Revised ISO 5840 Series Clarifies Testing, Evaluation Procedures for Cardiac Valves

Revised versions of the ISO 5840 series of standards, which focus on cardiac valve prostheses, were completed in summer 2020. The new family of standards will provide valuable guidance to manufacturers, heart valve device scientists, clinicians, and international regulators. The series will help ensure that device-related risks to patients have been adequately mitigated, quality assurance is properly facilitated, heart valve substitutes are effectively selected, and devices are presented in a convenient form.

ISO 5840 was first released as a single document in 1984. Since that release, much has been learned about heart valve substitutes in the four decades that followed, and an entirely new family of heart valve substitutes implanted by transcatheter techniques recently has become available.

Regarding in vitro testing and reporting, apart from basic material testing for mechanical, physical, chemical, and biocompatibility characteristics, the ISO 5840 series also covers important hydrodynamic and durability characteristics of heart valve substitutes and systems required for their implantation.

Although the ISO 5840 series does not specify exact test methods for hydrodynamic and durability testing, it offers guidelines for the test apparatus and test fixtures. The ISO 5840 series is intended to be revised, updated, and/or amended as knowledge and techniques in heart valve substitute technology improve.

The first part of ISO 5840, ISO 5840-1 (*Cardiovascular implants—Cardiac valve prostheses—Part 1: General requirements*)[1] is to be used in conjunction with ISO 5840-2 (*Cardiovascular implants—Cardiac valve prostheses—Part 2: Surgically implanted heart valve substitutes*)[2] and ISO 5840-3 (*Cardiovascular implants—Cardiac valve prostheses—Part 3: Heart valve substitutes implanted by transcatheter techniques*).[3] ISO 5840-1 contains the instructions that are common for all heart valve substitutes independent of whether they are implanted by traditional surgical or by transcatheter techniques. ISO 5840-2 and -3 provide guidance for surgical and transcatheter delivered heart valves, respectively. The previous versions of these standards were released in 2013 (ISO 5840-3) and in 2015 (ISO 5840-1 and ISO 5840-2).

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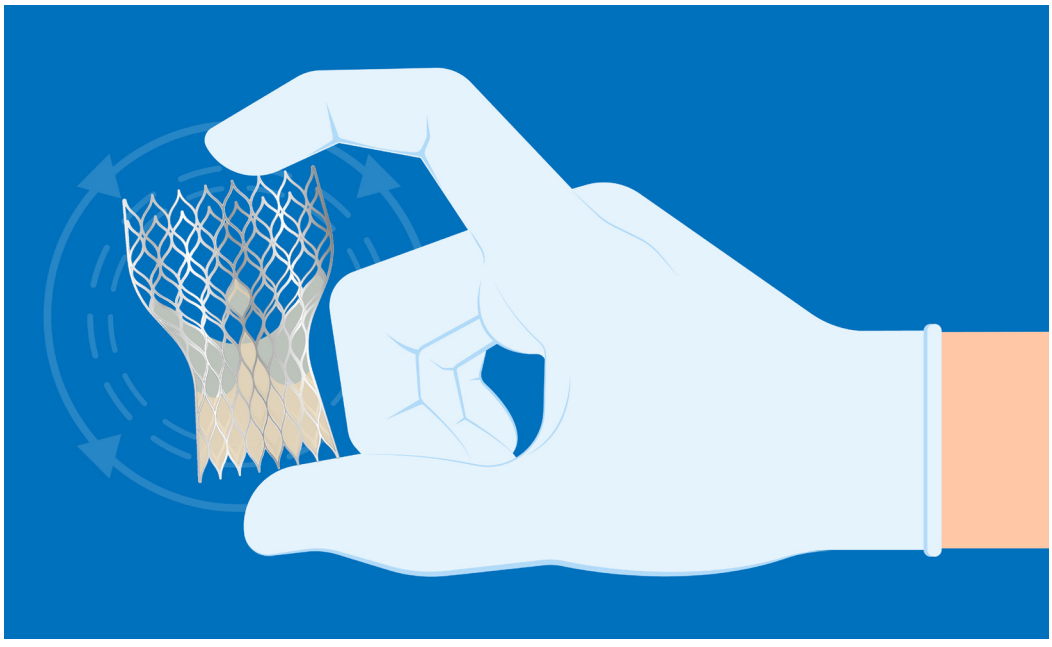

Much has been learned about heart valve substitutes since ISO 5840 was first released as a single document in 1984, including the introduction of an entirely new family of heart valve substitutes implanted by transcatheter techniques.

Since the previous versions of these standards were released, heart valve substitutes implanted by transcatheter techniques have played an increasing role in treating aortic stenosis. With improved understanding of this technology and its widespread use, ISO 5840-3 has undergone many changes to standardize testing across manufacturers and increase scrutiny during clinical evaluation. Part 3 now covers implantation within existing prostheses, standardizes testing for paravalvular leakage, and lays out clinical evaluation recommendations. The standard also includes guidelines for use of transcatheter valves in other anatomic locations of the heart.

