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**Cardiovascular implants and  
extracorporeal systems —  
Cardiovascular absorbable implants**

*Implants cardiovasculaires et systèmes extracorporels — Implants  
cardiovasculaires absorbables*

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## Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see [www.iso.org/directives](http://www.iso.org/directives)).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see [www.iso.org/patents](http://www.iso.org/patents)).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see [www.iso.org/iso/foreword.html](http://www.iso.org/iso/foreword.html).

This document was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

This third edition cancels and replaces the second edition (ISO/TS 17137:2019), which has been technically revised.

The main changes compared to the previous edition are as follows:

- considerations have been added to multiple clauses regarding degradation-induced device fracture and the generation of absorbable particulate matter after mechanical attributes are lost;
- clauses about labelling and instructions for use (IFU) have been modified;
- [Figure 2](#) has been modified to facilitate translation into multiple languages;
- standards with guidance for characterization of absorbable polymers and metals have been elaborated.
- additional guidance regarding animal and clinical study design, limitations, and assessment has been added.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at [www.iso.org/members.html](http://www.iso.org/members.html).

## Introduction

Absorbable cardiovascular implants are medical devices with various clinical indications for use in the human cardiovascular blood system. An absorbable cardiovascular implant, or at least a portion thereof, is designed to intentionally degrade over time into degradation products that are absorbed by the body through either metabolism, assimilation, or excretion (elimination), or all. Such implants can be either surgically introduced or introduced through intervention to the site of treatment.

This document outlines requirements for intended performance, design attributes, materials, design evaluation, manufacturing, sterilization, packaging, and information supplied by the manufacturer. This document is intended to be a supplement to ISO 14630, which specifies general requirements for the performance of non-active surgical implants. This document is intended to also be a supplement to relevant device-specific standards such as the ISO 25539 series specifying requirements for endovascular devices, which do not address degradation and other time dependent aspects of absorbable implants and coatings. Additionally, this document should be considered in conjunction with ISO 14155, which specifies proper practices in clinical investigations.

This document is not comprehensive with respect to the pharmacological evaluation of cardiovascular absorbable implants. More detailed safety and performance requirements for pharmacological agents included in the absorbable cardiovascular implant are described in ISO 124171.

Only issues related to degradation and absorption combined with the cardiovascular implant are covered by this document. Due to the variations in the design of implants covered by this document and in some cases due to the relatively recent development of some of these implants (e.g. absorbable stents), acceptable standardized in vitro tests and clinical results are not always available. As further scientific and clinical data become available, appropriate revision of this document will be necessary.

NOTE For issues related to the common mechanical function of the cardiovascular implant, it can be useful to consider a number of other international standards that are given in the Bibliography.

# Cardiovascular implants and extracorporeal systems — Cardiovascular absorbable implants

## 1 Scope

This document establishes design evaluation requirements and recommendations for absorbable cardiovascular implants used to treat vessels and/or the vascular space within the circulatory system, including the heart and all vasculature. This document is intended to supplement device-specific standards by providing guidelines specific for either absorbable implants or components, or both.

This document is applicable to implants in direct contact with the cardiovascular system, where the intended action is upon the circulatory system. This document does not address the specific evaluation of issues associated with viable tissues, viable cells, and/or implants with non-viable biological materials and their derivatives. Additionally, procedures and devices used prior to and following the introduction of the absorbable cardiovascular implant (e.g. balloon angioplasty devices) are excluded from the scope of this document if they do not affect the absorption aspects of the implant. A cardiovascular absorbable implant can incorporate substance(s) which, if used separately, can be considered to be a medicinal product (drug product) but the action of the medicinal substance is ancillary to that of the implant and supports the primary mode of action of the implant.

NOTE 1 Some aspects of absorbable components of cardiovascular device-drug combination products (e.g. coatings) in their connection with drug-related aspects of the device are addressed in ISO 12417-1.

NOTE 2 An explanation of the nomenclature of absorb, degrade and related terms can be found in [Annex A](#).

## 2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 5840 (all parts), *Cardiovascular implants — Cardiac valve prostheses*

ISO 10993 (all parts), — *Biological evaluation of medical devices*

ISO 11135, *Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices*

ISO 11137-1, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11137-2, *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose*

ISO 11137-3, *Sterilization of health care products — Radiation — Part 3: Guidance on dosimetric aspects of development, validation and routine control*

ISO 11607-1, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

ISO 12417-1, *Cardiovascular implants and extracorporeal systems — Vascular device-drug combination products — Part 1: General requirements*

ISO 14155, *Clinical investigation of medical devices for human subjects — Good clinical practice*

ISO 14630:2012, *Non-active surgical implants — General requirements*

## ISO/TS 17137:2021(E)

ISO 14937, *Sterilization of health care products — General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices*

ISO 14971, *Medical devices — Application of risk management to medical devices*

ISO 17665-1, *Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*

ISO 25539 (all parts), *Cardiovascular implants — Endovascular devices*

ISO/TS 37137-1, *Biological evaluation of absorbable medical devices — Part 1: General requirements*

### 3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

- ISO Online browsing platform: available at <https://www.iso.org/obp>
- IEC Electropedia: available at <https://www.electropedia.org/>

#### 3.1

##### **absorb**

##### **absorption**

<biomaterial> action of a non-endogenous (foreign) material or substance or its degradation products passing through or being assimilated by either cells or tissue, or both over time

#### 3.2

##### **degradation product**

intermediate or final result from the physical, metabolic, and/or chemical decomposition, of a material or substance

#### 3.3

##### **degrade**

physically, metabolically, and/or chemically decompose a material or substance

#### 3.4

##### **leachable**

substance that can be released from a medical device or material during clinical use

Note 1 to entry: In absorbable devices, leachables can be substances released from the as-manufactured product or substances generated and released as a consequence of its degradation (i.e. degradation products).

#### 3.5

##### **particulate**

##### **particle**

##### **particulate matter**

mobile material (other than gas bubbles) that are either present on or arise from the presence or use of the device

## 4 Device design, fabrication, packaging, and use considerations

### 4.1 Classification

A cardiovascular absorbable implant is a product that accomplishes its intended clinical use and performance through primarily either physical or mechanical, or both, means over a defined time period. An absorbable cardiovascular implant may also incorporate a medicinal substance. A cardiovascular absorbable implant accomplishes its intended clinical use and is then fully or partially absorbed by the body over a finite period of time. The implant's temporary nature is provided by its

ability to degrade and the resulting degradation products' ability to be metabolized, assimilated, and/or excreted (eliminated) over time.

The manufacturer shall determine the acceptability of the product for clinical use at all stages of the product life cycle.

#### 4.2 Intended clinical performance

The intended performance of an absorbable implant shall be described and documented by addressing at least the following, with particular regard to the patient's safety:

- a) intended purpose(s);
- b) functional lifetime – duration of intended mechanical function;
- c) in vivo longevity – approximate time to full absorption of the absorbable components; absence of histological (physical) presence in tissue.

#### 4.3 Intended clinical use

The intended clinical use shall, if applicable, be preferentially identified as one or more of the following:

- a) abdominal aorta;
- b) arterio-venous shunt for vascular access;
- c) carotid artery;
- d) coronary artery;
- e) heart chambers;
- f) femoral artery;
- g) iliac artery;
- h) popliteal artery;
- i) intra-cerebral artery;
- j) renal artery;
- k) thoracic aorta;
- l) thoraco-abdominal aorta;
- m) tibial artery;
- n) heart valve;
- o) venous valve;
- p) other heart, arterial, or venous anatomy to be specified as appropriate.

#### 4.4 Materials

The requirements of ISO 14630:2012, Clause 6, shall apply.

Additional testing appropriate to specific material types (e.g. metals, polymers, drugs) shall be performed to determine material acceptability for use in the design. For example, guidance for assessing absorbable polymeric implants can be found in ASTM F2902<sup>[39]</sup>, with ASTM F3160<sup>[42]</sup> useful for absorbable metal materials testing. In a more specific example, absorbable materials dependent on shape memory properties should be subjected to testing that assesses transformation properties.

For drug-eluting absorbable implants, the requirements of ISO 12417-1 should be addressed. Electrochemical potentials of differing metals (stents, guidewires, other accessory devices) can require additional types of testing.

## **4.5 Packaging, labelling and sterilization**

### **4.5.1 Packaging**

#### **4.5.1.1 General**

The requirements of ISO 11607-1 and ISO 14630:2012, Clause 10 shall apply.

Each device shall be packaged in a unit container with a sterile barrier, or a combination of unit container and an outer container. The unit container (within its outer container if applicable) may be packaged in a shipping container during transit and storage.

The device packaging configuration should be designed to protect the implant during normal conditions of handling, storage and transport such that device specifications are maintained. The sterile barrier shall be maintained throughout its designated shelf-life to permit the contents to be presented for use in an aseptic manner.

#### **4.5.1.2 Considerations for absorbable product**

For absorbable products, non-standard packaging attributes may be needed to mitigate or eliminate the effects of environmental factors in order to maintain the physical, chemical and/or mechanical specifications of the implant. Where the absorbable product is susceptible to hydrolytic or corrosive degradation, consideration should be given toward the control and/or removal of moisture from the package interior (e.g. through the use of moisture resistant packaging materials and/or desiccants). In addition, absorbable products may also be susceptible to physical, chemical, and/or mechanical degradation under extreme temperature conditions. For example, storage of polymeric products or components at temperatures that approach or exceed a glass transition temperature ( $T_g$ ) can adversely affect the physical and chemical state of the implant. Therefore, storage conditions should specify the acceptable temperature range and limit the duration of packaged product exposure to elevated thermal conditions.

### **4.5.2 Labelling**

#### **4.5.2.1 Label(s)**

Each device shall be accompanied by one or more labels, one on each of the containers.

The requirements of ISO 14630:2012, Clause 11, and the requirements of relevant device-specific standard (e.g. relevant parts of the ISO 25539 series) shall apply, with the following information to be supplied as part of the label(s):

- a) identification of the device;
- b) expiration date (indication of shelf-life) and the recommended storage conditions;
- c) indication of storage conditions to avoid (i.e. conditions that can have an impact on performance of the absorbable device or components thereof).

#### **4.5.2.2 Instructions for use (IFU)**

The requirements of ISO 14630:2012, Clause 11, and the requirements of relevant device-specific standard (e.g. relevant parts of the ISO 25539 series) shall apply together with the following information to be included:

- a) identification and description of the absorbable device or components thereof;

- b) recommendations for storage conditions and ranges determined to be acceptable for the packaged device, taking into consideration the absorbable properties of the implant or components thereof;
- c) location of the absorbable part of the device, if only a portion of the implant is absorbable;
- d) a general description of the principle of degradation along with both the expected time frame for loss of mechanical function and absorption of the implant;
- e) intended use or indications for use;
- f) contraindications, warnings and precautions;
- g) potential for interaction of the absorbable material with other materials used in the handling, preparation and implantation of the implant, considering direct contact and the effect of procedural fluids;
- h) potential adverse events, including known adverse events associated with either implant (or portion thereof) degradation or in vivo absorption process, or both;
- i) known device-specific adverse events with potential for increased occurrence due to absorbable material;
- j) recommended methods for the aseptic presentation and preparation of the implant considering the potential for interaction of the absorbable material with the environment or materials used;
- k) recommended methods for preparation of the implantation site, if applicable;
- l) recommendations for visualization, if applicable;
- m) if the implant is metallic, electrically conductive, or contains metallic or electrically conductive components, magnetic resonance imaging (MRI) safety information shall be provided, including any potential impact that an accompanying radio frequency (RF)-induced temperature rise may have on the absorbable properties of the implant or components thereof. Provided information may also include a post-implantation time period after which safety MRI precautions are no longer relevant or needed;
- n) differences in methods of preparation and implantation of the device when compared to a non-absorbable device of the same type, if applicable;
- o) differences in post-implant considerations for the device when compared to a non-absorbable device of the same type, if applicable.

