TECHNICAL SPECIFICATION

**ISO/TS 17137**

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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

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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. www.iso.org/directives

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The committee responsible for this document is ISO/TC 150, *Implants for surgery*, sous-comité SC 2, *Cardiovascular implants and extracorporeal systems*.

The following definitions apply in understanding how to implement an ISO International Standard and other normative ISO deliverables (TS, PAS, IWA):

— “shall” indicates a requirement;

— “should” indicates a recommendation;

— “may” is used to indicate that something is permitted;

— “can” is used to indicate that something is possible, for example, that an organization or individual is able to do something.

3.3.1 of the ISO/IEC Directives, Part 2 (sixth edition, 2011) defines a requirement as an “expression in the content of a document conveying criteria to be fulfilled if compliance with the document is to be claimed and from which no deviation is permitted.”

3.3.2 of the ISO/IEC Directives, Part 2 (sixth edition, 2011) defines a recommendation as an “expression in the content of a document conveying that among several possibilities one is recommended as particularly suitable, without mentioning or excluding others, or that a certain course of action is preferred but not necessarily required, or that (in the negative form) a certain possibility or course of action is deprecated but not prohibited.”

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# 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 products that are absorbed by the body through metabolism, assimilation, and/or excretion (elimination). Such implants can be either surgically or interventionally introduced to the site of treatment.

This Technical Specification outlines requirements for intended performance, design attributes, materials, design evaluation, manufacturing, sterilization, packaging, and information supplied by the manufacturer. This Technical Specification should be considered as a supplement to ISO 14630, which specifies general requirements for the performance of non-active surgical implants. This Technical Specification should also be considered as 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.

This Technical Specification 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/TS 12417.

Only issues related to absorption combined with the cardiovascular implant are covered by this Technical Specification.

NOTE For issues related to the common mechanical function of the cardiovascular implant, the reader might find it useful to consider a number of other International Standards (see Bibliography).

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# Cardiovascular implants and extracorporeal systems — Cardiovascular absorbable implants

## 1 Scope

This Technical Specification outlines design verification and validation considerations for absorbable cardiovascular implants.

NOTE Due to the variations in the design of implants covered by this Technical Specification 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 Technical Specification will be necessary.

For the purpose of this Technical Specification the terms "vessel and/or vascular space" refer to the entire circulatory system, including the heart and all vasculature.

This Technical Specification is applicable to implants in direct contact with the cardiovascular system, where the intended action is upon the circulatory system. This technical specification 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 Technical Specification if they do not affect the absorption aspects of the implant. A cardiovascular absorbable implant may 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 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/TS 12417.

## 2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

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

ISO 11135-1, *Sterilization of health care products — Ethylene oxide — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11137 (all parts), *Sterilization of health care products — Radiation*

ISO/TS 12417, *Cardiovascular implants and extracorporeal systems—Vascular device-drug combination products*

ISO 14155:2011, *Clinical Investigation of Medical Devices for Human Subjects — Good Clinical Practice*

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

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 14971:2007, *Medical devices — Application of risk management to medical devices*

ISO/TR 15499, *Biological evaluation of medical devices — Guidance on the conduct of biological evaluation within a risk management process*

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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 25539-2:2008, *Cardiovascular implants — Endovascular devices — Part 2: Vascular stents*

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

ISO 11607-1:2006, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

IEC 62366, *Medical devices — Application of usability engineering to medical devices*

ASTM F2394-07(2013), *Standard Guide for Measuring Securement of Balloon Expandable Vascular Stent Mounted on Delivery System*

## 3 Terms and definitions

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

**3.1**
**absorb**
<biomaterials> action of a non-endogenous (foreign) material or substance passing through or being assimilated by cells and/or tissue over time

**3.2**
**degradation product (noun)**
**byproduct (noun)**
any intermediate or final result from the physical, metabolic, and/or chemical decomposition of a material or substance

**3.3**
**degrade (verb)**
to physically, metabolically, and/or chemically decompose a material or substance

**3.4**
**leachable (adjective)**
substances that can be released from a medical device or material during clinical use

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

## 4 Implant considerations

### 4.1 Classification

A cardiovascular absorbable implant is a product that is considered to be a medical device that accomplishes its intended clinical use and performance over a defined time period. A cardiovascular absorbable implant accomplishes its intended clinical use and is then 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 products' ability to be metabolized, assimilated, and/or excreted (eliminated) over time.

