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Standardization of *in vitro* testing for cardiovascular implants in the era of European Medical Device Regulation

Abstract: In case of cardiovascular implants classified as class III medical products there is a specific responsibility for manufacturers as well as regulatory authorities to follow international standards to guarantee for safety and efficacy. Fast developments of science and technology as well as novel clinical findings create permanent needs to match the standardization. Therefore, a set of international standards is analyzed with respect to their use for particular coronary drug-eluting stents and artificial heart valves. It was found that standards (ISO, ASTM) exist for general requirements on passive implants, but also specifically relate to arterial stents, stent grafts, bioresorbable and drug-eluting stents, as well as artificial heart valves. New work items address new methods for characterization of coating integrity, particulate matter and simulated use testing.

European Medical Device Regulation (MDR) requires technical expertise and capacity at Notified Bodies supported by independent test laboratories. Generally, the interest in standardization from industry, test laboratories and authorities is high, but more input from medical experts would further improve the value of standardization and its relevance for safe and even more effective implants.

Keywords: Vascular stents, artificial heart valves, in-vitro testing, standardization, Medical Device Regulation

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1 Introduction

Technical standards represent a consensus of the current state of technology. They support product development and guarantee their safe and efficient use. In case of cardiovascular implants which are classified as class III medical products there is a specific responsibility for manufacturers as well as regulatory authorities to follow these recommendations. However, there is a permanent need to adapt these standards to the fast progress of science and technology, which results in a complex and time-consuming process of standard development.

European Medical Device Regulation (MDR) was passed to improve the quality of medical device approval. A couple of new requirements came up. Referencing standards can help to reduce the efforts to the technically relevant minimum without losing information about product safety and efficacy.

This study is considering normative and informative guidance from standardization under the new requirements of the MDR.

A summary of international standards is analyzed with respect to their use for cardiovascular implants, in particular coronary drug-eluting stents and artificial heart valves. The need for new test methods is derived by presenting exemplary technical solutions.

2 Standards on cardiac and cardiovascular implants

Standardization is a process which is usually driven by national or international organisations. It requires a high level of coordination and systematic development to achieve a system of usable documents. Due to the international character of the medical device market requests for cross-country accepted solutions, national developments are rare, at least in the field of cardiovascular implants.

The most relevant organisation is the International Organization for Standardization (ISO) which brings national

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standard organisations together in order to create a world-wide common sense. The process of development and passing of standards is determined by voting processes. Germany participates in ISO work by several contributions such as governing committees and working groups and delegating experts for specific tasks. These activities are directed by the German Institute for Standardization (DIN).

The DIN sub-committee for cardiac and vascular implants had decided not to work on own tasks which could later be presented to the international community, but to support the standardization activities at ISO level. The results are thought to be harmonized back to European and German standards (DIN EN ISO).

In parallel to ISO, other organisations actively work on specific standards as well. In particular, the American Society for Testing and Materials (ASTM International) claims to develop internationally applicable documents. Due to active participation of experts from all over the world, the active contributions of US American authorities, the importance of the American market for medical device industry, as well as the special focus on more detailed and mostly technical driven procedures, these activities were quite successful in the past.

Additional assistance is given by guidance documents issued by national authorities, probably best known from the U.S. Food and Drug Administration (FDA).

Against this background, the following review focusses on ISO and ASTM standards and guidelines being relevant for vascular stents and artificial heart valve implants.

2.1 ISO standards

The analysis provided a list of ISO standards covering the field of cardiovascular implants and related accessories (Table 1). Further ISO standards are referenced to address additional issues, such as biological evaluation, sterilization and manufacturing of cardiovascular implants.

General requirements are commonly referenced but are of less relevance when developing a specific test method. A straightforward approach for testing and testing limits is found in the standards at different levels. It has to be noted that in some cases the methods are informative only, and not mandatory. However, by being published they represent a common sense of the current state of the art.

The aim to create more flexible standards lead to risk based approaches. This way the selection of test methods depends on the assessment of the user and requires responsible planning and documentation based on a profound technical and clinical knowledge. The standards then provide criteria and parameters for device characterization.

Table 1: Summary of current ISO standards for cardiovascular implants – general and specific requirements.