NOTE These post-implant considerations include those during the implantation procedure (e.g. post-implant dilatation of an absorbable vascular stent) or following the implantation procedure (e.g. considerations during follow-up imaging).

- p) date of or reference relating to the publication of the text, indicating if the text has been revised.

### 4.5.3 Sterilization

#### 4.5.3.1 General

The sterilization requirements of ISO 14630 shall apply.

The entirety of the device and packaging shall be compatible with the chosen sterilization method. The following provides a list of typical sterilization methods and a brief description of their applicability to absorbable implants or components thereof.

#### 4.5.3.2 Radiation sterilization

If devices are to be sterilized by gamma, electron beam or X-ray radiation sterilization, ISO 11137-1, ISO 11137-2, ISO 11137-3 shall apply, including the provision (which can be found in ISO 11137-1) that

the product meet its performance specifications throughout its intended lifetime at its maximum acceptable dose. Radiation sterilization processes in polymers can generate free radicals and a potential for change in absorbable material properties that can impact product performance.

### 4.5.3.3 Ethylene oxide sterilization

If devices are to be sterilized by ethylene oxide, ISO 11135 shall apply, including the provision that the product meets its performance specifications at the most challenging parameters. Ethylene oxide sterilization processes involve exposure to heat and humidity parameters that may impact absorbable material properties that can impact product performance.

### 4.5.3.4 Steam sterilization

If devices are to be sterilized by steam, ISO 17665-1 shall apply. Steam may not be a viable sterilization option for hydrolysable polymers that are highly susceptible to uncontrollable damage under autoclave conditions.

### 4.5.3.5 Alternative sterilization

If devices are to be sterilized by use of any other sterilization method, such as dry heat sterilization, hydrogen peroxide sterilization, ozone or nitrogen dioxide sterilization, ISO 14937 shall apply.

## 4.6 Product shelf-life considerations

### 4.6.1 General information

Shelf-life is the amount of time that a packaged product can be expected to be stored under specified conditions and meet critical performance properties. Establishment of shelf-life should directly or indirectly assess the device's ability to meet its specified functional requirements upon its removal from its packaging after appropriate storage. For absorbable devices, storage conditions can be vitally important (e.g. temperature and humidity) and deserve careful consideration. A detailed understanding of implant susceptibility to degradation under expected storage conditions is paramount to a successful shelf-life program.

Establishment of product shelf-life shall be through evaluation of one or more appropriate implant performance tests conducted on the final product, with justification for the selection of tests provided. Refer to ASTM F2914<sup>[40]</sup> for guidance in selecting appropriate tests for the determination of shelf-life in endovascular devices. If different finished product manufacturing sites are used, generation of appropriate batch release and stability data, including appropriate performance specifications to ensure the consistency and equivalency of the finished product across manufacturing sites, should also be considered.

ISO/IEC Guide 51, ISO/IEC Guide 63, ISO 10993-1, and ISO 11135 provide guidance regarding shelf-life establishment. It is often unnecessary to assess every device attribute measured at time 0 (i.e. no aging) and after appropriate storage conditions to establish shelf-life. ASTM F2914<sup>[40]</sup> provides guidance for the determination of the appropriate attributes for testing as part of establishment of shelf-life for endovascular devices. Accelerated aging can be appropriate to establish the shelf-life of an absorbable device in a timely manner. AAMI TIR17<sup>[27]</sup> contains guidance regarding accelerated aging programs and provides a brief discussion of aging theory. Also, ASTM F1980<sup>[30]</sup> provides guidance on accelerated aging parameters and discusses humidity. Absorbable device shelf-life establishment requires special consideration. ASTM F2902<sup>[39]</sup> provides guidance regarding the shelf-life of absorbable polymeric implants.

### 4.6.2 Real-time aging

Shelf-life assessment of packaged and sterilized absorbable products should include real-time exposure to temperature and humidity challenge conditions that, at minimum, are reflective of the expected storage environment.

Guidance regarding transportation related risk management is provided in [4.7.2](#).

Real-time testing of the absorbable device's critical attributes under conditions analogous to actual storage conditions is the most definitive means for assessing the shelf-life of a packaged absorbable device. Multiple time points (e.g. 6, 12, and 24 months) are recommended to mitigate risk associated with a failure to meet the requirements at later time points.

#### 4.6.3 Accelerated aging

Accelerated aging allows medical devices to be provided to health care professionals with specified shelf-life in a timely manner. However accelerated aging can lead to an inaccurate assessment of the shelf-life of a product, providing additional risk to the patient. Thus, when accelerated aging programs are designed, conservatism is recommended. Real-time aging studies should be conducted in addition to the accelerated aging studies to validate the shelf-life established by accelerated aging testing.

The testing plan to establish the shelf-life of an absorbable device using accelerated conditions should consider the mechanism of degradation of the implant. The rationale for the accelerated aging factors should be provided. Conservative aging factors should be chosen. AAMI TIR17<sup>[27]</sup> provides conservative accelerated aging factors. However, these conservative factors might not be appropriate for absorbable devices and should be used with caution.

Exposure to humidity, ultraviolet light, ozone, or other gases can also be used to establish the shelf-life of an absorbable device if the aging process of the materials can be shown to correlate with these environmental factors. It should be noted that aging can be further accelerated when multiple aging processes are involved. One should carefully define the combined effect of aging processes when establishing the test method for accelerated aging.

### 4.7 Risk management

#### 4.7.1 General

The manufacturer shall define and implement a risk management system in accordance with ISO 14971. The entire system shall provide intended users the ability to safely and effectively perform all required preoperative, intra-operative, and post-operative procedural tasks and achieve all desired objectives.

This shall include all other tools and accessories that intended users will use to complete the procedure.

NOTE For guidance on how to determine and establish design attributes pertaining to the use of the system to conduct the implant procedure, see IEC 62366-1.<sup>[8]</sup>

#### 4.7.2 Failure modes

There exist three major categories of failure modes. Examples of possible failure within each category specific to absorbable cardiovascular implants include the following:

- Design related: One or more implant design deficiencies (e.g. materials, dimensions, construction) can result in unintended functional failure (e.g. selection of an absorbable material that degrades prematurely). In addition, implant design should provide a safety margin adequate to provide appropriate temporal function in all indicated and reasonably anticipated clinical uses.
- Manufacturing related: Inappropriate manufacturing conditions (e.g. excess moisture), storage (e.g. defective packaging) and/or transport (e.g. excess thermal exposure) can potentially result in functional compromise or failure.
- Application or use related: Situations that can arise from unintended (abnormal) use errors (e.g. over-expansion resulting in excessive particulate generation or fracture at implantation) as described in IEC 62366-1<sup>[8]</sup> and/or from intended (correct) use errors (e.g. unable to deliver device past tortuous anatomy that was not excluded in the IFU).

An example of a failure mode for a stent embodiment is the presence of a portion of the implant's structure in the lumen (e.g. strut dislocation or dismantling). Such an event may be design related – resulting from a dimensional deficiency creating a weak portion of the structure that degrades more quickly than the remainder of the implant or resulting from a material deficiency (e.g. impurities or inclusions) leading to a change in degradation profile. Non-uniform degradation can also be manufacturing related – driven, for example, by varying levels of molecular orientation within the device or from different metal hardening processes (especially in corrosion mechanisms). This failure mode can also be use related – either from incomplete deployment or apposition against the vessel wall or from over-expansion resulting in dislocation.

Poor tissue coverage can also contribute to a clinical failure mode, which can range from poor healing within a diseased patient population to improper deployment (placement) of the device that reduces the probability of achieving predictable tissue coverage. For example, stent under-deployment, where the device protrudes into the lumen due to poor sizing or radial expansion, can lead to degradation outside the confines of the vessel wall. Conversely, over-dilatation or overloading of stents can induce stress hardening or molecular orientation that carries potential to change the degradation rate of the affected regions.

The clinician deploying the device may not be aware of these relatively subtle changes, which may even include crack initiation or strut fracture, until the issue is revealed as degradation progresses. As a result, the IFU should provide deployment procedural guidance (e.g. staged deployment for relaxation times in polymeric stents) in order to ensure appropriate apposition and mechanical integrity of the device. Vessel disease state considerations are also needed, such as the risk of inconsistent healing from deployment near calcified tissue.

While the above examples are stent-focused, similar failure modes can potentially be found with other cardiovascular implants, such as vascular closure devices. Regardless, all the factors that can affect the degradation rate of a particular device, which include the environment in which it is placed, need to be considered for their potential impact on the healing response and, in turn, the overall clinical outcome.

NOTE The ISO 25539 series and the ISO 5840 series contain lists of potential cardiovascular hazards that can provide a basis for a risk analysis of an absorbable implant. Additional risk analysis guidance can be found in ISO 10993-1, ISO/TS 37137-1 and ISO 14971.

### 4.7.3 Risk mitigation

These risks can be mitigated by the following three mechanisms derived from ISO/IEC Guide 63:2019, 7.3.7.2 (see supplemental discussion specific to medical devices found in ISO 14971:2019, A.2.7.1):

- a) inherent safety by design;
- b) protective measures in the medical device itself or in the manufacturing process;
- c) information for safety.

### 4.7.4 Specific aspects for absorbable implants

Absorbable implants exhibit time-dependent sensitivities to temperature and moisture due to the degradable or corrodible nature of these implant materials. Therefore, the whole life span of the implant from the raw material up to the complete absorption of the implant should be analysed carefully to identify the potential for risk related to premature degradation during processing, distribution, and implantation (see [Figure 1](#)). Potential approaches for mitigating such risks are discussed throughout this document.