An absorbable cardiovascular implant may also incorporate a medicinal substance. However, for the purposes of this Technical Specification, if the action of the medicinal substance is ancillary to a device's primary mode of action, the product is considered to be a surgical implant.

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

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## 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 patient's safety:

a) intended purpose(s);

b) intended lifetime.

## 4.3 Intended clinical use

The intended clinical location shall be 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) coronary 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) other arterial or venous vessels to be specified.

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## 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, a general guide for assessing absorbable polymeric implants can be found in ASTM F2902. 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, drug identity testing shall be performed, including the identification of impurities and degradants. Electro-chemical potentials of differing metals (stents, guidewires, other accessory devices) might require additional types of testing.

## 4.5 Packaging, labelling, and sterilization

### 4.5.1 Packaging

#### 4.5.1.1 General

The requirements of ISO 11607-1:2006 and ISO 14630:2012, Clause 10 shall apply.

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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.

For devices that are supplied sterile, the sterile barrier shall be maintained 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 at temperatures that approach or exceed the glass transition temperature of absorbable polymeric products might adversely affect the physical and chemical state of the implant. Therefore, storage conditions should be specified that limit the temperature range and time limit of implant exposure.

### 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, shall apply, with the following information to be supplied as part of the label(s):

NOTE Items with particular relevance to absorbable implants are italicised.

a) name or trade name of the device;

b) recommendations for storage; the actual modelled storage range determined to be acceptable for the packaged device, taking into consideration the absorbable properties of the device or components thereof;

c) description and/or list of the package contents;

d) size and device type (if applicable);

e) dimensions applicable for clinical use;

f) sterilization method and the notification ‘STERILE’ if applicable;

g) for implants supplied sterile, a warning against the use of the device if the package is damaged;

h) reference to consult Instructions for Use for user information;

i) chemical nature of any storage medium in the unit container, with appropriate hazard warning.

#### 4.5.2.2 Instructions for use (IFU)

The requirements of ISO 14630:2012, Clause 11, shall apply together with the following information to be included, if applicable:

a) name or trade name of the device;

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b) recommendations for storage; the actual modelled storage range determined to be acceptable for the packaged device, taking into consideration the absorbable properties of the implant or components there-of;

c) statement that the device can or cannot be re-sterilized, including the statements 'STERILE', 'DO NOT RESTERILIZE' in prominent form, if applicable;

d) the statement 'SINGLE USE ONLY' in prominent form, if applicable;

e) description and/or list of the package contents;

f) available models and sizes applicable for intended clinical use;

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

h) location of the absorbable part of the device, if only a portion of the implant is absorbable;

i) a general description of the principle of degradation along with both the expected time frame for loss of mechanical properties and *in vivo* absorption of the implant;

j) intended use/indications for use;

k) contraindications, warnings and precautions;

l) the 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;

m) potential adverse events, including known adverse events associated with implant (or portion thereof) degradation and/or *in vivo* absorption process;

n) 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;

o) recommended methods for preparation of the implantation site if applicable;

p) recommendations for visualization if applicable;

q) if the implant is metallic, electrically conductive, or contains metallic or electrically conductive components, 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;

r) 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 requirements of ISO 14630:2012, Clause 9, 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.

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#### 4.5.3.2 Radiation sterilization

If devices are to be sterilized by gamma, electron beam or X-ray radiation sterilization, ISO 11137 Parts 1, 2 and 3 shall apply, including the Part 1 provision that the product meet its performance specifications throughout its intended lifetime at its maximum acceptable dose.