Paravalvular leakage is an important negative outcome in transcatheter-delivered valves because the diseased tissue is left in place during replacement. The uneven surfaces of the calcified native valve can create channels for blood flow that work against the pumping actions of the heart. High levels of paravalvular leakage have been associated with poor clinical outcomes. In addition, each manufacturer tests for paravalvular leakage using a different method, making it difficult for regulatory bodies to correlate the in vitro design verification data with expected clinical outcomes. Annex C of ISO 5840-3 defines test fixtures for evaluating paravalvular leak to standardize testing among manufacturers.

Table C.2 of ISO 5840-3 provides a recommended fixture for evaluating the hydrodynamic performance of transcatheter aortic valves. The fixtures described are intended to be simplified representations of typical implantation scenarios for trileaflet calcific stenosis, for comparison with minimum performance requirements. Figure C.1 provides a schematic of a representative hydrodynamic test fixture. Recommendations for the fixture diameter, height, thickness, and compliance are provided. Dimensions for a single, medium-sized rigid calcification nodule are also provided.

The fixture attributes were established based on review of published literature, clinical results, and in vitro testing conducted by manufacturers for currently marketed transcatheter aortic valves, including balloon-expandable, self-expanding, and mechanically expanding devices. Testing of a commercially available reference valve of a similar design and construction may provide useful indications of clinical performance expectations.

Clinical investigation recommendations for sample size and study duration also underwent considerable revision in ISO 5840-3. Transcatheter heart valves originally were thought to be useful in the limited population of patients who could not undergo or had a high risk of mortality with open heart surgery. As a result, sample size and duration were not well defined in the earlier version of the standard. Decisions were left to the manufacturer and regulatory bodies to determine what was appropriate for the population being treated.

With the current use of transcatheter heart valve substitutes to treat lower-risk and younger patients, more clearly defining the sample size and duration of clinical studies is important. The clinical investigation section of the revised ISO 5840-3 will specify a minimum number of 150 patients for each indicated valve location and require at least 400 patient-years in the premarket setting to assess late adverse events. Postmarket clinical follow-up to 10 years, with endpoints based on the risk assessment and device claims, is also required.

Several changes also have been made to ISO 5840-1 and -2. Part 1, as the title states, describes general requirements for testing all heart valve substitutes, independent of delivery by surgical or transcatheter techniques. The 2015 release of ISO 5840-1 coincided with the publication of ISO 5840-2 but occurred two years after the release of ISO 5840-3. By releasing the three updated modules of the series simultaneously, duplication of sections and definitions has been eliminated.

All common definitions and testing methods have been moved to ISO 5840-1. Sections that address operational environment, recommended physical conditions for in vitro testing, material and mechanical property testing, implant durability assessment, structural component fatigue assessment, and implant thrombogenic and hemolytic potential assessment have been consolidated in the Part 1 standard and apply

to all cardiac valve prostheses implanted by either surgical or transcatheter techniques. Annexes addressing packaging, labeling, sterilization, and pediatric guidelines are included in Part 1.

New, informative annexes on echocardiographic protocols and assessment of implant thrombogenic and hemolytic potential also have been added to ISO 5840-1. The thrombogenic and hemolytic potential annex provides guidance on test equipment, test equipment validation, formulation of test protocols, and reporting requirements for flow visualization using digital particle image velocimetry; provides detail on computational models, error analysis, computational simulations, and reporting for computational flow field assessment; and provides guidance on test equipment, test procedures, data evaluation, and test reports for the experimental ex vivo assessment of the thrombogenic and hemolytic potential of the heart valve substitute using human and/or animal blood as test medium.

ISO 5840-2 is the most mature of the three modules and is a descendant of the original 1984 release of ISO 5840. Changes to Part 2 synchronize this module with the Part 1 and 3 modules, add an informative annex for surgical heart valve substitute hazard analysis examples, and include annexes providing definitions and examples of surgical heart valve substitutes and systems. Two annexes also provide guidelines for verification of hydrodynamic performance and examples of design-specific testing for surgically implanted heart valve substitutes. A more transparent, normative requirement for valve sizing and labeling has been added.

Final drafts of the internal standard documents of all three modules of ISO 5840 were circulated to member countries for voting and commenting, and balloting concluded in August 2020 with unanimous acceptance. All parts of ISO 5840 are expected to be released in fall or winter 2020.

References

1. ISO 5840-1:2020. *Cardiovascular implants—Cardiac valve prostheses—Part 1: General requirements*. Geneva, Switzerland: International Organization for Standardization.
2. ISO 5840-2:2020. *Cardiovascular implants—Cardiac valve prostheses—Part 2: Surgically implanted heart valve substitutes*. Geneva, Switzerland: International Organization for Standardization.
3. ISO 5840-3:2020. *Cardiovascular implants—Cardiac valve prostheses—Part 3: Heart valve substitutes implanted by transcatheter techniques*. Geneva, Switzerland: International Organization for Standardization.