Standard	Scope
DIN EN ISO 14630:2013-03	**Non-active surgical implants** - General requirements (except for i.e. intraocular lenses, dental implants ..)
DIN EN ISO 25539-1:2018-05	**Endovascular prostheses** - Performance, design attributes, materials, design evaluation, manufacturing, sterilization, packaging and information
DIN EN ISO 25539-2:2013-05	**Vascular stents** - Performance, design attributes, materials, design evaluation, manufacturing, sterilization, packaging and information New revision is expected in 2020
DIN EN ISO 25539-3:2012-03	**Vena cava filters** used to prevent pulmonary embolism by mechanical filtration in the inferior vena cava (IVC)
DIN EN ISO 7198:2017-07	**Tubular vascular prostheses** and patches, references to DIN EN ISO 25539-1:2018-05
ISO/TS 17137:2019(E)	**Cardiovascular absorbable implants** – Particular requirements
DIN EN ISO 12417-1:2016-02	**Vascular device-drug combination products** - Minimum requirements for vascular implants to be used in combination with medicinal products in which the medicinal product serves an additional function
DIN EN ISO 5840-1:2015-12	**Cardiac valve prostheses** - General requirements: types of in vitro testing, preclinical in vivo and clinical evaluations, reporting, labelling and packaging To be replaced by DIN EN ISO 5840-1:2019-04 - Draft
DIN EN ISO 5840-2:2016-05	**Cardiac Valve prostheses** - Surgically implanted heart valve substitutes, To be replaced by DIN EN ISO 5840-2:2019-04 - Draft
DIN EN ISO 5840-3:2013-06	**Trancatheter Heart Valves** - Risk based selection of test methods, physical, chemical, biological and mechanical properties of heart valve substitutes, preclinical in vivo and clinical evaluation, design specifications and minimum performance criteria with scientific and/or clinical evidence. To be replaced by DIN EN ISO 5840-3:2019-04 - Draft
DIN EN ISO 10555-4:2013-11	**Intravascular catheters** – Balloon catheters for vascular dilatation, provided sterile and intended for single use
DIN EN ISO 16061:2020-02 – Draft	**Instruments for non-active surgical implants** - General requirements

2.2 ASTM standards

The list of ASTM standards providing guidance or specifying test methods applicable and relevant to cardiovascular implants is given in Table 2.

Table 2: Selection of ASTM standards on vascular stents and particulate evaluation.

Standard	Scope
ASTM F2081:2006 (2017)	**Dimensional Attributes** of Vascular Stents
ASTM F2079:2009 (2013)	Intrinsic **Elastic Recoil** of Balloon-Expandable Stents
ASTM F2394:2007 (2017)	**Securement** of Balloon Expandable Vascular Stent Mounted on Delivery System
ASTM F 2606:2008 (2014)	**Three-Point Bending** of Balloon Expandable Vascular Stents and Stent Systems
ASTM F 3067:2014	**Radial Loading** of Balloon Expandable and Self Expanding Vascular Stents
ASTM F 2514:2008 (2014)	**Finite Element Analysis** (FEA) of Metallic Vascular Stents Subjected to Uniform Radial Loading
ASTM F 2942:2019	In vitro Axial, Bending, and Torsional **Durability Testing** of Vascular Stents
ASTM F 2477:2019	In vitro **Pulsatile Durability Testing** of Vascular Stents
ASTM F 3036:2013	Testing of **Absorbable Stents**
ASTM F 2743:2011 (2018)	**Coating Inspection** and Acute Particulate Characterization of Coated Drug-Eluting Vascular Stent Systems
ASTM E3060:2016	Subvisible **Particle Measurement** in Biopharmaceutical Manufacturing Using Dynamic (Flow) Imaging Microscopy

3 Current test developments

Among the complexity of requirements and established tests for medical devices, two applications will be presented to illustrate the state of the art.

Assessment of coating integrity is required for mostly all coated implants. It is strongly connected to particle analysis which is demonstrated here. Transcatheter heart valves represent another revolutionary field of implant technology leading to more and more sophisticated testing.

3.1 Particle characterisation for assessment of coating integrity

Coated medical devices, such as balloon catheters, drug eluting stents and their delivery systems are introduced in the vascular system and carry the risk of emitting particles, especially during the implantation process [1][2]. Thus, the evaluation of the particulate generation during a simulated use is requested by several standards such as the DIN EN ISO 25539-2:2013-05, to assess coating delamination and its particular risks. ASTM F2743-11(2018) provides guidance how to perform the analysis. It describes specific methods for particulate characterization, e.g. light microscopy, scanning electron microscopy and light obscuration method (LOM). Test procedures for the light microscopy and LOM are described in USP 788 [3]. It provides also safety limits for the amount of particles allowed in small-volume pharmaceutical solutions for parenteral use.