NOTE Radiation sterilization (of polymers) commonly results in a residual presence of free radicals and an increase in the rate of degradation.

#### 4.5.3.3 Ethylene oxide sterilization

If devices are to be sterilized by ethylene oxide, ISO 11135-1 shall apply, including the provision that the product meet 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 could in turn impact product performance specifications.

#### 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 since hydrolysable polymers 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 Risk management

#### 4.6.1 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 ANSI/AAMI HE74 and IEC 62366.

#### 4.6.2 Failure modes

There exist three groups of failure modes. Examples of possible failure within each group 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 functional integrity in all clinical indications (e.g. force differences in the coronary vs tibial artery).

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/User Interface related: Unintended (abnormal) use errors (e.g. over-expansion resulting in excessive particulate/fragment generation at implantation) as described in IEC 62366. Intended

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(correct) use errors (e.g. unable to deliver device past tortuous anatomy that was not excluded in the IFU).

NOTE ISO 25539-2:2008, Annex C and ISO 5840-3:2013, Annex G. contain lists of potential cardiovascular hazards that can provide basis for a risk analysis of an absorbable implant.

### 4.6.3 Risk mitigation

These risks can be mitigated by three mechanisms (see also ISO 14971:2007, A.2.6.2):

a) inherent safety by design;

b) protective measures in the medical device itself or in the manufacturing process;

c) information for safety.

### 4.6.4 Specific aspects for absorbable implants

Absorbable implants exhibit time dependent sensitivities to temperature and moisture due to the degradable/corrosive nature of these implant materials. Therefore, the whole life cycle 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 means for mitigating such risks is discussed at various locations throughout this Technical Specification.

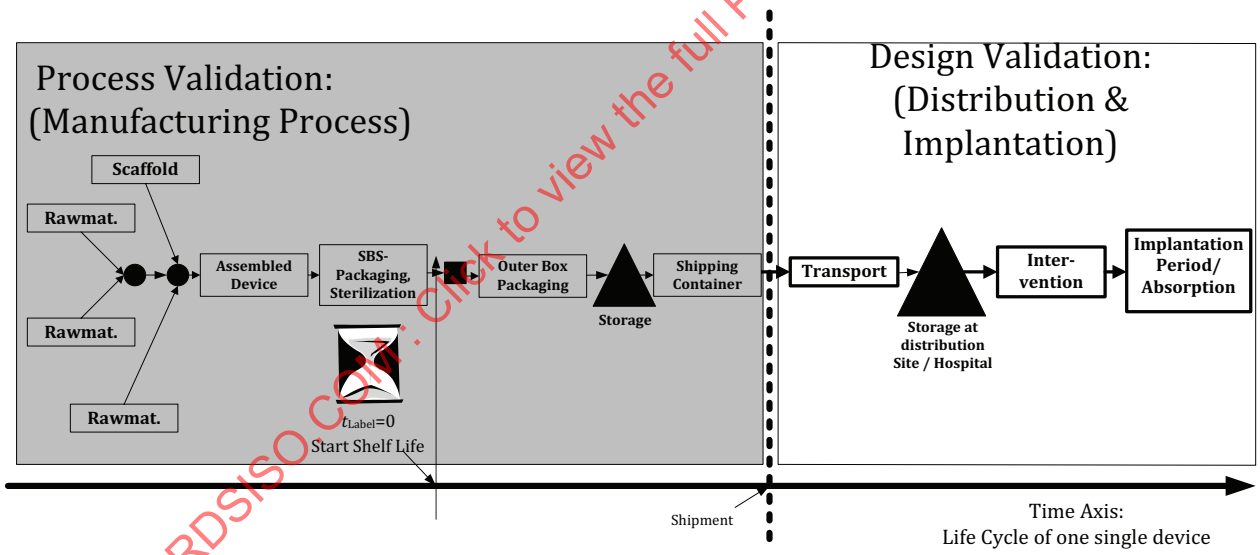


**Figure 1 — Life cycle of one single device/implant**

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## 5 Design verification and validation — Testing and analysis

### 5.1 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 from its initial pre-implanted

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state until measurement of the degraded implant becomes impractical. An overview of the assessment guidance provided herein is as follows:

— Clause 5.2 Summarizes the *in vitro* evaluation steps and describes general considerations and relevant pre-test characterizations and treatments.