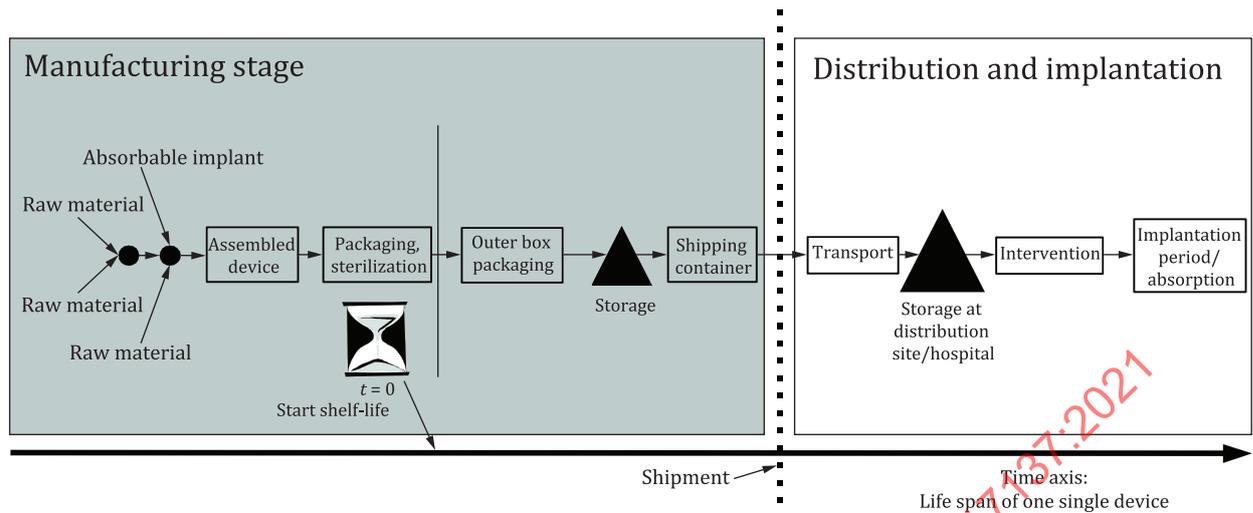


Figure 1 — Life span of one single device or implant

## 5 Design evaluation

### 5.1 Evaluation overview and general considerations

#### 5.1.1 Overview

A general characterization of the implant's composition, structural features, and degradation properties needs to be included in a design verification or validation. The relevant material and mechanical properties of the as-manufactured implant should be characterized at their initial pre-implanted state and at select time points during degradation until measurement of the partially degraded implant becomes impractical.

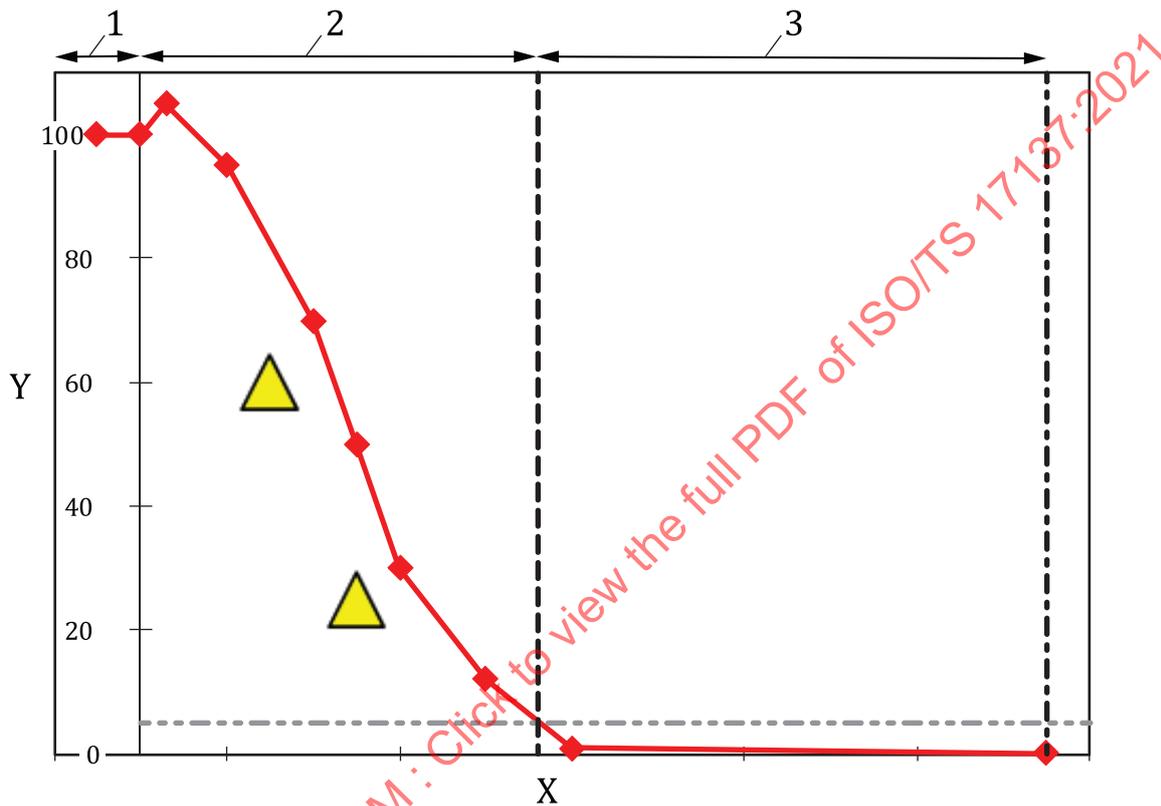
The implant should be characterized either in vitro or in vivo, or both, at multiple time points that encompass the following time frames:

- procedural stage: time preceding implantation;
- intermediate stage: time after implantation and during active degradation with decreasing retention of mechanical attribute;
- advanced stage: time after loss of mechanical attributes until final in vivo histological disappearance of the absorbable implant or component.

An overview of the assessment guidance provided herein is as follows.

- [Subclause 4.6](#) covers shelf-life and product aging considerations (covered previously).
- [Subclause 5.1](#) summarizes the in vitro evaluation steps and describes general considerations and relevant pre-test characterizations and treatments.
- [Subclause 5.2](#) guides product assessment at time frames based on package opening through vessel closure, which includes the delivery, placement, and initial function of the device (depicted as procedural stage in [Figure 2](#)).
- [Subclause 5.3](#) addresses appropriate characterization of the post-procedure mechanical, dimensional, mass, and chemical changes that occur as the implant (and any included coating) adjust to the physiological environment and encounter degradation over time (depicted as the intermediate stage in [Figure 2](#)).

- [Subclause 5.4](#) describes the biological evaluation testing of absorbable implants, including reference to specific guidance for testing in accordance with the various parts of ISO 10993.
- [Subclause 5.5](#) discusses some of the issues and potential barriers to successful generation of a correlation between in vitro and in vivo results.
- [Subclause 5.6](#) covers both cardiovascular and absorbable specific concerns when conducting a preclinical in vivo evaluation.
- [Subclause 5.7](#) covers absorbable-specific concerns when conducting a clinical evaluation.



<b>Key</b>	
X	evolved time after implantation (axis not to scale)
Y	percentage of original mechanical attribute
1	procedural stage
2	intermediate stage
3	advanced stage
	degradation profile (hypothetical)
	measurement limit
	loss of mechanical attribute
	histological disappearance
	acceptance criteria (1 or more)

NOTE The procedural stage (Figure 2, Key element 1) precedes the final device placement (i.e. Y-axis at the evolved time  $t_e = 0$ ); the intermediate stage (Figure 2, Key element 2) spans between the Y-axis and the loss of mechanical attribute; the advanced stage (Figure 2, Key element 3) spans between the loss of mechanical attribute and histological disappearance.

**Figure 2 — Schematic representation of stages in the degradation of an absorbable implant**

Degradation of the implant should be characterized at multiple time points that encompass the time frame for implantation (procedural stage), active degradation (intermediate stage), and the expected final in vivo histological disappearance of the absorbable implant or component (advanced stage). Attributes representing relevant chemical, physical, and mechanical degradation should be monitored. In this example figure, the decline in mechanical attributes is schematically represented. The degradation profile for some materials may exhibit alternate trends but generally will include a decay to measurement limits. Acceptance criteria (examples shown as yellow triangles in [Figure 2](#)) at multiple relevant time points can be defined based on the needs of the end user and requirements of the device for treatment. Examples shown in [Figure 2](#) depict how the degradation profile should compare to depicted acceptance criteria. Also, as degradation proceeds it is likely that the attribute being measured will approach or coincide with measurement limits in the advanced stage.

**NOTE** Certain device attributes can only be measured as long as the sample has adequate structural integrity. For example, a stent in the advanced stage will likely disintegrate upon movement, although it can retain its dimensions when surrounded by tissue in vivo.

### 5.1.2 General considerations

ASTM F2902<sup>[39]</sup> and ASTM F3160<sup>[42]</sup> provide information on material characteristics and applicable evaluation methods for absorbable polymers and metals, respectively. A non-exhaustive listing of material and implant characteristics that should be considered for inclusion and subsequent assessment are:

- a) Composition, chemical and purity properties (e.g. molecular weight, inherent viscosity, alloy composition) and thermal properties (e.g. polymeric glass transition temperature, melting point).
- b) Microstructure of materials
  - 1) degree of crystallinity and spatial distribution in polymers, and
  - 2) grain size (in metals).
- c) Pore characterization (in porous constructs).
- d) Degradation mechanism and rate profiling, including consideration of either potential variations or material interactions, or both, in different applicable environments (e.g. extreme storage or in vivo service conditions).
- e) Changes that occur over the lifetime of the implant with respect to its chemical, thermal, and/or physical properties (e.g. molecular weight, mass), as well as the implant's mechanical behaviour and degradation products.

Degradation products can be released into the media or tissue or reside in the degrading implant. Released degradation products that are generated prior to product use (i.e. during processing or shelf life) and following implantation should be characterized (e.g. chemical identity, quantity, and toxicity). Identification of the degradation products may be derived from chemical analyses of the implant or in some cases a theoretical analysis, which is discussed in detail within ISO/TS 37137-1.

**NOTE** Guidance regarding the identification and assessment of chemical degradation products and leachables can be found in ISO 10993-9 and ISO 10993-17.

- f) Integrity of the implant under both normal and extreme handling and in vivo service expectations.
- g) Anticipated impact of clinically utilized visibility methods [e.g. X-ray, MRI, ultrasound, optical coherence tomography (OCT)] on the material and/or implant (e.g. effects of magnetic fields).
- h) Consideration should also be made regarding potential for interaction with other devices or implants that may be commonly used in conjunction with the absorbable implants.
- i) Drug-substrate interaction considerations; in drug-device combination products, potential exists for an absorbable component (coating and/or structure) to interact with any accompanying pharmaceutical ingredient(s), possibly affecting degradation rate and/or drug strength (potency),

stability, and/or purity. While this document provides guidance toward the direct assessment of absorbable component(s) and their degradation properties in the presence of a pharmaceutical, it does not address their impact on a pharmaceutical or its rate of release. General guidance regarding the assessment of pharmaceutical components contained within cardiovascular drug-device combination products is detailed in ISO 12417-1.

The requirements of ISO 14630:2012, Clause 7, regarding general requirements for non-active surgical implants shall apply.

A justification or rationale shall be provided for the partial or full omission of testing regarding potentially relevant chemical, mechanical, or structural attributes. For example, a rationale is not needed to justify omission of stent securement testing during in vitro degradation since the attribute is only relevant during the procedural stage (can ignore or designate as “not applicable”). Conversely, a rationale may be required for either omitting or substituting for radial force characterization during intermediate stage degradation due to its primary role in providing mechanical support. However, it is recognized that certain absorbable device attributes can only be evaluated if the degraded sample retains adequate structural integrity to be both retrieved and measured.