LOM offers a fast counting of the analyzed volume at single particle level. Particles are counted in suspension. Additional filtration is not necessary. This method is well suited for size characterization of particles generated during the simulated use of medical devices, but it is not sensitive to agglomeration and does not give information about the shape or the transparency of the particles.

Dynamic image analysis offers the opportunity to automatically record particle images in suspension. The method is standardized for testing of biotherapeutic drugs (ASTM E3060 – 16, see Table 2). The test procedure is described precisely and is applicable for use with the FlowCAM device (Fluid Imaging, Scarborough, Maine, USA). Advantageous is the size determination on the basis of particle images added by information on particle shape and transparency (Figure 1) [4]. These data help to identify the nature and origin of the particulates and thus to assess their risk in medical application.

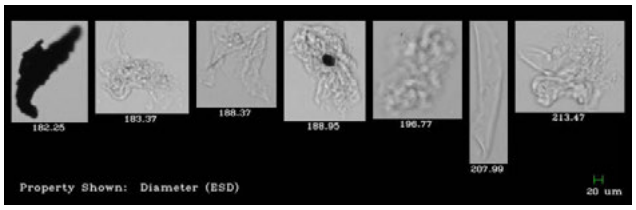

Figure 1: Exemplary images of particles by the FlowCAM device (ESD - equivalent spherical diameter). Particulate matter was generated during a simulated use test procedure of drug coated balloons.

3.2 Testing of artificial transcatheter heart valves

The recently published set of ISO 5840-3 drafts massively expands the hemodynamic investigations, in particular the assessment of the haemolytic and thrombogenic potential of implants for transcatheter aortic valve replacement (TAVR). Previously it was reported that reduced leaflet motion could

be detected commonly in surgical bioprosthetic as well as transcatheter aortic valves [5]. The FDA stated that even when the available clinical evidence supports the conclusion that these valves remain safe and effective, the potential risk related to reduced leaflet motion and thrombosis leads to a demand for sophisticated investigation [6].

The novel requirements of the ISO 5840 draft standards follow these suggestions regarding thrombogenic potential evaluation based on flow field assessment by using particle image velocimetry (PIV), see Figure 2, and computational fluid dynamics (CFD). Furthermore, best practice guidelines for PIV and CFD were published recently [6][8].

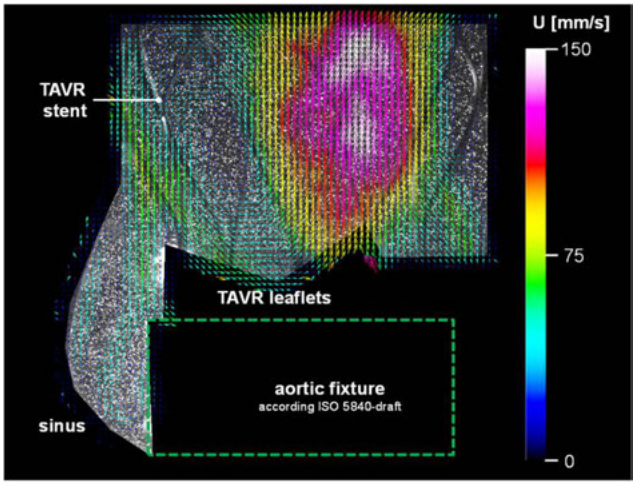

Figure 2: Particle image velocimetry measurement of end-systolic flow field in TAVR, own measurement with PIV-System (Dantec Dynamics, Denmark)

4 MDR Requirements

With the commencement of the European MDR on May 25, 2017 and the transition period ending on May 26, 2020, medical device approval has to follow MDR. Several new requirements arose, such as

- Detailed requirements for the Technical Documentation (TD) with permanent updates by the manufacturer,
- Clinical assessment and clinical testing with defined extent and consideration of post-market surveillance,
- Definition of common specifications in case of missing or insufficiently harmonised standards by the EU Commission.

Thus, in the context the role of up-to-date standards is obvious for medical device development and CE certification.

Furthermore, the requirements for Notified Bodies as the approving authorities were restated. In particular, it has to be noted that the need for technical competence for the devices and the capacity for testing them is emphasized.

In Germany, Notified Bodies, as well as national authorities have been involved in development of technical standards for a long time. They contribute valuable input and act similar to the FDA in the USA, which is a governmental institution.

Independent test laboratories are not explicitly mentioned in the MDR; however, the need for more detailed TD and the clearly accented responsibility of manufacturers and authorities results in high-quality test procedures also for laboratories.

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