— Clause 5.3 guides product assessment from opening of the package through simulated vessel closure, which includes the delivery, placement, and initial function of the device (depicted as Procedural Stage in Figure 2).

— Clause 5.4 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).

— Clause 5.5 discusses some of the issues and potential barriers to successful generation of a correlation between *in vitro* and *in vivo* results.

— Clause 5.6 describes biocompatibility testing of absorbable implants, including reference to specific guidance for testing in accordance with the various parts of ISO 10993.

— Clause 5.7 covers both cardiovascular and absorbable specific concerns when conducting a pre-clinical *in vivo* evaluation.

— Clause 5.8 covers absorbable-specific concerns when conducting a clinical evaluation

— Clause 5.9 covers shelf-life and product aging considerations.

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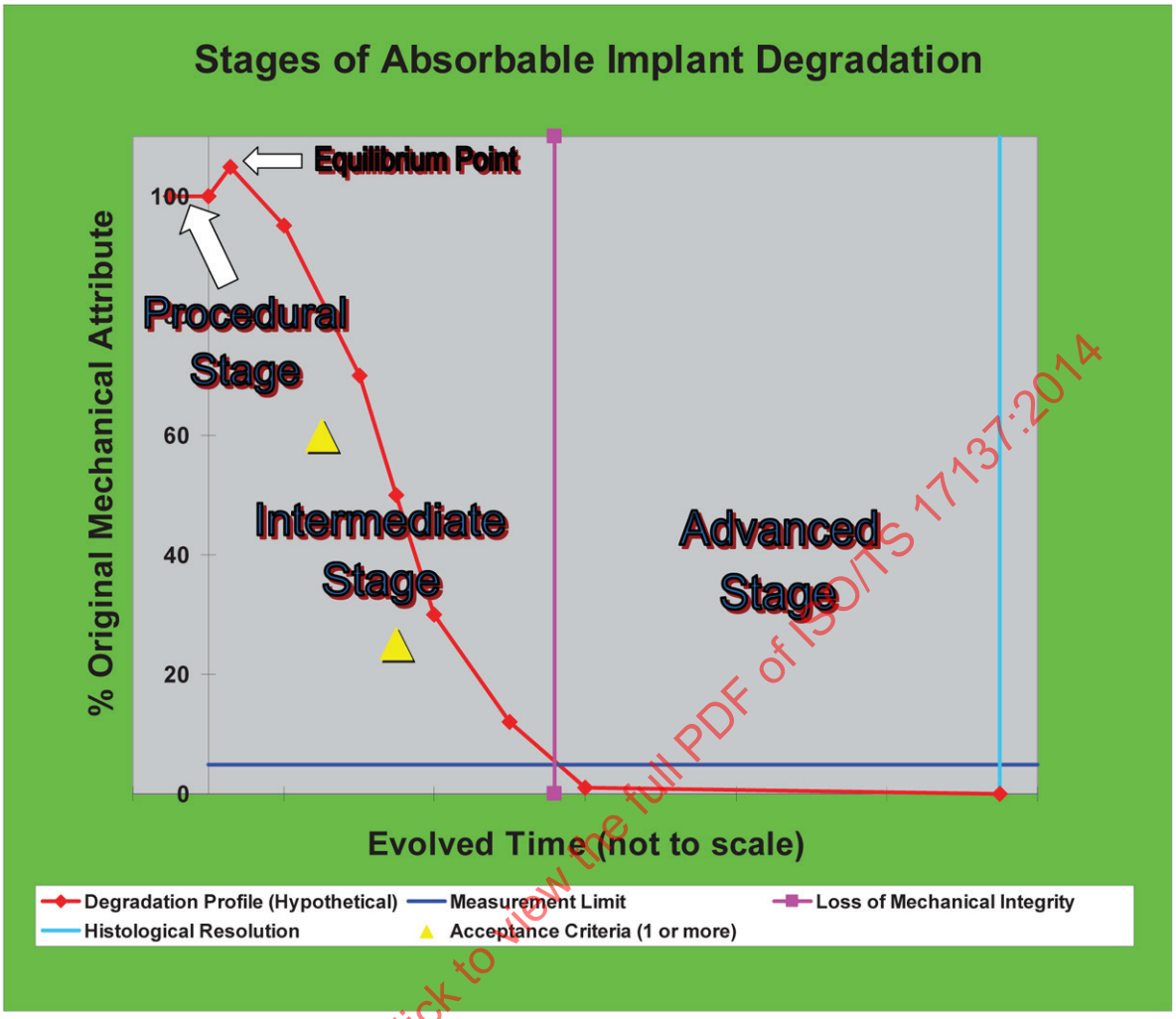