Since it is impossible to take into consideration all current and future technologies, absorbable cardiovascular implants evaluated following the basic requirements of this document can also need additional testing to adequately characterize a device system. When deciding on the type of testing that is needed, consideration should be given to the device's failure mode(s) and the related effects they can have on the performance of either the implant or the implant component, or both. In addition, the applicability of standards such as ISO 12417-1 regarding drug device combination products and relevant parts of the ISO 25539 series regarding endovascular devices should be considered. Whenever changes are made in materials, construction, configuration, application or processing methods, appropriate analyses need to be undertaken regarding the potential impact the change can have on the failure modes and performance of the absorbable implant or component. The use of a control device for comparison should be considered when evaluating performance of the implant's design attributes.

All test samples shall be completed final sterilized devices. If the evaluated samples comprise implant components/sub-components that are not sterilized or otherwise differ from final devices, a justification shall be provided.

## 5.2 In vitro procedural evaluation

### 5.2.1 Summary of in vitro evaluation steps

Briefly, [subclause 5.2](#) describes how relevant properties of the as-manufactured implant are characterized from its initial pre-implanted state until monitoring of the relevant attribute in the partially degraded implant becomes impractical due to measurement limitations. The following provides a summary description of the progression of degradation for absorbable implants following procedural placement (as depicted in [Figure 2](#)). Characterization of degradation shall be completed as relevant for the attribute (e.g. mechanical, chemical, physical) and time frame being evaluated.

- Procedural stage: Attributes relevant to the procedure for device implantation are assessed in vitro prior to subjecting the device to simulated degradation using physiologically relevant conditions. This assessment is described in detail in [subclause 5.2](#) on in vitro procedural assessment. During this stage, the absorbable device is subjected to unpackaging and preparation per IFU (see [5.2.1](#)). In order to simulate advancement to the treatment site, this assessment may include utilizing an anatomically relevant simulated use model (see [5.2.2](#)) for tracking and subsequent implantation or deployment of the device within simulated vasculature. Once the device has been implanted or deployed, some assessment of its initial function (see [5.2.3](#)) should be made. This may include assurance that the device fulfills design requirements through placement and closure (e.g. provides adequate crush resistance).
- In vitro degradation assessment: While degradation can occur at any stage, even during manufacturing and before opening of the package, [subclause 5.2](#) refers to the period post-placement where exposure to the physiological environment leads to intentional degradation of the implant.

[Subclause 5.3](#) on in vitro degradation evaluation provides information on characterizing this stage of degradation.

- Intermediate stage:
  - This stage of degradation spans from the end of the procedural stage to where the measured mechanical attribute of the implant being tested is no longer detectable.
  - The evaluation time point frequency needs to be sufficient to allow at least an extrapolated understanding of the approximate time at which the mechanical attribute of the implant is unable to be measured.
- Advanced stage: This stage of degradation spans from the time point when the mechanical attribute is unable to be measured to the full absorption of the implant, as determined by either the substantial absence or stable state of fragmentation particles, gels, or other physical degradation products – regardless of whether the implant is evaluated in an in vitro or an in vivo context. While mechanical characterization of the degrading implant will be inherently limited to the intermediate stage, material characterization may continue through the advanced stage until evaluation becomes impractical or the acquired data are below the quantification limit or is no longer meaningful.

## 5.2.2 Conditioning of test samples

Pre-treatment or conditioning of the samples should simulate relevant procedural steps described in the IFU and exercised prior to insertion of the device. This conditioning includes all preparation activities from opening of the package up to, but not including, introduction into the vasculature. Introduction or post-insertion activities, such as tracking through an anatomically relevant simulated vasculature, and device deployment are described in the following procedural-related subclauses.

## 5.2.3 Assessment of delivery and placement

An assessment of the device's ability to be reliably implanted (via either percutaneous access or surgical placement) needs to be included in a design verification or validation.

A discussion of the design attributes necessary to meet the intended performance of a percutaneous delivery system can be found in the following documents:

- Guidance for Industry and FDA Staff – Non-Clinical Engineering Tests and Recommended Labelling for Intravascular Stents and Associated Delivery Systems<sup>[69]</sup>
- the ISO 25539 series, *Cardiovascular implants — Endovascular devices*
- ASTM F2394, *Standard Guide for Measuring Securement of Balloon Expandable Vascular Stent Mounted on Delivery System*<sup>[36]</sup>
- ASTM F2606, *Three-Point Bending of Balloon Expandable Vascular Stents and Stent Systems*<sup>[70]</sup>
- ISO 10555-1, *Sterile, Single-Use Intravascular Catheters — General Requirements*
- ISO 10555-4, *Sterile, Single-Use Intravascular Catheters — Balloon Dilation Catheters*

Regarding particulate evaluation methods:

- ASTM F2743, *Standard Guide for Coating Inspection and Acute Particulate Characterization of Coated Drug-Eluting Vascular Stent Systems*<sup>[38]</sup>
- AAMI TIR42, *Evaluation of particulates associated with vascular medical devices*<sup>[28]</sup>
- ISO 12417-1, *Cardiovascular implants and extracorporeal systems — Vascular device-drug combination products — Part 1: General requirements*
- ASTM F3320, *Standard Guide for Coating Characterization of Drug Coated Balloons*<sup>[45]</sup>

Regarding imaging evaluation methods:

- ASTM F640, *Standard Test Methods for Determining Radiopacity for Medical Use*<sup>[90]</sup>
- ASTM F2119, *Test Method for Evaluation of MR Image Artefacts from Passive Implants*<sup>[32]</sup>

#### 5.2.4 Assessment of initial function post-deployment

The ability of the absorbable implant to meet its initial functional design performance specification should be assessed immediately after placement. The ability of the implant to be reliably deployed, placed, and then remain in its initially targeted position is essential for clinical success, regardless of any subsequent enhancement or decline in mechanical properties. Structural characterization of the implant immediately post-placement is conducted on devices that have been fully pre-conditioned as described in 5.2.1. Most considerations for inclusion in the initial functional performance specification and the characterization of the deployed implant can be summarized as follows:

- a) confirmation of adequate mechanical function post-deployment (e.g. absence of any unintended loss of strength);
- b) identification of relevant defects in the device affecting structural integrity [e.g. strut fractures, structural segmentation, or de-laminations of the coating(s)];
- c) absence of premature degradation or release of degradation/corrosion product(s), including particles, in excess of design expectations;
- d) absence of shrinkage/swelling of product in excess of design expectations (e.g. from fluid uptake or physical factors such as creep while under storage);
- e) confirmation of the post-placement ability to determine the intravascular location of the deployed implant by radiological or other imaging procedure.

NOTE An inadequate initial functional performance specification can result in implant characteristics that can lead to clinical events.

### 5.3 In vitro degradation evaluation

#### 5.3.1 General

The objective of [subclause 5.3](#) is to guide characterization of the chemical, mechanical, dimensional and structural degradation that occurs over time in the implant and/or any included coating (as illustrated in [Figure 2](#)). Relevant properties of the as-manufactured implant are characterized from their initial pre-implanted state (as described in [5.2](#)) until mechanical measurement of the degraded implant becomes impractical to capture clinically relevant phenomena with sufficient resolution. Prior to undertaking the described evaluations, the implant should be prepared, inserted, or deployed, (each as appropriate) in a manner consistent with clinical use as described in [5.2](#) and illustrated as the procedural stage in [Figure 2](#). All test samples tested should be finished sterilized devices.

During in vitro degradation studies, conditions are applied to simulate in vivo degradation, typically using a physiologically-relevant aqueous solution with specific pH and thermal conditions maintained as appropriate for the material being evaluated (e.g. ASTM F3268<sup>[44]</sup> for absorbable metals and ASTM F1635<sup>[29]</sup> or ISO 13781 for hydrolyzable absorbable polymers). With adequate justification and validation specific to the material being tested, non-physiologic pH or thermal conditions may be used to accelerate degradation, justify less stringent control limits, or simulate special physiological conditions (e.g. inflammation).

Anticipated in vivo loading conditions (e.g. axial, pulsatile, torsional, bending) should be considered in in vitro degradation studies, along with consideration for both practical limitations and the significance of the applied loading.

The type and magnitude of the applied loading needs to meet or exceed anticipated physiological conditions. In some cases, hyper-physiologic loading may be of interest to characterize the structural mechanical behaviour (e.g. failure mechanisms). See ASTM F3211<sup>[43]</sup>. All simulated degradation studies and their subsequent evaluations shall be performed on implants after sterilization, unless otherwise justified.

### 5.3.2 Sample conditioning

#### 5.3.2.1 General

The following listing describes the range of conditioning options that can be considered. Dependent on the testing objective, one or more of the listed conditions can be relevant.

#### 5.3.2.2 Simulated use (optional)

If it is important for the outcome of the test, include expected simulated use that occurs prior to implantation, such as the anatomical model conditioning that is described in ISO 25539-2 if evaluating a stent.

#### 5.3.2.3 Baseline conditioning

This evaluation encompasses exposure to a physiologically relevant environment without application of applied mechanical loading during conditioning.

#### 5.3.2.4 Static load conditioning

This evaluation encompasses exposure to a physiologically relevant environment with application of a constantly applied mechanical loading during conditioning (e.g. static pressure, fixed radial force).

#### 5.3.2.5 Cyclic load conditioning

This evaluation encompasses exposure to a physiologically relevant environment with application of a cyclically applied mechanical loading during conditioning (e.g. pulsatile, axial, bending). This conditioning prior to evaluation is differentiated from fatigue testing where specific time (test-to-success) or failure (test-to-failure) end points are applied.

### 5.3.3 Mechanical evaluation

When characterizing the degradation of absorbable implants over time, changes in either relevant mechanical, or performance properties, or both, need to be evaluated. Mechanical evaluations shall be performed at time intervals appropriate for the characteristics and longevity of the implant(s) being evaluated. The selected evaluation points need to characterize the time course of the intermediate stage of degradation (as illustrated in [Figure 2](#)), which spans from the end of the procedural stage to the time point where the mechanical attribute of the implant or implant component can no longer be measured. Mechanical properties of the implant during the advanced stage of degradation are not evaluated because they are below measurement limits.

It should be noted that for some absorbable implants, some mechanical attributes may temporarily increase in magnitude soon after exposure to physiologically relevant conditions of body temperature and immersion in fluid due to temperature equilibration, swelling, and/or reorganization of polymer chains. The expected time frame for this increase in magnitude to occur will be nearly immediate (i.e. upon deployment), as can be expected with absorbable metal implants, to days, as can be the case for full hydration of some polymers. It may be desirable to characterize this initial increase in value for some mechanical attributes (e.g. strength) in order to provide a more relevant reference point for comparison to measurements of the attribute at later timepoints during degradation.

