How the 30-year-old standard for implantable heart valves is keeping up with technological advances

by Sarah Zanon

Sarah Zanon of Premier Research discusses how the international standard relating to implantable heart valves has evolved in tandem with the growth in transcatheter-based implantation technologies, and highlights how the latest editions of ISO 5840 will impact manufacturers’ product verification and validation processes.

The ISO 5840 family of standards is intended to provide guidelines for the appropriate pre-market qualification of the design and manufacture of permanent implantable heart valve substitutes.

The current active standards within this family are ISO 5840:2005, covering the traditional surgically implanted heart valve substitutes and the most recently introduced ISO 5840-3:2013, dealing with the new prostheses suitable to be implanted by transcatheter techniques. Both standards strongly highlight the central role of risk management in the entire qualification process. Qualification of a new heart valve substitute is achieved through testing it. As a basic approach, the risk assessment developed for the device is the tool by which the appropriate verification and validation tests and methods are selected.

ISO 5840 – A dynamic family of standards

The ISO 5840 standards are currently evolving to address the continuous technological innovation in implantable heart valves.

The standard ISO 5840:2005, which was reviewed and confirmed in 2008, is active and applicable to all devices intended for implantation in human hearts as heart valve substitutes, including newly developed and modified heart valve substitutes and the accessory devices, packaging and labeling required for their implantation and for determining the appropriate size of heart valve substitute to be implanted.

What is noteworthy is that the standard excludes heart valve substitutes designed for use in artificial hearts or heart assist devices.

However, since the first transcatheter implantation of a prosthetic valve took place in September 2000, a roaring revolution has taken place in the field of implantable devices for treating valvular dysfunctions. A significant number of companies – from startups to large multinational corporations – have embarked on the development of variegated solutions for transcatheter prostheses. This extraordinary technological development created a sort of watershed between prostheses suitable for implantation using traditional surgical procedures (ie open heart and on-pump) and prostheses designed to be implanted with minimally invasive transcatheter techniques (basically beating heart and off-pump). The latter are heart valve substitutes designed to have self-anchoring and self-sealing capabilities, suitable to be positioned over the native valve, without excising it, and significantly collapsible in their overall size for the span of the implanting procedure.

Due to the strong technological differences between surgical and transcatheter heart valve substitutes, the ISO 5840:2005 soon proved to be substantially inadequate to provide guidance on how to implement a robust and efficient verification and validation testing program for both these types of heart valves.

In order to fill this regulatory gap, ISO Subcommittee TC150/SC2 (Cardiovascular implants and extracorporeal systems) started a comprehensive revision of this standard. The final plan for the updated ISO 5840 is structured in three parts:

- ISO5840-1 - Cardiovascular implants - Cardiac valve prostheses - Part 1: General requirements
- ISO5840-2 - Cardiovascular implants - Cardiac valve prostheses - Part 2: Surgically implanted valve substitutes
- ISO5840-3 - Cardiovascular implants - Cardiac valve prostheses - Part 3: Heart valve substitutes implanted by transcatheter techniques

These three parts are at different stages of development. Part 1 (ISO/
WD 5840-1) is in working draft form, with only some preparatory studies initiated. The working draft of Part 2 (ISO/CD 5840-2) has been already voted on and is currently in the “comment period”.

In contrast, Part 3 is already active, having been published in March 2013 as ISO 5840-3:2013, first edition. This standard is applicable to all devices intended for implantation in human hearts as a transcatheter heart valve substitute. Accessory devices (e.g. the delivery system) and packaging and labeling required for their implantation are also covered by this standard. The valve-in-valve configuration, i.e. the implant of a transcatheter cardiac prosthesis inside a pre-implanted cardiac prosthesis (of any type compatible with this procedure) is explicitly excluded by this standard.


One of the most interesting aspects introduced in the fourth edition (2005) of ISO 5840 is the implementation of the risk management principles, according to ISO 14791 - Application of risk management to medical devices. The aim was to identify the appropriate qualification process for a cardiac valve prosthesis, and a meritorious effort was made to harmonize as much as possible the two standards.

ISO 5840:2005 is justified for moving away from the “requirements-based” approach of the former editions of ISO 5840 – which was acceptable for a mature technology – to a “risk-based” approach that would more adequately meet the needs of a rapidly evolving technology. This appears to be a wise stance, considering that the requirements-based approach may drive the manufacturer to wrongly spend much of their time finding ways to comply with the requirements of the standard, instead of focusing their efforts on developing solutions that would lead to safer and high-performance devices. Instead, the risk-based approach is designed to encourage the manufacturer to continuously evaluate the risks associated with the device under development, to identify the most appropriate methods for mitigating such risks and to implement the appropriate tests and investigations to demonstrate that the risks have been reduced to an acceptable level.

The same risk-based approach is preserved and even enhanced in the ISO 5840-3:2013. The great variety of solutions and the continuous innovation involved in the transcatheter heart valve systems, combined with a substantial lack of consolidated scientific knowledge due to the limited clinical history, has led the standard to transfer onto the manufacturers the burden and responsibility not only to develop test methods and protocols, but also to identify which tests are more appropriate to address each aspect of the risk analysis.