**Figure 2 — Schematic representation of stages in the degradation of an absorbable implant**

In this example figure, the decline in mechanical attributes is schematically represented through time ("Intermediate Stage") in comparison with the time frame for implantation ("Procedural Stage") and the period between loss of mechanical integrity and final *in vivo* resolution of the implant ("Advanced Stage"). The degradation profile for some materials may exhibit alternate trends but generally will include a decay to measurement limits. Relevant non-mechanical attributes should also be monitored at pertinent evaluation intervals, potentially throughout both the Intermediate and Advanced stages of degradation. Also, note that the graphically depicted Measurement Limit and Acceptance Criteria are hypothetical values that will vary dependent on measurement methods and the specific product's characteristics and performance requirements.

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## 5.2 Considerations in the characterization and assessment of material and implant properties

### 5.2.1 General considerations

A non-exhaustive listing of material and implant characteristics that should be considered for inclusion and subsequent assessment are:

a) composition/chemical/purity properties (e.g. molecular weight, inherent viscosity), thermal properties (e.g. polymeric Tg, melting point), and microstructure [e.g. degree of crystallinity (in polymers), grain size (in metals), pore characterization (in porous constructs)];

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b) corrosion/degradation mechanism and rate profiling, including consideration of potential variations and/or material interactions in different applicable environments (e.g. extreme storage or *in vivo* service conditions);

c) 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.

NOTE 1 Degradation products may be released into the media/tissue or reside in the degrading implant. Released degradation products that are generated either prior to product use (i.e. during processing or shelf-life) or during degradation 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 a theoretical analysis. Literature data for implants manufactured from absorbable materials with an established history of safe clinical use (e.g. PGA) at the intended location may be helpful in identifying expected degradation products and potential toxicities - if one can demonstrate that equivalent manufacturing processes were used. A toxicological risk assessment of degradation products over time in conjunction with toxicity data from the literature may be sufficient to support an omission of biocompatibility testing from various stages of material degradation (either during device storage or in clinical use).

NOTE 2 Guidance regarding the identification and assessment of chemical degradation products and leachables may be found in ISO 10993, parts 9 and 17.

d) integrity of the implant under both normal and extreme handling and *in vivo* service expectations.

e) anticipated impact of clinically utilized visibility methods (for example, X-ray, MRI, ultrasound, OCT) on the material and/or implant (e.g. effects of magnetic fields). Consideration should also be made regarding potential for interaction with other commonly used implants.

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 radial force characterization during only a portion of the Intermediate Stage.

