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Standard Guide for Design Verification Device Size and Sample Size Selection for Endovascular Devices[1]

This standard is issued under the fixed designation F3172; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This guide provides guidance for selecting an appropriate device size(s) and determining an appropriate sample size(s) (that is, number of samples) for design verification testing of endovascular devices. A methodology is presented to determine which device size(s) should be selected for testing to verify the device design adequately for each design input requirement (that is, test characteristic). Additionally, different statistical approaches are presented and discussed to help guide the developer to determine and justify sample size(s) for the design input requirement being verified. Alternate methodologies for determining device size selection and sample size selection may be acceptable for design verification.

1.2 This guide applies to physical design verification testing. This guide addresses in-vitro testing; in-vivo/animal studies are outside the scope of this guide. This guide does not directly address design validation; however, the methodologies presented may be applicable to in-vitro design validation testing. Guidance for sampling related to computational simulation (for example, sensitivity analysis and tolerance analysis) is not provided. Guidance for using models, such as design of experiments (DOE), for design verification testing is not provided. This guide does not address sampling across multiple manufacturing lots as this is typically done as process validation. Special considerations are to be given to certain tests such as fatigue (see Practice E739) and shelf-life testing (see Section 8).

1.3 Regulatory guidance may exist for endovascular devices that should be considered for design verification device size and sample size selection.

1.4 *Units*—The values stated in SI units are to be regarded as the standard. No other units of measurement are included in this standard.

1.5 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.6 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E739 Practice for Statistical Analysis of Linear or Linearized Stress-Life (*S-N*) and Strain-Life (ε-*N*) Fatigue Data

F2914 Guide for Identification of Shelf-life Test Attributes for Endovascular Devices

2.2 *ISO Standards:*[3]

ISO 14971:2012 Medical devices—Application of risk management to medical devices

3. Terminology

3.1 *Definitions:*

3.1.1 *attribute data, n*—data that identify the presence or absence of a characteristic (for example, good/bad or pass/fail).

3.1.2 *design input requirements, n*—physical and performance requirements of a device that are used as a basis for device design (typically defined as test characteristics such as balloon burst pressure, shaft tensile strength, and so forth).

3.1.3 *design output, n*—features of the device (that is, dimensions, materials, and so forth) that define the design and make it capable of achieving design input requirements.

3.1.4 *design subgroup, n*—set defined by the device sizes within the device matrix in which the essential design outputs do not vary for a specified design input requirement (that is, device sizes that share the same design for a specified design input requirement).

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

[3] Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, http://www.ansi.org.

3.1.5 *design validation, n*—establishing by objective evidence that the device conforms to defined user needs and intended use(s).

3.1.6 *design verification, n*—confirmation by examination and provision of objective evidence that the device design (design output) fulfills the specified requirements (design input).

3.1.7 *device matrix, n*—entire range of available models/sizes for the device family.

3.1.8 *device size, n*—individual model/size (for example, 6 mm diameter by 25 mm length balloon on 135 cm length catheter or a 6Fr 100 cm length guide catheter).

3.1.9 *endovascular device, n*—device used to treat vascular conditions from within the vessel.

3.1.10 *essential design output, EDO, n*—design feature(s) or characteristic(s) of the device that affects its ability to achieve the design input requirements (that is, design output(s) that has a relevant effect on the test results).

3.1.11 *process validation, n*—establishment by objective evidence that a process consistently produces a result or device achieving its predetermined requirements.

3.1.12 *safety factor, n*—ratio of the device performance to the specification requirement (for example, how much stronger the device is than it needs to be to meet its specification requirement).

3.1.13 *sample size, n*—quantity of individual specimens of a device tested.

3.1.14 *variables data, n*—data that measure the numerical magnitude of a characteristic (how good/how bad).

4. Significance and Use

4.1 The purpose of this guide is to provide guidance for selecting appropriate device size(s) and determining appropriate sample size(s) for design verification of endovascular devices. The device size(s) and sample size(s) for each design input requirement should be determined before testing. The device size(s) selected for verification testing should establish that the entire device matrix is able to achieve the design input requirements. If testing is not performed on all device sizes, justification should be provided.

4.2 The sample size justification and statistical procedures used to analyze the data should be based on sound scientific principles and should be suitable for reaching a justifiable conclusion. Insufficient sample size may lead to erroneous conclusions more often than desired.