Whenever it is reasonably practical, the specimen shall be evaluated for its mechanical performance directly in a fully immersed state at 37 °C. For those mechanical tests that cannot be performed when

fully immersed, the implant may be removed from the conditioning environment prior to testing. However, dependent on the characteristics of the particular sample and material type being evaluated, care should be exercised to ensure that the sample does not dehydrate or change its properties due to loss of fluid or cooling as the test is being performed. A justification for mechanical tests necessitating evaluation under dry, room temperature conditions shall be provided.

Additional tests to quantify the impact of loading on the implant's mechanical properties and/or performance during degradation may be performed (e.g. stent radial force following fatigue loading to different cycle numbers). Mechanical evaluation of the implant shall be performed in accordance with the requirements of the product specific relevant vertical standards, for example, from the ISO 25539 series or the ISO 5840 series.

#### 5.3.4 Cyclic fatigue durability evaluation

For cardiovascular implants, whether absorbable or not, completion of fatigue durability evaluates the functional performance of the implant (or implant component) under cyclic physiologic loading conditions (i.e. radial, axial, bending, and/or torsional loading). Absorbable cardiovascular implants should also be assessed for their ability to withstand cyclic physiologic loading in order to determine if the expected loading has a significant impact on the degradation profile. Where meaningful data can be generated, demonstrate that the device does not completely lose structural integrity before it is no longer required to achieve the intended therapeutic benefit. Such *in vitro* fatigue testing shall be of sufficient duration to characterize the anticipated functional life of the implant, which may vary depending on the design attribute being evaluated. That period begins upon placement (end of procedural stage) and continues into the intermediate stage (see [Figure 2](#)) but does not proceed to the advanced stage. Evaluation shall be performed under physiologically relevant conditions that mimic the performance of the implant *in vivo*. Additional accelerated assessments at hyperphysiological loading conditions may be conducted in conjunction with FEA analysis to understand the complex interaction of employed material, production processes and device design. Appropriately justified accelerated conditions at elevated immersion temperatures may also be considered.

ASTM F3211<sup>[43]</sup> provides guidance to experimental methodology to assess and determine the structural fatigue life of permanent implantable cardiovascular medical devices, which may be applicable in part or adjustable to absorbable implants.

For absorbable metals, *in vitro* tests may not adequately represent the *in vivo* environment (e.g. the passive mechanical support provided by tissue coverage/ingrowth, cell and blood interactions). If the limitations of the *in vitro* test do not allow an adequate replication of the *in vivo* behaviour of the implant, alternative methods/test conditions may be evaluated. In this context, *in vitro* fatigue testing may be supplemented or replaced by preclinical studies, if appropriate.

For traditional metallic devices, *in vitro* fatigue testing is often conducted at highly accelerated loading rates while maintaining physiologically relevant temperature.

If the user wishes to accelerate the fatigue loading applied to an absorbable cardiovascular implant, the test condition may incorporate a method that synchronizes the chemical degradation rate of the implant with the accelerated loading rate because the device's fatigue performance *in vivo* will be linked to ongoing degradation. Synchronization of the chemical degradation rate with the accelerated loading rate may be most relevant for absorbable polymeric devices but consideration on how to accomplish this goal is also relevant for absorbable metals since their degradation profile has been shown to be dependent on fatigue loading. Therefore, for example, if the test frequency is increased by a factor of 3 from the physiologically expected rate, then the degradation should also be increased by a factor of 3. Relevant methods for synchronizing the chemical degradation with the accelerated loading rate include temperature increases or pH shifts depending on the material and amount of acceleration required. A justification should be provided if accelerated loading and degradation are not synchronized.

### 5.3.5 Physical and chemical degradation evaluation

#### 5.3.5.1 General

If characterization of the device's mechanical properties during in vitro simulation of the intermediate stage of degradation is not undertaken, characterization of the physical degradation of the implant shall be undertaken. Such physical characterization should be conducted with a relevant validated method (e.g. mass loss via gravimetry). Typically, both mechanical and mass loss characterizations are performed and can be undertaken concurrently. Mass loss characterization can also be combined with composition characterizations, such as (for polymers) hydrolytic reduction of  $M_w$  (see 5.3.5.2).

Guidance regarding methods for the determination of the physical mass lost from a retrievable degrading implant can be found in either ASTM F1635<sup>[29]</sup> or ISO 13781. Experimental approaches for the optional collection and gravimetric quantification of a degrading device's retrieved particulate matter is additionally available in ISO 13781, a feature that allows potential continuation of degradation characterization into the advanced stage.

Guidance regarding considerations critical to meaningful comparative evaluation of the in vitro degradation properties of an absorbable metal construct can be found in ASTM F3268<sup>[44]</sup>. Aside from describing potential experimental approaches, this document includes guidance regarding selection of physiologically relevant electrolyte solutions that are appropriate to the evaluation of absorbable metals.

As is the case with mechanical degradation, physical degradation characterization needs to be undertaken at time points that are relevant to the degradation profile of the device. These should include a minimum of two intermediate stage data points, with additional points added based on a combination of the needs of the application and the practicality of retrieval.

For absorbable components, such as coatings for the controlled release of pharmaceuticals, where mechanical testing is either difficult or impractical, then a physical and/or chemical degradation characterization would be mandatory. Such an evaluation can include mass loss, particulate evaluation, or other physical evaluations such as systematic imaging at selected time points. Chemical evaluation of degradation [e.g. via gel permeation chromatography/size exclusion chromatography (GPC/SEC), metal ion monitoring] may also be utilized as a means to determine the rate and extent of degradation.

Potential additional guidance regarding the selection of appropriate degradation assessments and procedures for different types of implants can be found in:

- polymers – see ISO 10993-13;
- ceramics – see ISO 10993-14;
- metals and alloys – see ISO 10993-15.

NOTE Metal degradation can occur through numerous mechanisms, which can include pitting, fretting, crevice and galvanic corrosion.

#### 5.3.5.2 Material and degradation product evaluation

The composition of the implant material(s) and any expected sub-components (e.g. reactive chemical by-products, trace metals, catalysts) shall be identified and their impact on degradation evaluated as guided in ISO 10993-18. The significance of potential alterations to either the composition or chemical properties of the implant, or both, over its lifetime shall be evaluated. Degradation products that are released into the surrounding media or tissue should be evaluated per ISO 10993-1. Quantification of each expected component shall be undertaken at an analytic level that ensures the final degraded implant will be suitable for the intended application.

In polymers, composition can be also construed to refer to the mass-average molar mass ( $M_w$ ), number-average molar mass ( $M_n$ ), z-average molar mass ( $M_z$ ), or viscosity average molar mass ( $M_v$ ). In hydrolysable polyesters, all these molecular size related properties can be reduced through hydrolysis.

The reduction of one or more of these molar mass (also known as molecular weight) properties can be determined through either GPC or SEC, or inherent viscosity (IV) evaluations, provided all characterizations are undertaken with the same analytic method. Inherent viscosity, which is typically reported as dl/g and is convertible into viscosity averaged molar mass ( $M_v$ ), is a particularly useful method when only either highly aggressive or corrosive solvents, or both, are required to completely dissolve the absorbable polymer being evaluated.

It is important to differentiate between reduction of a device's polymeric molar mass, which is quantified in grams/mole (also described as daltons) and an implant's actual physical mass, which is determined gravimetrically (typically in grams). It is also important to recognize that physical mass loss in hydrolysable polymers typically commences as molar mass approaches or falls below the GPC/SEC molar mass detection limit. An example of a comprehensive characterization of hydrolytically degraded poly(L-lactide) homopolymer (PLLA) both by molar mass (via GPC) and by direct mass loss (via gravimetry) is detailed in Pistner, et al. (1993) wherein it was observed that a >96 % drop in  $M_n$  determined molar mass resulted in only a 5 % loss of gravimetrically determined mass – See Reference [59]<sup>1)</sup>. Consequently, a lack of detection of molar mass (either in vitro or in vivo) via GPC/SEC analysis cannot be construed as an indicator of either implant mass loss or complete absorption.

Although absorbable metals will corrode under most in vitro test conditions, no correlation is currently known to exist between those in vitro tests and actual in vivo results. Thus, common corrosion assessments (e.g. ASTM F2129<sup>[33]</sup> or ASTM F3044<sup>[41]</sup>) of metallic absorbable implants are inappropriate and are thereby not required. Initial estimates for the degradation time frame of the degradable metallic implant shall be obtained through alternate methods (e.g. animal studies). However, guidance regarding considerations critical to meaningful comparative evaluation of the in vitro degradation properties of absorbable metal constructs can be found in ASTM F3268<sup>[44]</sup>.

The biological evaluation of either the particulate matter or soluble degradation products, or both, generated during testing is addressed in 5.4.

Where the utilized material is chemically identical to devices with a history of safe use under similar exposure, then a materials-characterization-based approach per the provisions of ISO 10993-1 may provide sufficient compositional and degradation product characterization.

### 5.3.5.3 Degradation particulates (particulation)

#### 5.3.5.3.1 General

Within the context of cardiovascular implants, particulate matter is broadly considered to be any mobile material (other than gas bubbles) that are either present on or arise from the presence or use of the device. Degradation particulates are inherently transient and are those generated from an absorbable device during its intermediate or advanced stages of degradation and excludes any acute particulates generated during the procedural stage (prior to the onset of degradation). Such absorbable particulate matter inherent to the degradation process can present at different rates and in different geometric or morphological forms dependent on the formulation chemistry, the implant's size and shape, as well as on material processing – all of which can in turn affect biological response. The presence of such matter and any accompanying potential for exposure to flowing blood can also bring a risk of embolism – both locally and, through mobility, to other distal locations.

Normal degradation of an absorbable implant can be expected to generate interim particulate matter that will ultimately transition into the final degradation product(s). The amount and rate of particulate generation will be a function of the implant's rate of degradation combined with both the mechanical and physical environment within which the implant resides. Thus, in any risk assessment it is important to consider the in vivo environment within which the absorbing particulate matter is present, with effectively immobilized particles embedded within a healthy tissue bed generating a distinctly different response from that of the same particulate matter mobile within flowing blood. Thus, the impact and

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1) For initially ~132,000 dalton ( $M_n$ ) PLLA ("PLLA-A2") polymer after 60 weeks hydrolysis, see both Table 1 for remaining 4,600  $M_n$  (>96 % drop) and Figure 9 for <5 % weight loss (>95 % original mass).

any related particulation risk presented by the normal degradation process needs to be evaluated within the context of the intended clinical application.

### 5.3.5.3.2 In situ biocompatibility/biological response considerations

General guidance regarding the assessment of the absorbable particulate matter can be found in ISO/TS 37137-1. The following should be considered for absorbable implants in cardiovascular applications.