Since it is impossible to take into consideration all current and future technologies, absorbable cardiovascular implants evaluated following the basic requirements of this specification 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 may have on the performance of the implant and/or implant component. In addition, the applicability of standards such as ISO/TS 12417 regarding drug-device combination products and ISO 25539-2 regarding endovascular devices need to 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 may 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 complete final sterilized devices. If the evaluated samples are comprised of implant components/subcomponents that are not sterilized or otherwise differ from final devices, a justification shall be provided.

Establishment of product shelf life shall be through evaluation of one or more appropriate implant performance tests conducted on the final product (see 5.9), with justification for the selection of tests provided. Refer to ASTM F2914 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/stability data including appropriate performance specifications to ensure the consistency and equivalency of the finished product across manufacturing sites should also be considered.

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### 5.2.2 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 standard 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/TS 12417.

### 5.2.3 Summary of *in vitro* evaluation steps

The following provides an outline of implant characterizations described within this section.

— Section 5.3 – *In vitro* procedural assessment

  — Section 5.3.1 – Conditioning of test samples

    — Unpacking;

    — Preparation of device per IFU.

  — Section 5.3.2 - Assessment of delivery and placement

    — Insertion through sheath or guide catheter, if interventionally placed;

    — Advancement to target lesion;

      — Utilizing vascular tracking model;

    — Implantation/deployment.

  — Section 5.3.3 Assessment of initial function post-deployment

    — Includes assurance that the device fulfills design requirements through placement and closure (e.g provides adequate radial crush resistance).

— Section 5.4 - *In vitro* degradation assessment (post procedure)

NOTE While degradation can occur at any stage, even during manufacture and before opening of the package, this section refers to the period post-placement where exposure to the physiological environment leads to intentional degradation of the implant.

Briefly, this section 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 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 and time frame being evaluated.

— Equilibrium

  — Equilibrium encompasses changes driven by implant adaptation to the physical environment and not changes that occur as a result of degradation of the absorbable material. The actual duration of this equilibrium process can be considered as implant dependent, ranging from immediate (i.e. upon deployment), as could be expected with metallic implants, to days, as could be the case for a full hydration of some polymers. Equilibrium duration is also dependent on the mechanical property being measured.

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  - Other than experimentally approximating the time point where equilibration occurs (Equilibrium Point) for the system being evaluated and the relevant characteristic (e.g. strength), no further direct characterization is needed.

- Intermediate Stage
  - This stage of degradation spans from the end of the Procedural Stage to where integrity of the implant is no longer detectable.
  - The acquired 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 the substantial absence 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.

## 5.3 *in vitro* procedural assessment

### 5.3.1 Conditioning of test samples

Pre-treatment/conditioning of the samples should simulate relevant procedural steps described in the instructions for use (IFU) and exercised prior to insertion of the device. This 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 a simulated vasculature, and device deployment are described in the following procedural-related subsections.

### 5.3.2 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. The design attributes necessary to meet the intended performance of a delivery system can be summarized by the following:

a) the ability of the delivery system to permit consistent, accurate and safe access to the intended location;

b) the ability of the delivery system to permit consistent, accurate and safe deployment and placement of the absorbable implant;

c) the ability of the delivery system to permit consistent and safe withdrawal of all necessary auxiliary devices;

d) the ability of the delivery system to be adequately visualized under fluoroscopy or other relevant imaging technologies.

For additional general guidance regarding the assessment of intravascular implant delivery systems, see:

- Guidance for Industry and FDA Staff - Non-Clinical Engineering Tests and Recommended Labelling for Intravascular Stents and Associated Delivery Systems (issued: April 18, 2010)

  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071863.htm

- ISO 25539-2 Cardiovascular implants – Endovascular devices, Part 2 – Vascular stents

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— ASTM F2394-07(2013) Standard Guide for Measuring Securement of Balloon Expandable Vascular Stent Mounted on Delivery System

### 5.3.3 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 5.3.1. 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 (structural) integrity post-deployment (e.g. absence of any unintended loss of strength);

b) identification of any strut fractures or de-laminations of the coating(s);

c) absence of 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.