4.3 Guidance regarding methodologies for determining device size selection and appropriate sample size is provided in Sections 5 and 6.

5. Selection of Device Size(s)

5.1 Design input requirements are the physical and performance requirements of a device that are used as a basis for device design. Once the device design is defined, testing is typically performed to verify that the design input requirements are met. The appropriate device size(s) for verification testing should be determined for each design input requirement. Testing the same device size(s) is typically not appropriate to verify all design input requirements. Differences in the device design throughout the device matrix will drive which device size(s) is selected for verification of each design input requirement.

5.1.1 As explained in subsequent sections, when determining device size(s) for testing, the following should be considered for each design input requirement:

5.1.1.1 Essential design outputs,

5.1.1.2 Design subgroups, and

5.1.1.3 Other considerations.

5.2 *Define Essential Design Outputs (EDOs)*—The design outputs of the device are the features of the device (that is, dimensions, materials, and so forth) that define the design and make it capable of achieving design input requirements. Not all design outputs are essential for each design input requirement. Therefore, for each design input requirement, the essential design outputs (EDOs) should be identified. In Table 1, example EDOs for design input requirements of a balloon catheter device are provided.

5.3 *Define Design Subgroups:*

5.3.1 The design subgroups should be defined for each design input requirement based on the EDOs identified.

5.3.2 For a specific design input requirement, the design subgroups can be defined as one of the following:

5.3.2.1 The entire device matrix if the EDOs for the design input requirement are constant throughout the entire device matrix,

5.3.2.2 Subsets of the device matrix if the EDOs for the design input requirement vary in groups or stages throughout the device matrix, or

5.3.2.3 Each individual device size of the device matrix if EDOs for the design input requirement are different for each individual device size.

5.3.3 Fig. 1 represents the device matrix (entire range of available device sizes) for a 135 cm length balloon catheter device that has balloon diameters ranging from 3 to 7 mm and balloon lengths ranging from 10 to 50 mm. Balloon catheters are available in any combination of balloon diameter and length resulting in 25 unique device sizes in the device matrix.

5.3.4 Figs. 2-4 illustrate how the device matrix in Fig. 1 is defined by different design subgroups for different design input

TABLE 1 Example EDOs for Design Input Requirements for a Balloon Catheter Device

Design Input Requirement	EDOs
Manifold connection/Luer lockability	Luer thread dimensions Manifold material
Catheter shaft tensile strength for a single lumen catheter	Shaft material Shaft cross-sectional area (diameter and wall thickness) Shaft bond design
Balloon compliance (diameter versus pressure)	Balloon diameter Balloon material Balloon wall thickness
Balloon deflation time	Balloon volume Shaft deflation lumen design

Device Matrix		Balloon Length				
		10 mm	20 mm	30 mm	40 mm	50 mm
Balloon Diameter	3 mm	x	x	x	x	x
	4 mm	x	x	x	x	x
	5 mm	x	x	x	x	x
	6 mm	x	x	x	x	x
	7 mm	x	x	x	x	x

FIG. 1 Device Matrix for a Balloon Catheter Device (25 unique device sizes)

Design Subgroup: EDOs Constant		Balloon Length				
		10 mm	20 mm	30 mm	40 mm	50 mm
Balloon Diameter	3 mm	Manifold/Luer Lock "A"				
	4 mm					
	5 mm					
	6 mm					
	7 mm					

FIG. 2 Design Subgroup for Manifold Connection/Luer Lockability Testing (EDOs remain constant throughout the device matrix)

requirements. Fig. 2 represents a design subgroup that is defined by the entire device matrix because all device sizes share the same design for the specified design input requirement (that is, the EDOs remain constant for all device sizes). The design input requirement is manifold connection/luer lockability testing, and the EDOs (luer thread dimensions and manifold material) are the same for all sizes in the device matrix.

5.3.5 Figs. 3 and 4 represent design subgroups that are subsets of the device matrix because the EDOs for the design input requirement vary throughout the device matrix. Fig. 3 represents design subgroups for shaft tensile strength for a device that contains two different shaft designs in the device matrix, but the other EDOs that were identified (shaft material and shaft bond design) are the same for the entire device matrix. Therefore, there is a design subgroup that is defined by the device sizes that have shaft design "A" and a design subgroup that is defined by the device sizes that have shaft design "B." Fig. 4 represents design subgroups for balloon compliance in which each balloon diameter defines a unique design subgroup.