- a) Particulate chemistry; generally, degradation particulates are physical fragments of an originating structure that has been weakened through progression of an anticipated chemical degradation process. The chemistry of the implant's degradation process is typically known and can be expected to generate particles with composition that reflects the anticipated transition between the base material and its ultimate degradation products. If, due to degradation chemistry, the generated particulate matter is of a chemical composition that fundamentally differs from the previously characterized base material or the anticipated final degradation product, the composition of the particulate's intermediate state should be assessed for its impact on the biological response to the degrading implant.
- b) Particulate geometry or morphology; aside from the chemistry of the degrading particulate, its morphological features can also influence the local tissue response. Metallic fragments, corrosion products, and persistent polymeric crystallites that can possess sharp particulate edges may generate adverse morphologically driven tissue responses independent of their underlying composition or degradation chemistry. The morphological features of degradation particulates and fragments can be driven by both composition and processing. ISO 10993-1:2018, Annex B provides some guidance on the assessment of particulate physical form. However, as stated previously, the impact of that physical form needs to be considered within the context of its in vivo mechanical environment.
- c) Particulate observation, measurement or assessment in vitro; static in vitro degradation testing is usually highly valuable toward understanding an implant's inherent rate of degradation and structural fragmentation. Additionally, valuable is degradation fatigue testing, which provides a preliminary assessment of the mechanical service life of the absorbable device while under cyclic load. While the absence of the reinforcement that tissue attachment and overgrowth provide will inherently confound any fatigue observation, such testing provides insight as to the onset timing and overall nature of load induced device fragmentation.

Generally, within cardiovascular applications, attention within in vitro assessments needs to be directed toward the presence and implications of fragments and particulates with dimensions greater than 10 µm (per USP <788> and AAMI TIR 42), with less than 5 µm considered to have low embolic risk (but elevated quantities can still present risk).

Characterization (e.g. size, number) either the degradation fragments or particulates of an implant, or both, at a specific time interval, should be performed in a manner that minimizes further degradation or loss between retrieval and assessment. While observational and test conditions need to consider any differences from the in vivo environment (e.g. temperature, level of hydration), specific considerations are provided in the following:

- Absorbable metals related: consult guidance in ASTM WK61103<sup>2)</sup>[72] for, for example, grain dislocation.
- Absorbable polymer related: where practical, undertake observational and mechanical assessments at hydration levels and temperatures representative of the in vivo environment. See guidance provided in ASTM F2902[39], ASTM F3036[73], ASTM F1635[29], and ISO 13781.

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2) Under preparation.

Some potentially relevant guidance regarding the collection and quantification of particulates can be found in:

- a) ASTM F2743-11, *Standard Guide for Coating Inspection and Acute Particulate Characterization of Coated Drug-Eluting Vascular Stent Systems*<sup>[38]</sup>;
- b) ASTM WK70330, *New Test Method for Standard Guide for Chronic Particulate Characterization and Coating Integrity Testing of Coated Vascular Stents*<sup>[74]</sup>.

### 5.3.6 Imaging compatibility evaluation

#### 5.3.6.1 Evaluate using relevant imaging modalities

Device safety and compatibility with clinically relevant imaging modalities shall be evaluated.

#### 5.3.6.2 Radiopacity

The radiopacity of the device shall be characterized if intended for use under fluoroscopy. This characterization shall confirm adequate visibility of the device location under fluoroscopic imaging equipment at a time point or points relevant to the device application. If intended for use under fluoroscopy, radiopacity is required at placement (see [Figure 2](#), procedural stage). Since it is expected that the radiopacity of the device can change during degradation, in vivo assessment of radiopacity is optional during later stages of degradation.

NOTE Test methods for determining radiopacity for medical use can be found in ASTM F640<sup>[90]</sup>.

#### 5.3.6.3 MRI compatibility

MRI safety shall be assessed for any absorbable implant that contains a potential magnetism susceptibility or electrically conductive metallic component.

NOTE Assessment of RF induced heating during MRI can be found in ASTM F2182<sup>[34]</sup>. Assessment of magnetically induced displacement force can be found in ASTM F2052<sup>[31]</sup>. Assessment of magnetically induced torque can be found in ASTM F2213<sup>[35]</sup>. Assessment of image artefact can be found in ASTM F2119<sup>[32]</sup>. Recommendations for MRI Labelling can be found in ASTM F2503<sup>[37]</sup>. General guidance regarding MRI safety can be found in Reference [\[75\]](#).

## 5.4 Biological evaluation

### 5.4.1 General considerations

Biological evaluation is the assessment of the ability of a device, device component, or a material to be present in the body with an appropriate host response for the specific application and without creating either an adverse systemic impact or local effect, or both, on either the surrounding cells or tissue, or both. Biological evaluation of an absorbable material shall be conducted in accordance with ISO 10993-1 and other relevant parts (see ISO 10993-1:2018, Table A.1). For the absorbable cardiovascular implants covered by this document, testing shall also consider the biological evaluation guidance in ISO/TS 37137-1, which provides supplemental information when evaluating absorbable devices in accordance with the ISO 10993 series. [Subclause 5.4](#) describes considerations for biocompatibility assessment per the ISO 10993 series and does not include discussion on the animal safety study, which is described in [5.6](#).

For absorbable devices, standard extraction methods can result in the degradation of the device. The presence of these degradation products within the extraction media can potentially impact the results of some biocompatibility tests. Since standard extraction methods were originally intended for non-degradable materials, interpretation of these results often cannot be distilled to simple pass or fail criteria. For example, in some cases if the degradation rate of an absorbable material is sufficiently rapid, elevated concentrations of one or more of the intended degradation products can alter either the pH or the osmolality of an in vitro test system, or both. Since the in vivo condition can provide the

combined presence of perfusion and carbonate equilibria, such in vitro results might not reflect in vivo response.

Additionally, standard extraction conditions and biocompatibility tests for finished devices are not designed to assess biological responses to the device throughout degradation. Thus, testing at different stages of device degradation can be needed to demonstrate safety, as absorbable devices are constantly changing in the physiological environment and can present different biological responses at different stages of degradation. Guidance regarding conducting a biological risk assessment and determining the need for such testing can be found in ISO/TS 37137-1, which also provides direction on evaluation of absorbable medical devices in accordance with various parts of the ISO 10993 series. Any modifications to the methods specified in the ISO 10993 series shall be justified.

#### 5.4.2 Particulate observation, measurement and assessment — In vivo

Since absorbable materials are intended to degrade, potential exists for generation of transient particulate matter as the implant breaks down. In the hydrolysable polyesters, this typically occurs in the early portion of the advanced stage and after most of the implants mechanical strength has been lost and molar mass is very low to undetectable by GPC methods (see Reference [59]). An understanding of the potential clinical impact of such degradation is needed (e.g. for intravascular implants, potential for thrombosis or embolization leading to coronary or cerebral infarction). Formulation chemistry as well as particle size can affect biological responses, which should be discussed in the risk assessment.

While in vitro testing is usually highly valuable toward understanding an implant's degradation, the impact of degradation particulate matter ultimately needs to be assessed within the context of both a tissue type and an in vivo mechanical environment that is similar to that of the intended clinical application. Thus, a suitable animal model is needed with a lifetime that ensures full survival through the implant's degradation and fragmentation (intermediate stage to advanced stage transition region) and preferably complete absorption (end of advanced stage). For absorbable stents, this is typically porcine, which can accommodate both degradation and complete absorption monitoring (i.e. to approximately five years).

With timing informed as much as possible through monitoring during in vitro degradation fatigue testing, planned in vivo retrievals intended to assess the impact of degradation particulates are to coincide with their anticipated peak presence, which will be dependent on the specific implant's rate of physical degradation – something likely affected by the mechanical forces applied to the device in the intended implant location.

The selection of draining organs or other anatomic locations evaluated for particulate distribution and their accompanying biological response can be influenced by the results of a risk assessment for target organs, necropsy, and/or observations of animal behaviour prior to necropsy. Once retrieved, the distribution of the particulates and their accompanying biological response on the surrounding tissue needs to be determined. Consideration is needed on the potential influence of the observed degradation fragments/particulates on the stability of the immediately surrounding tissue as well as that of the overlying tissue coverage, including the nature and health of that populating the lumen. Additionally, the assessment of degradation particulation under higher risk but clinical possible situations (e.g. overlapping stents; strut-on-strut) needs to also be undertaken. In all situations, the respective animal model needs to be assessed with consideration for inherent differences with that of the intended clinical population, which can present with multiple morbidities not present in an animal model.

#### 5.4.3 Sterilization considerations

Evaluations are to be conducted post-packaging and post-sterilization, either separately or as part of the as-manufactured device. While biological evaluation can be conducted on any component at any stage in the manufacturing process, finished product evaluation needs to be conducted following terminal sterilization at a level that meets or exceeds anticipated maximum exposure. While higher sterilization durations and intensities are generally considered as providing a more stringent evaluation, caution should be undertaken when sterilizing under harsher conditions (i.e. higher radiation dose) as more and different chemical by-products can be produced.

#### 5.4.4 Drug-device combination product considerations

For implants that include an active pharmaceutical ingredient (API), the presence of a pharmaceutical can affect the biological response. If a potentially API-driven failure occurs, separate testing of the finished device, excluding the drug component, should be considered and the results included in the evaluation. In addition, any potential for interaction between the pharmaceutical ingredient(s) and the as-manufactured or degrading absorbable component(s) should be both understood and assessed for its impact on device biocompatibility and the drug component itself.

NOTE Additional guidance regarding evaluation of drug-device combination products can be obtained in ISO 12417-1, which was developed for cardiovascular medical devices.

Biological evaluation of identifiable and already previously well characterized chemical components, such as degradation products from many intentionally absorbable materials in drug-device combination products, may be optionally substituted with an appropriate toxicological evaluation. Such a justification can be generated through a chemical characterization of device extracts in conjunction with a toxicological risk assessment for the specifically identified chemicals.

#### 5.5 In vitro-in vivo correlation (IVIVC)

Correlation of in vitro with in vivo degradation results may be considered to reduce the need for preclinical animal studies associated with future device changes. However, limited methodological information currently exists to formalize either such correlation steps or attributes, or both. In addition, the degree of necessary correlation between in vitro and in vivo measures can vary by implant type and clinical indication.

Correlation may be sought for the following areas:

- degradation time frames;
- drug release rate, if applicable.

The user should consider potentially different mechanisms of degradation and drug release when correlating in vitro and in vivo data.

Absorbable metals will corrode during most in vitro tests, the rate of which will vary depending on the test conditions, but no correlation or preferred method is currently known to exist between in vitro tests and in vivo results. However, absorbable metals can be evaluated by analysing the degradation of implanted in vivo samples at certain time points and trying to replicate the respective state of degradation in vitro (knowing that there is no linear relationship in the degradation time frames). However, by showing that the degradation cascade and products are comparable to the reactions in vivo, a corresponding test of mechanical properties of in vitro degraded samples that correspond to a given in vivo time point may be conducted.

Isolation of the explanted partially degraded implant for analytical or physical investigation can require tissue dissection and removal, possibly through chemical digestion. When removing tissue by chemical means, care should be undertaken to choose solvents and digestion agents that do not further degrade the implant of interest. However, such practices can become impractical or impossible with either some materials or stages of degradation, or both.

#### 5.6 In vivo preclinical evaluation

##### 5.6.1 Purpose

NOTE See ISO 10993-2 (animal welfare requirements), ISO 10993-6 (local effects after implantation), ISO 10993-11 (tests for systemic toxicity), ISO 10993-16 (toxicokinetic study design for degradation products and leachables), ISO/IEC 17025 (laboratory quality management), and Reference [76] for additional guidance on appropriate preclinical laboratory practices, and Reference [77].

