testing – Design Verification – Delivery System

The majority of the functional assessments for a delivery device are described in ISO 25539-1:2003 - Cardiovascular implants -- Endovascular devices ^{ref 6}. This standard gives a guide to design verification. With tests encompassing strength and durability, dimensional characteristics, and forces to deploy and remove.

Important strength factors are: tensile strength of all joints, circumferential strength, kink resistance in bending, and rotational rigidity.

Other more subtle characteristics are the acceptability and robustness of user ergonomics and the low trauma requirements of components passing through vessels.

Test benches are available which simulate different vascular geometries and allow insertion and removal forces of delivery systems to be analysed. These benches can simulate blood flow within the vasculature and a variety of vessel wall compliances. Also, linear force transmission, torque transmission and resistance to kinking can be evaluated on these test benches.

Delivery System Test Requirements	
Dimensional verification	Pressure vs. flow characterization
Catheter body tensile strength	Catheter burst pressure
Tubing to connector bond strength	Leakage between lumena
Catheter elongation	Leakage at hub
Tip attachment strength	Balloon inflation /deflation time
Catheter stiffness	Balloon related burst pressure
Catheter flexural fatigue	Balloon fatigue
Insertion and removal forces	Torque transmission
Coating performance and stability	
Guide wire Test Requirements	
Surface inspection	Corrosion resistance
Bond strength needle to hub	Force at break
Leakage from sheath introducer	Leakage through haemostasis valve
Guide wire fracture test	Guide wire flexing test
Safety wire to coil strength	Core wire to coil strength
Bond strength hub to dilator	Coating performance and stability

TABLE I: Summary of functional test requirements for an intravascular stent delivery system.

Functional Testing – Design Verification – Stent

Implanted devices such as stents are required to function for a long period in a hostile environment. Durability testing is key to proving that performance does not decay *in-vivo*. This involves pulsing a number of stents (within artificial vessels at body temperature) at an accelerated rate. Simulating conditions in the body, whilst giving quicker feedback on performance. Typically 10 years use is simulated over 400 million cycles. The product under test is periodically examined under the microscope to identify any early signs of fatigue and any particles released are trapped for analysis. Following fatigue testing a full examination of mechanical and surface properties is carried out including electron microscope analysis. Mechanical testing includes a comparison of tensile strengths, burst resistance and crush resistance before and after use.



Image 2: Examples of stents used in Aortic Endovascular Repair (EVAR) procedure.

All testing should be carried out on samples, which are representative of the finished product. They should have undergone all production processes including maximum sterilisation and have any surface coatings in place.

The outward radial force delivered by a stent is also an important factor as it may damage a vessel or become dislodged if it is too loose. Sophisticated equipment is available for mapping this force against an array of pressure sensors. Equally the vessel wall may collapse a stent and hence the stiffness and radial strength (defined as force to produce permanent distortion) is important. Similarly, flexural testing is important for stents and grafts. This information should be combined with a stress analysis.

In vitro testing should be combined with finite element, stress strain analysis using data on the mechanical properties of materials combined with stent design and stress history during fabrication and use.

The behaviour of stents during delivery is also important. The retention force of the stent on its shaft should be detailed as well as any dimensional changes occurring during deployment (recoil and foreshortening). Test methods for dimensional changes are described in ASTM 2079^{ref 7} and ASTM 2081^{ref 8}.

Corrosion is of particular concern for metallic stents and there are a variety of standards recommending test methods. Key among these is ASTM F2129-06^{ref 9}.

MRI compatibility, force and heating, should be demonstrated including damaged and overlapping stents as well as any heat effect on drug elution. ASTM F2213 - 06^{ref 10} and ASTM F2052 - 06e1^{ref 11} give advice here.

Stent Test Requirements	
Dimensional Verification, including vessel contact area	Radial stiffness and strength (crush and kink resistance)
Corrosion resistance	Retention force – stent securement
Behaviour of any memory metals	Stability and function of any coatings
Stent integrity	
Dimensional Verifications	
Physical dimensions contracted and expanded.	Stent diameter vs. balloon inflation pressure.
Vessel contact area	Crossing profile / diameter
Foreshortening	Recoil

TABLE II: Summary of functional test requirements for a stent.

Summary

The functional and biological evaluation of a new medical device should be planned early, during the R&D phase, bearing in mind prior history of the materials in medical devices, the chemical characterisation of the materials and the available literature. Discuss your strategy with your regulatory agency: both parties will benefit. Bear in mind the regulatory differences of your target markets. Use a risk based approach: be certain of your device classification and subject all biological data to toxicological risk assessment. As with any medical device the testing requirements are dictated by the product claims and risk analysis. The degree of novelty of designs, materials and production methods will have a very important bearing on the risk analysis. Fatigue testing for implants is essential as are a large range of dimensional and build quality tests.

Details in this article are not comprehensive and are limited by space requirements. Contact the author for further details.

References

FDA: Guidance for Industry and FDA Staff. Non-Clinical Tests and Recommended Labelling for Intravascular Stents and Associated Delivery Systems, 1 January 2005.
Guidance for Industry: Coronary Drug-Eluting Stents- Nonclinical and Clinical Studies, March 27, 2008
ISO 10993 - Biological evaluation of medical devices
ASTM F748-04 Standard practice for selecting generic biological test methods for materials and devices.
ISO 14971 Application of risk management to medical devices.
ISO 25539-1:2003 - Cardiovascular implants -- Endovascular devices
ASTM F 2079 Standard Test Method for Measuring Intrinsic Elastic Recoil of Balloon-Expandable Stents
ASTM F 2081 Standard Guide for Characterization and Presentation of the Dimensional Attributes of Vascular Stents
ASTM F2129-06, Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices
ASTM F2213 - 06 Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment
ASTM F2052 - 06e1 Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Devices in the Magnetic Resonance Environment

Other Standards of Interest

ISO 11070:1998 Sterile, single-use intravascular catheter introducers

ISO 10555-1:1995 Sterile, single-use intravascular catheters -- Part 1: General requirements amended in 1999 and 2004

ASTM F 2004 Standard Test Method for Transformation Temperature of Nickel-Titanium Alloys by Thermal Analysis

ASTM F 2082-02 Standard Test Method for Determination of Transformation Temperature of Nickel-Titanium Shape Memory Alloys by Bend and Free Recovery

ASTM F746 - 04 Standard Test Method for Pitting or Crevice Corrosion of Metallic Surgical Implant Materials

ASTM F2119 - 07 Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants

ISO 7198:1998
Cardiovascular implants -- Tubular vascular prostheses

ISO 14971:2000
Medical devices -- Application of risk management to medical devices

ISO 25539-2:2008
Cardiovascular implants -- Endovascular devices -- Part 2: Vascular stents

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Image 2- Source http://en.wikipedia.org/wiki/File:Covered_Stent_Graft.jpg (Public Domain).