5.4 *Design Input Requirements and Other Considerations*—In addition to design subgroup definition, design input, device labeling, or regulatory requirements may make it necessary to test additional sizes.

5.5 *Device Size Selection Approach:*

5.5.1 *Approach*—Once the design subgroups are defined for a given design input requirement, the device size(s) to be tested for design verification testing can be appropriately selected by using one of the following approaches:

5.5.1.1 Test each design subgroup,

5.5.1.2 Test the worst-case design subgroup, or

5.5.1.3 Test a subset of the design subgroups.

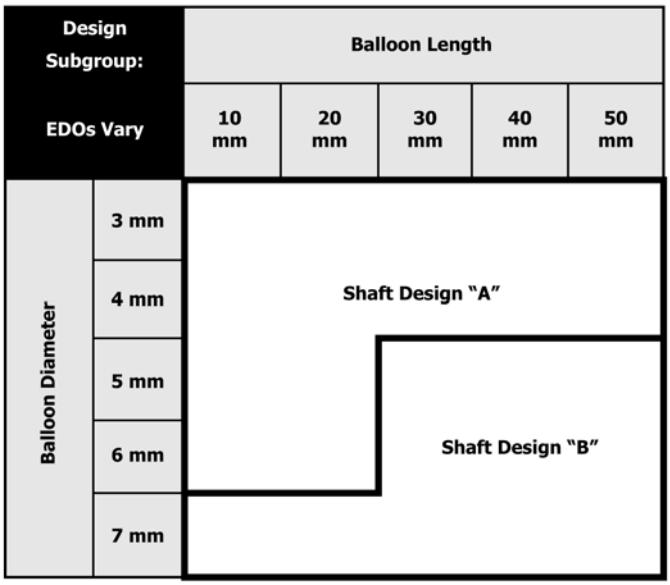

FIG. 3 Design Subgroups for Shaft Tensile (EDOs vary throughout the device matrix but are constant within each design subgroup)

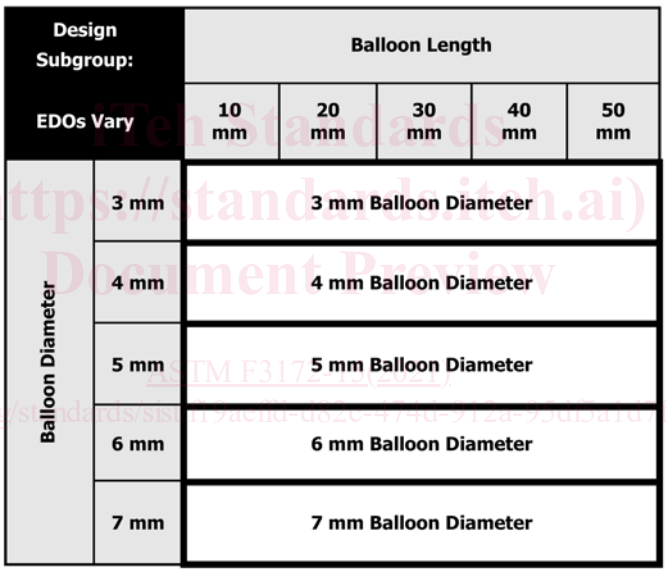

FIG. 4 Design Subgroups for Balloon Compliance (EDOs vary throughout the device matrix but are constant within each design subgroup)

5.5.2 *Test Each Design Subgroup:*

5.5.2.1 Depending on the design subgroup definition, testing each design subgroup may translate into testing one device size or multiple device sizes to verify the entire device matrix.

5.5.2.2 When the design subgroup is defined by the entire device matrix and the requirement is the same throughout the device matrix, any device size may be selected for verification testing to represent the entire device matrix. This approach is appropriate since all device sizes share the same design for the specified design input requirement (that is, the EDOs are the same for all device sizes). Fig. 5 illustrates the design subgroup and example device size selection for verification testing for manifold connection/luer lockability. Since any device size represents the entire device matrix, factors such as device sizes used for other testing to minimize total test units or device size with the highest sales volume may be considered.