The purpose of preclinical in vivo testing includes the evaluation of delivery/placement of the implant (and use of any related accessories), degradation of the implant, and evaluation of the biological response to the implant. For interventional devices, this testing would include the introduction, deployment of the implant, and subsequent withdrawal of the delivery system. The implant shall be evaluated at appropriate follow-up end points in order to determine the response of both the host and the cardiovascular absorbable implant. In particular, preclinical in vivo testing shall provide data pertaining to safety and shall evaluate the suitability of the cardiovascular absorbable implant for its intended use in clinical investigation. [Subclause 5.6](#) should be considered as a supplement to the information provided in ISO 10993-2 (animal welfare requirements), ISO 10993-6 (local effects after implantation), and ISO 10993-16 (toxicokinetic study design for degradation products and leachables).

The animal species to be used for the preclinical in vivo testing should be selected in accordance with the principles of ISO 10993-2, ISO 10993-6, and ISO 10993-11. The choice of species can be influenced by a variety of factors, including:

- expected clinical use, and relation to clinically-relevant implant test site(s) in the species;
- size of implant test samples and of the delivery system, and relation to species anatomical dimensions;
- intended implant duration, and relation to the expected species lifespan;
- end points of the in vivo testing, and potential differences in species biological responses; for example, thrombosis has been reported to differ between pigs, dogs, and primates (see Reference [78]), and rodents and pigs have been reported to have different primary mechanisms for wound healing (see Reference [79]).

The choice of animal species shall be scientifically justified in accordance with ISO 10993-2 and this justification shall be documented.

### 5.6.2 Specific objectives

The specific objectives of a study shall be stated and may include those detailed in device relevant parts of the ISO 25539 series, the ISO 5840 series, or other applicable standards along with the following considerations specific to absorbable implants:

- a) Since traditional fluoroscopy procedures can be inadequate to visualize absorbable implants, the study should assess the ability to both deploy the implant and confirm its intravascular location through use of a suitable imaging procedure and with consideration for the test animal's body mass with respect to the intended patient population.
- b) Evaluate the structural integrity and absorption of the cardiovascular implant, with at least one retrieval time targeted toward the early advanced stage that follows the expected complete loss of mechanical properties and poses the highest potential for generation of particulates and low molar mass degradation products.
- c) Assess local biological responses (e.g. vascular trauma, thrombus deposition, inflammation, endothelialization, necrosis, neointimal proliferation, aneurysm formation). Additional considerations are provided in ISO 10993-6.
- d) Assess downstream and systemic effects (e.g. embolism, infarction) through an evaluation of histology and pathology of explants and pertinent tissues/organs and whether these effects can be device or procedure related. Additional considerations are provided in ISO 10993-11 and ISO 10993-16.
- e) Record adverse events and potential contributing factors (e.g. implant versus catheter delivery system). More than one study may be used to address the specific objectives. Animal studies are designed to demonstrate safety. Animal studies are not designed for demonstrating either efficacy or effectiveness. However, a preclinical study may be designed with specific end points related to the local biological response (e.g. reduced neointimal proliferation, improved rate of endothelialization, benign response to degradation related particulation) that can demonstrate a potential clinical benefit.

It may not be possible to address all specific objectives within one in vivo study. For example, retrieval of implant materials for assessment of structural integrity and degradation products can disrupt the adjacent tissue and limit the ability to assess local biological response. Some examples of specific objectives for absorbable implants are as follows.

- Degradation status: assess the presence of implant, degradation products, mechanical, integrity, and impact of any fragmentation. The testing is focused on the implanted device. Once explanted, processing steps are designed to retain the device and its degradation products. The device and materials may be assessed via multiple techniques, for example, Nano-CT, Xray, SEM, EDS, optical microscopy, GPC, FTIR, to assess integrity and degradation status.
- Local biological response: assess the biological effects near to and in response to the implant. The testing is focused on the biological material, typically using classical histological assessment. Once explanted, processing steps are designed to minimize disruption to the biological material; note that there is the potential for these processing steps to disrupt the implant and degradation products. Tissues and implants may be embedded and sectioned for tissue or implant interface evaluation. Tissues and implants may also be prepared to view the luminal surface of the implant to evaluate tissue coverage.
- In situ tissue coverage and mechanical integrity: assess device degradation status and biological response without explanting the device or tissue. This may be performed via OCT or intravascular ultrasound (IVUS) depending on the choice of animal species, implant location, and implant dimensions. These assessments may be performed at multiple timepoints with the same animal and implant since they do not require implant retrieval or tissue sample collection. There is the potential for the OCT or IVUS device to disrupt the implant and/or local tissue depending on the degradation status of the implant and maturity of the biological response. This potential for disruption may be evaluated by comparing OCT or IVUS results to the degradation status and/or local biological response assessments listed above, where those devices did not have an OCT or IVUS passed through them. The results of these evaluations can also help inform the assessment of the clinical risk from in-patient imaging and the potential for disrupting either the implant or tissue, both.

When evaluating the IVIVC of drug release from an absorbable component, consider (if applicable) the correlation between an in vitro property of an extended release dosage form and the in vivo response. The correlation should describe the in vitro rate or extent of drug dissolution or release and the measured in vivo effect (e.g. drug tissue level). Due to local application, low drug doses, and potential for drug uptake into the tissue, IVIVC evaluation of drug release with systemic blood plasma level measurements might not be feasible. Additionally, local tissue measurements often cannot be obtained or validated because of measurement variability (i.e. either inconsistent quantification or sample preparation issues, or both). In the absence of appropriate methods for systemic blood or local tissue sampling, evaluation of the amount of drug remaining on the cardiovascular absorbable implant can be used to estimate the in vivo release rate.

### 5.6.3 Protocol

Each cardiovascular absorbable implant shall be tested at the intended, or at an anatomically analogous vascular site, with justification for the alternate site. Whenever possible, animal models should be chosen to most closely mimic clinical site and vascular anatomy. The number of animals used for testing shall also be justified. As far as permitted by the limitations of the animal model, all cardiovascular absorbable implants used shall be of clinical quality and size, and of the design intended for clinical use.

The study follow-up time points should take into consideration how long the device and drug-containing parts of the cardiovascular absorbable implant remain [e.g. acutely (<24 h), short-term (<30 d), or permanently]. Long-term in-dwelling cardiovascular absorbable implants or implants with absorbable components can require additional study follow-up time points. Guidance on the minimum requirements for time point selection is provided in ISO 10993-6. Assessment intervals should be targeted in accordance with the expected pattern of degradation, including multiple assessments during the intermediate stage, leading to final disappearance of the implant or absorbable component. The results of in vitro degradation tests described in 5.3 should be used to inform the selection of

timepoints corresponding with the pattern of degradation. For materials where correlation of in vitro and in vivo degradation rate is not possible, pilot animal studies can be required to define these time points. Consideration needs to be made regarding the impact that normal physiological temperature of the test species can have on the degradation rate of the implant. In the absence of complete degradation, the data collected and resulting trend can be sufficient to allow characterization of local effects after implantation, provided that both substantial absorption and the restoration of normal tissue structure and function (e.g. vascular contractility, endothelial coverage), as appropriate, has been obtained. While gross and microscopic evaluation after complete implant absorption is highly desirable, in vivo degradation profiling of either the absorbable material or its degradation products, or both, to a state of limited visually-identifiable histological presence can also be considered acceptable. Additionally, an assessment needs to be made regarding the reversibility of any accompanying adverse pathology. As a result, long-term studies that span a significant portion of the degradation time frame for the implant are recommended, unless justification for a shorter-term study is provided.

In an attempt to preclinically assess risk of late events (e.g. thrombus) generated by either implant degradation or collapse, or both, a retrieval time point should be selected at which the device's mechanical properties are expected to be substantially absent and both structural deterioration and the rate of mass loss are elevated. This retrieval period of expected intensified tissue response will vary based on implant material and degradation rate. In absorbable polymers, this can be reasonably expected to occur within the first 1/4 of the advanced stage of degradation. In absorbable metals, in vitro evaluation of ion release may be utilized in lieu of mass loss for determining the retrieval period of expected intensified tissue response. Histological observations and assessments during this time period should consider the selected animal model's relative rate and level of tissue coverage/proliferative response when compared with the anticipated diseased state of the patient population(s) for the device's intended clinical application. Such an assessment need not be limited to a single animal model.

For implants that include a drug component, at least one study (in multiple animals) should evaluate the complete in vivo elution profile (in vivo pharmacokinetics) to include drug plasma levels, drug tissue levels, and residual drug remaining on the cardiovascular absorbable implant. Safety studies of drug containing cardiovascular absorbable implants should include assessment of dose-dependent effects, including the effect of overdosing (e.g. no drug, nominal drug dose, and 3× overdose) unless justification can be provided for omission of this type of testing. Local, regional (down-stream), and systemic toxicities should be assessed. Guidance toward the evaluation of drug-device combination products can be found in ISO 12417-1.

If patients are anticipated to be clinically treated with multiple cardiovascular absorbable implants, additive dose and/or product compatibility issues may need to be considered for animal study design.

An appropriate control device should be selected. The control may be a non-absorbable implant from current clinical best practice with a mechanism of action similar to that of the absorbable cardiovascular implant. However, if available, an absorbable best-practice control is preferred since absorbable implants possess an inherently different mechanism of action and related local tissue response when compared with a non-absorbable implant. A rationale should be provided if a control implant is not used in the study. For implanted products, if an absorbable component is not expected to remain over the implant life, additional testing of the underlying materials should be considered. If the proposed cardiovascular absorbable implant is intended for use with an already implanted cardiovascular absorbable implant (another product), there can be product compatibility issues that may need to be considered for the animal study design.

In accordance with the specific objectives detailed in [5.6.2](#), the objective of the study should be clearly defined in the protocol. The design of the preclinical in vivo testing including the implant route and procedures, measurement methods, tissue handling, pathological evaluation plan, and data analysis shall be specified. In addition, the choice of animal model such as species, gender, age, and whether a healthy animal or disease model is used, shall be justified and shall be consistent with the study objectives.

Implantation shall be consistent with the recommended instructions for clinical use, as far as permitted by the limitations of the animal model, including overlap of devices, if applicable. Deviations from the

device's IFU should be justified. The protocol should be informed by the study objective and by the range of uses permitted in the IFU. For example, overlapped stents can provide a worst case for a mechanical integrity or tissue coverage evaluation. In addition, medications relevant to the implantation (e.g. anti-platelet therapy) and post-operative management (e.g. analgesics, antibiotics), with animal model dependent considerations, should follow the intended clinical application.

The use of intravascular imaging of the implant by IVUS or OCT should be defined in the protocol. Such intravascular imaging can provide additional information on healing and degradation, but can also pose a risk for tissue damage (e.g. endothelial loss or injury) or implant damage from passing other devices through or alongside the implant, and this damage can be interpreted inappropriately during subsequent assessment. IVUS or OCT measurements should be adjusted by comparison to a reference anatomic area, to compensate for any growth during the course of the study.