Longer testing checklist

In this perspective, the claimed goal of both standard versions of 2005 and 2013 is to combine in a balanced way the requirement for implementing the risk-based model with a listing of best practice methods for verification testing, appropriate to the evaluation of heart valve substitute, either surgical or transcatheter. Consequently, in addition to a significant increase in the list of testing for in-vitro performance of the device and its accessories, the standards include the tighter involvement of the manufacturer in the selection of tests to be performed and in the way they have to be performed, which means greater freedom but also greater responsibility in the definition of the testing plan.

This innovative approach is well illustrated in the introductory paragraph (“General Requirements”) of the device qualification section. This paragraph states clearly the ultimate responsibility of the manufacturer, which cannot be ever delegated to the standard itself:

1. The manufacturer shall perform verification testing in order to demonstrate that the design output meets the design input.
2. The test program shall consist of those tests identified from the risk analysis (prepared by the manufacturer).
3. The manufacturer shall establish those tests relating to hazards identified from the risk analysis (prepared by the manufacturer).

Conducting clinical trials

Something worth noting is that the ISO 5840-3:2013 further emphasizes this aspect. A clear and enlightening example of this innovative paradigm, mainly forced by the demands of a technology that quickly grows up and differentiates, is the requirements for the conduct of clinical investigations.

In ISO 5840:2005, the requirements for the validation of the safety and performance of the heart valve substitutes are given according to the previous ISO 5840. The standard clearly specifies the minimum number of patients to be enrolled (a minimum number of 150 recipients for each implanting position or each valve type), the minimum number of clinical sites to be involved (clinical investigation shall be conducted in a minimum of eight institutions), the minimum study duration (at least 1-year follow-up for all recipients and at least 400 cumulative patient years of follow-up for each implanting position or valve type).

With the new ISO 5840-3:2013 applicable for transcatheter heart valve substitutes, the monolithic and well-defined guidance for clinical investigation disappears. While the ISO 14155 – Clinical investigation of medical devices for human subjects, remains the reference standard for the conduct of clinical investigation, the clinical validation for transcatheter heart valve devices broadens its horizons, and different options of study design (feasibility study, randomized or non-randomized, superiority or non-inferiority, observational, registry, etc.) are introduced. The clinical investigation plan is entirely dependent on the specific purposes of the study, the specific intended application and the specific type of transcatheter heart valve system. No minimum requirements are recommended, or specific instructions provided. For instance, the standard does not indicate any limit on the sample size of the study (the protocol shall specify the planned number of institutions and minimum and maximum number of subjects and investigators per institution, in order to be reasonably representative of the intended patient and user populations) or its duration (the protocol shall specify the duration of the study) as well as the criteria for enrollment (the protocol shall clearly establish the inclusion and
exclusion criteria). Consequently, the manufacturer is ultimately responsible for finalizing and justifying the study protocol and its consistency with the risk assessment.

Particular emphasis is given to the adverse event classification during clinical investigation (Annex R). The classification and categorization of adverse events (AEs) refers to the definitions as provided in ISO 14155. Published guidelines, such as the VARC (Valve Academic Research Consortium) can be used, where appropriate. In case the risk analysis identifies AEs not included in published guidelines, the manufacturer is responsible to define them in the clinical investigation plan.

Finally, a brief curiosity: for the first time, the ISO 5840-3:2013 refers to the IEC 62366 Medical devices - Application of usability engineering to medical devices.

The standard requires qualification for the delivery system, the device used for implanting the prosthesis from a remote access. It is evident and proven that the quality and accuracy of the prosthesis implantation has significant influence on device reliability and performance. To address this critical issue, ISO 5840-3:2013 recommends conducting simulated user tests, in an appropriate model, as part of the required usability assessment as per IEC 62366.

The main objective of the usability assessment is to validate that the intended users of the transcatheter system can use the product safely and effectively to deliver and deploy the device in the patient. According to the concept of usability engineering, the assessment shall primarily focus on whether or not the design of the system appropriately mitigates potential use errors identified in the risk assessment.

ISO 5840:2013 could be robust tool when complete
Both ISO 5840:2005 and ISO 5840-3:2013 recommend specific tests to be performed by manufacturers; these tests can be grouped into three major areas:

1. Preclinical in-vitro verification, including those tests aimed to assess the physical, chemical, biological, and mechanical properties of the finished prosthetic device as well as its materials and components.
2. Preclinical in-vivo validation, requiring in most cases chronic implants of the finished prosthesis in appropriate animal models.
3. Pre-market clinical investigation, aimed to obtain clinical data on the safety and performance of the heart valve prosthesis in humans according to the intended use, within a limited and well-controlled cohort of patients.

Under specific circumstances, one or more groups of tests are not strictly required by the standard (e.g. minor changes in the design of a device already approved for clinical use) but this must always be exhaustively justified on the basis of the pertinent risk assessment and documented in the risk management file.

The central role of the manufacturer as decision maker of the testing plan for critical device as a heart valve substitute becomes more and more evident in the most recent ISO 5840-3. With the release of Part 1 and Part 2 of ISO 5840, this complex standard will become a modern and robust tool for the appropriate qualification of heart valve substitute, regardless of the technology used. Obviously, this statement is doomed to fail if, in the meantime, breakthrough technological innovations in this field are introduced, requiring additional efforts to update the standard accordingly.

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