5.5.2.3 When the design subgroups are defined by subsets of the device matrix, a device size should be selected from within each design subgroup to verify the design adequately since EDOs vary throughout the device matrix. Fig. 6 illustrates the design subgroups and example device sizes selected for verification testing for shaft tensile strength. Note that the shaft tensile strength requirement is the same for all device sizes and the other EDOs identified (shaft material and shaft bond design) are the same for all device sizes.

EDOs: Manifold Material and Luer Lock	Balloon Length				
Balloon Diameter	10 mm	20 mm	30 mm	40 mm	50 mm
3 mm	Manifold/Luer Lock "A"				
4 mm					
5 mm					
6 mm					
7 mm					

Verification Device Sizes	Balloon Length				
Balloon Diameter	10 mm	20 mm	30 mm	40 mm	50 mm
3 mm					
4 mm		X			
5 mm					
6 mm					
7 mm					

FIG. 5 Example Design Subgroup and Verification Device Size Selection for Manifold/Luer Lockability Testing

EDO: Shaft Design	Balloon Length				
Balloon Diameter	10 mm	20 mm	30 mm	40 mm	50 mm
3 mm	Shaft Design "A"				
4 mm					
5 mm					
6 mm					
7 mm	Shaft Design "B"				

Verification Device Sizes	Balloon Length				
Balloon Diameter	10 mm	20 mm	30 mm	40 mm	50 mm
3 mm					
4 mm					X
5 mm					
6 mm				X	
7 mm					

FIG. 6 Example Design Subgroups and Verification Device Size Selection for Shaft Tensile Strength

•	Stent Fatigue Safety Factor	Worst-Case Size for Verification Test
Stent Diameter		
3 mm	2.0	
4 mm	2.1	
5 mm	1.9	X
6 mm	2.2	

FIG. 7 Worst-Case Size May Be Selected Based on a Safety Factor Calculation

5.5.2.4 An alternate approach to selecting one device size to represent each design subgroup would be to pool multiple sizes within a design subgroup for testing. Refer to Section 7 for more information on data pooling.

5.5.3 *Test the Worst-Case Design Subgroup:*

5.5.3.1 For certain design input requirements, testing only the worst-case design subgroup adequately verifies the entire device matrix. The worst-case design subgroup is determined by considering how the EDOs impact performance to the design input requirements. If the design input requirement limit varies throughout the device matrix (for example, different rated burst pressure (RBP) requirements for different diameter balloon catheters), a worst case could be tested for each specification limit or one worst-case subgroup could be tested by performing a worst-case analysis that accounts for the differences in the specification limits, such as a safety factor

EDO: Shaft Deflation Lumen	Balloon Length				
Balloon Diameter	10 mm	20 mm	30 mm	40 mm	50 mm
3 mm	Shaft Design "A"				
4 mm					
5 mm					
6 mm					
7 mm	Shaft Design "B"				

EDO: Balloon Volume (Length and Diameter)	Balloon Length				
Balloon Diameter	10 mm	20 mm	30 mm	40 mm	50 mm
3 mm	Volume "A"	Volume "B"	Volume "C"	Volume "D"	Volume "E"
4 mm	Volume "F"	Volume "G"	Volume "H"	Volume "I"	Volume "J"
5 mm	Volume "K"	Volume "L"	Volume "M"	Volume "N"	Volume "O"
6 mm	Volume "P"	Volume "Q"	Volume "R"	Volume "S"	Volume "T"
7 mm	Volume "U"	Volume "V"	Volume "W"	Volume "X"	Volume "Y"

FIG. 8 Example Design Subgroups to Consider for Balloon Deflation Time

Verification Device Sizes	Balloon Length				
Balloon Diameter	10 mm	20 mm	30 mm	40 mm	50 mm
3 mm					
4 mm					X
5 mm					
6 mm					
7 mm					X

FIG. 9 Xs Represent Worst Case (Largest Balloon Volume) Within Each Shaft Design Subgroup (these are the device sizes selected to verify that the entire device matrix can achieve the design input requirement)

calculation. Additionally, if the design input requirement has both an upper and a lower specification limit, there may be a worst case for the upper specification and a different worst case for the lower specification.

5.5.3.2 Testing the worst-case design subgroup is a commonly used verification method when EDOs vary throughout the device matrix and their impact to the design input performance is well understood/defined (for example, increasing diameter has a negative impact on achieving the design input requirement and decreasing the diameter has a positive impact on achieving the design input requirement).