All animals in the study shall be monitored daily and examined as determined necessary by appropriate veterinary staff. All animals shall undergo post-mortem examination, including any that expire prior to scheduled termination. The cause of death or illness, and the extent to which the implant was implicated shall be documented. Histological and pathological assessment of explants and appropriate tissues/organs shall be provided. This assessment includes down-stream histopathologic assessments in order to assess potential clinical implications of particulates released from the cardiovascular absorbable implant.

Histology processing steps can affect the retention of either the absorbable material or its degradation products, or both. This can lead to artefactually accelerated degradation or absence of material that does not reflect the actual degradation of the device. Implantation studies to evaluate degradation and biological response may therefore need to be performed separately.

Quantitative morphometrics and qualitative morphologic assessments can be helpful to the histopathologic analysis. Scanning electron microscopy can be helpful to assess completeness of endothelialization along the length and circumference of the vessel. Special staining can be necessary to investigate neointimal composition, fibrin deposition, or mineralization. Angiographic assessments can be useful in follow-up observations, depending on the product type.

Recognition and adherence to appropriate animal husbandry-related precautions can prevent poor outcomes not related to the product. Refer to the Bibliographic references to the US-FDA guidance for cardiovascular animal studies<sup>[50]</sup>, the Institute for Laboratory Animal Research (ILAR) guide for care of laboratory animals<sup>[54]<sup>3)</sup></sup>, and the ISO 12417-1 guide for drug-device combination products for a detailed listing of the aspects to be considered. Also see ISO 10993-2 (Animal Welfare) and ISO 10993-6 (Local effects after implantation) for additional guidance on appropriate preclinical laboratory practices.

### 5.6.4 Data collection

The minimum data, as detailed in device relevant parts of the ISO 25539 series or other applicable standards, shall be recorded for each animal receiving a control or cardiovascular absorbable implant. Either exceptions or considerations, or both, relevant to absorbable implants are detailed in the preceding 5.7.3. General guidance also is provided in ISO 10993-6 and ISO 10993-11.

### 5.6.5 Test report and additional information

Results of all animals enrolled in the study shall be recorded and reported even if excluded from the final analysis.

The test report shall include, as appropriate, those detailed in the ISO 25539 series, the ISO 5840 series, and/or other applicable standards with exceptions or additional considerations pertinent to

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3) This guide is authored by the Committee for the Update of the Guide for the Care and Use of Laboratory Animals; Institute for Laboratory Animal Research (ILAR); Division on Earth and Life Studies (DELS); National Research Council.

cardiovascular absorbable implants as detailed in 5.6.3 also being included, as well as the following key points:

- the sample(s);
- the International Standard(s) used (i.e. ISO/TS 17137:2021);
- the method(s) used (if the standard includes several);
- the result(s), including a reference to the clause which explains how the results were calculated or otherwise assessed;
- any deviations from the procedure;
- any unusual features observed;
- the date of the test.

## 5.7 Clinical evaluation

### 5.7.1 Purpose

The purpose of clinical evaluation is to evaluate the performance of the delivery system, if applicable, and assess the safety and effectiveness of the absorbable cardiovascular implant. Included in the clinical investigation shall be appropriate testing of any absorbable cardiovascular implant incorporating design characteristics for which the safety and effectiveness have not been previously demonstrated. An investigation shall be carried out for each new implant device or new clinical application of a device prior to market approval, using the principles given in ISO 14155 or an equivalent publication. The absorbable cardiovascular implant shall satisfy all appropriate preclinical in vitro and in vivo testing requirements of this document before starting the clinical investigation. Refer to ISO 12417-1 for absorbable implants with active pharmaceutical ingredients or degradation products considered to be bioactive.

It has been reported in literature that late adverse events can occur during the clinical evaluation of absorbable devices (see References [57]<sup>4)</sup>, [58], [60], [61] and [62]). According to current knowledge, there is no in vitro test or in vivo animal study capable of predicting such a behaviour. Therefore, users should be cautious about the interpretation of preclinical data regarding the prediction of long-term clinical outcomes. The negative clinical outcomes have been related to one specific product made of an absorbable polymer and it is unclear whether other factors such as insufficient clinical practice in the use of these devices or off-label use can contribute to these results. Although there is not enough statistical evidence available at the moment to conclusively assess the long-term clinical success of other absorbable implants, there is no indication of a class effect that would link late adverse events to the use of absorbable implants in general.

### 5.7.2 Specific objectives

The objectives of the clinical evaluation shall be informed by the preclinical evaluations that have been performed on the implant (bench and animal testing), and by an analysis of clinical data concerning safety or performance of the implant, its materials, and similar devices or therapies (particularly of other absorbable implants evaluated in the same or similar clinical indications). The specific objectives of the study shall be stated and can include the following, which are relevant for absorbable cardiovascular implants, as appropriate:

- a) evaluation of the position, structural integrity and functionality of the implant immediately after placement (and withdrawal, if interventionally placed) as well as at clinically relevant time points and during intermediate and advanced degradation;
- b) monitoring of local and systemic effects (over time) due to degradation of the material;

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4) See investigation of over three-year clinical events from persistent, approximately 5 500 Mn PLLA particles.

- c) comparison of the absorbable cardiovascular implant to current clinical best practice, in the form of a non-inferiority study or a superiority study against an appropriate comparator.

### 5.7.3 Clinical investigation plan (CIP)

The number of study centers and the number of patients shall be justified. General guidelines for the CIP can be found in ISO 14155. Guidelines for the evaluation of cardiovascular device-drug combination implants, including patient selection, duration of follow-up, control groups, clinical end points, data reporting and analysis are outlined in ISO 12417-1. While these guidelines are specific to device-drug combination implants, the temporal nature of drug delivery may make these guidelines relevant to absorbable vascular devices, which have a temporal degradation process.

The duration of patient follow-up for absorbable cardiovascular implants can differ from durable cardiovascular implants. In addition to meeting the objectives of the clinical investigation, the duration of the trial for an absorbable cardiovascular implant shall consider the expected duration of

- a) mechanical support or structural integrity of the implant,
- b) physical presence of the absorbable material or degradation products, and
- c) complete absorption.

Specifically, the clinical study duration should be guided by both bench and animal studies, and should be sufficient to capture clinical events at key time points during and potentially after complete implant degradation. Absorbable metal implants should emphasize the use of animal studies for determining clinical study duration, given the challenges with using bench studies for assessing degradation rates (see 5.5).

NOTE Regarding hydrolysable polymers, ASTM F2902<sup>[39]</sup> states that it is important to recognize that the body temperatures of animal models vary and are typically higher than humans, thereby carrying the potential to accelerate the degradation rate when compared with human clinical conditions (see Reference [91]).

A justification shall be required for follow-up intervals but may be based on either clinical end points or expected degradation times of interest, or both. The follow-up period shall be chosen to represent a realistic test of the performance of the implants and to allow any risks associated with adverse device effects to be identified and assessed. Selected intervals should include the ability to assess the patient's response to loss of the implant's mechanical properties and generation of potentially elevated amounts of degradation products.

Preliminary prospective, observational studies may be necessary to characterize the absorption of the absorbable implant and any APIs prior to initiation of the clinical trial. If patients are to be treated with multiple absorbable cardiovascular implants clinically, additive-dose and/or product compatibility issues of the degradation products and/or any drug component may need to be considered in the clinical study design. In addition, if degradation products are bioactive, pharmacokinetic studies to assess the degradation products can be needed.

The CIP should identify and include an appropriate comparator or control. A randomized trial powered for detection of differences with an existing control device is recommended. Control devices should be contemporary non-absorbable devices, unless absorbable devices have been established as the preferred mode of treatment in the intended clinical application.

A justification for the number of investigation sites shall be provided. A justification for the number of patients studied shall also be provided. The calculation of the number of patients to be enrolled shall take into account patients who will be lost to follow-up.

The duration of patient follow-up shall be determined in relation to the objectives of the clinical investigation. The duration of follow-up shall also take into account the effect of comorbidities on the life expectancy of the patient population. All patients treated with either test or control devices, including those excluded from the final analysis, shall be recorded. The final report shall include all follow-up data as specified by the investigation plan.

If an appropriate control is not, or cannot be identified, or a concurrent control is unnecessary, a method for evaluating the clinical outcomes shall be prospectively defined and justified. The control should be appropriate to the questions being addressed in the study.

The CIP shall identify the critical data points and end points for the study. Definitions of success and failure shall also be prospectively defined for all primary and any secondary end points where statistical analysis (and presentation of descriptive statistics) will be used to support marketing approval.

Careful consideration shall be given to the choice of clinical-investigation-related procedures that subjects undergo during the clinical investigation. This may include increased frequency or types of imaging compared to that used in current clinical best practice in order to allow a more in-depth examination or characterization of implant deployment, degradation, structural integrity, and presence of degradation products during the follow-up period (see Reference [63]). Increased usage of intravascular imaging via IVUS or OCT may be considered, in preference to lumen assessment via angiography or venography, to more accurately evaluate structural integrity, suboptimal implant deployment or positioning, dissection of the target blood vessel, and biological coverage of the implant. The risk of either disrupting the device or the tissue at sensitive stages of degradation, or both, shall also be considered. Imaging modalities such as angiography or venography can be preferred over IVUS or OCT at these time points to avoid passing a device through or alongside the implant.

#### 5.7.4 Data collection

ISO 14155 provides specifications on the use of case report forms for capturing the data for each enrolled subject as required by the CIP. Additional specifications for absorbable vascular implants including an API are provided in ISO 12417-1. The following data may be particularly relevant for absorbable implants and shall be recorded for each patient in the study:

- a) Relevant medications taken prior to and post-surgery, such as antithrombotics or antibiotics, during the hospital stay, and prescribed at discharge. Because there can be some unanticipated interactions between the absorbable implant and pre- or post-operative medications, especially those that include an API, consider capturing all medications.
- b) Reportable clinical events as defined by the protocol. Special care should be taken when adjudicating an adverse event to be non-implant related, since effects of either material degradation or API, or both, may be observed systemically or at sites distal to the implant site.

#### 5.7.5 Final report

In addition to the final clinical investigation reporting of specifications outlined in ISO 14155 and ISO 12417-1, a rationale shall be provided for the selection of patient follow-up intervals and for the selection of assessments at each time point based on the degradation profile of the implant.

### 5.8 Post-market surveillance

A systematic procedure to review post-market experience gained from absorbable cardiovascular implants shall be in place, using the principles given in ISO 14630, ISO 14971, ISO/TR 20416, or an equivalent publication. For absorbable cardiovascular implants, post-market surveillance shall consider the expected time course of implant degradation as determined from preclinical testing. Investigators should be aware that late adverse events have been observed at the final stages of the degradation process of absorbable cardiovascular devices.

### 5.9 Select clinical trials of absorbable cardiovascular implants

The following provides a non-exhaustive listing of potentially useful articles of clinical trials for various cardiovascular absorbable implant applications. These articles can provide added insights as to the