5.5.3.3 The worst-case design subgroup may be determined by one of the following methods:

(1) Historical data (similar predicate device or development characterization of current device) or

(2) Engineering judgment, analysis, computational simulation, or safety factor calculation.

NOTE 1—While the engineering or computational analysis, or both, may be applied to determine the worst-case size selection, additional considerations that could impact which device size to test may exist. For example, manufacturing process variations between device sizes could result in an actual worst-case device size that is different than the theoretical worst case. Additionally, the assembly of a multi-component device could result in failures that would not be predicted by an engineering analysis applied to only one component of the device. Use of historical knowledge of failures can be used to justify whether these factors should be considered in the device size selection. The following

		Balloon Length				
		10 mm	20 mm	30 mm	40 mm	50 mm
Balloon Diameter	3 mm	X				X
	4 mm					
	5 mm					
	6 mm					
	7 mm	X				X

FIG. 10 A 2-by-2 Factorial May Be Selected for Evaluation When One Device Size Does Not Represent the Entire Device Matrix or a Worst-Case Device Size is Not Known

are a couple examples of types of analysis to determine worst case:

(a) Hoop stress calculation—The highest balloon hoop stress may represent the worst-case situation for balloon burst testing when it is known that the finished device always fails in the balloon.

(i) By using a thin-walled pressure vessel assumption, the hoop stress of a cylindrical balloon could be calculated by:[4]

$$Hoop\ Stress = \frac{P*D}{(2 * T)} \quad (1)$$

where:

P = pressure (rated burst pressure (RBP) design input requirement),
D = diameter (EDO), and
T = wall thickness (EDO).

(ii) By using the rated burst specification requirement for P in the hoop stress formula, the worst-case size (that is, the size with the highest hoop stress at rated burst pressure) can be calculated.

(b) Fatigue safety factor calculation—Appropriately validated finite element analysis may be used on each implant diameter or other relevant property (for example, design platform, length) to determine the fatigue safety factor as well as the critical stress and strain values and locations. The predicted stresses and strains are compared to the fatigue life line to determine the fatigue safety factor. The implant with the lowest fatigue safety factor may be tested as the worst case in design verification (see Fig. 7 for a stent example).

5.5.3.4 Balloon deflation time is an example of a design input requirement for which a worst-case design subgroup approach may be acceptable to verify the entire device matrix. The EDOs defined for deflation time are balloon volume and shaft deflation lumen design. For the example in Fig. 8, the balloon volume and the shaft deflation lumen design both vary throughout the device matrix; therefore, there are multiple design subgroups that should be considered when selecting the device size(s) for testing. Fig. 8 illustrates the design subgroups to consider for balloon deflation time testing (two different shaft design subgroups and 25 different balloon volume design subgroups).

5.5.3.5 Since the relationship between deflation time and balloon volume for a constant shaft design is well understood (that is, the larger the balloon volume, the longer the deflation time), a worst-case approach can be used to verify each shaft design subgroup. Fig. 9 illustrates that the worst-case balloon volume device is selected within each shaft design to verify that the entire device matrix has acceptable deflation times.

5.5.3.6 Note that if the design input requirement for deflation time is not the same for all balloon sizes, then additional sizes may need to be tested to verify the worst case for each specification requirement.

5.5.3.7 Other examples of tests that may rely on the worst-case device size rationale for selecting the device sizes for testing are the following: accelerated durability, particulate generation, corrosion, and magnetic resonance imaging (MRI) compatibility. The rationale and device size for each test is different because each test evaluates a different aspect of device performance.

5.5.4 *Test a Subset of the Design Subgroups*—For certain design input requirements, a subset of the design subgroups may be required for verification testing. This approach may be used when EDOs vary throughout the device matrix and a worst-case device size is not known. For example, a two-by-two factorial (Fig. 10) of the largest and smallest diameters and lengths may be an approach to device size selection to capture the performance at the corners of the design space.

6. Statistical Approaches for Sample Size Determination

6.1 Once the device size(s) has been selected for verification testing per the methodology presented in Section 5, the sample size needs to be defined. The sample size justification and

[4] Hibbele, R. C., *Mechanics of Materials*, Third Edition, 1997.