## 5.4 *in vitro* degradation assessment (post procedure)

### 5.4.1 General

The objective of this section is to guide characterization of the chemical, mechanical, dimensional, and structural loss changes that occur 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 its initial pre-implanted state (as described in Section 5.3) until mechanical measurement of the degraded implant becomes impractical and with sufficient resolution to capture clinically relevant phenomena. Prior to undertaking the described evaluations, the implant needs to be prepared and procedurally deployed in a manner consistent with clinical use as described in 5.3 and illustrated as the Procedural Stage in Figure 2. All test samples tested should be finished sterilized devices.

### 5.4.2 Implant integrity

#### 5.4.2.1 Mechanical evaluation

When characterizing the degradation of implant over time, changes in relevant mechanical and/or performance properties need to be evaluated under simulated *in vivo* conditions. Such degradation is simulated by immersion in a physiologically-relevant pH stable aqueous solution maintained at (37 ± 2)° C (ASTM F1635, ISO 13781). With adequate justification and validation, non-physiologic thermal conditions may be used to accelerate degradation. For some anticipated *in vivo* environments, the user may consider possible interactions of the expected physiologic loading conditions on degradation.

If the implant or implant component is expected to undergo minimal loading post implantation, mechanical evaluations may be conducted on samples that are unloaded during conditioning. Conversely, if the implant is expected to be subjected to mechanical loading while *in vivo*, it is important to consider characterizing the influence that static (constant) and/or fatigue (cyclic) loading may have on the

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mechanical performance of the degrading implant ("mechanical degradation"). The type and magnitude of the applied loading needs to be representative of anticipated physiological conditions.

If accelerated loading is applied, the test condition should consider synchronizing the chemical degradation rate of the implant with the accelerated loading rate. A justification should be provided if accelerated loading and degradation are not synchronized. Additional tests to quantify the impact of degradation loading on the implant's mechanical properties and/or performance 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, e.g. from the standards series of ISO 25539 or ISO 5840.

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 integrity of the implant or implant component can no longer be measured. Mechanical properties of the implant during the Advanced Stage of degradation between loss of integrity and histological resolution are not evaluated.

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, care should be exercised to ensure that the sample does not dehydrate or change its properties due to loss of fluid as the test is being performed. A justification for mechanical tests necessitating evaluation under dry, room temperature conditions shall be provided.

#### 5.4.2.2 Cyclic fatigue durability

Evaluation of fatigue durability is to assess the long-term structural integrity of the absorbable implant (or implant component) under cyclic physiologic loading conditions. 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). Evaluation shall be performed under physiologically relevant or accelerated immersion conditions.

#### 5.4.2.3 Physical characterization of degradation/corrosion

Evaluation of the physical degradation of the implant needs to be evaluated under *in vitro* conditions that are as representative as possible to expected *in vivo* use conditions.

Potential guidance for the selection of appropriate assessment methods and procedures are:

— Polymers - ISO 10993-13;

— Ceramics - ISO 10993-14;

— Metals and alloys - ISO 10993-15.

NOTE 1 Metal degradation can occur through numerous mechanisms, which can include pitting, fretting, crevice and galvanic corrosion.

Evaluations shall be performed on implants that after sterilization and removal from packaging are immersed and then deployed into a physiologically relevant fluid and temperature. The evaluation requires special attention toward the following:

a) Duration of implantation procedure and volume of injected auxiliary fluids (e.g. saline or contrast media).

NOTE 2 The hydration behaviour of the absorbable implant and/or component needs to be considered with respect to any expected clinical preparation activities as well as to the duration of immersion in the solution.

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b) Contact or exposure time to the physiologically relevant solution (e.g. contrast media, blood, body fluid and/or tissue).

NOTE 3 In addition to monitoring the overall loss of the implant's physical and morphological properties over time, any preferential (i.e. non-homogeneous) degradation should be identified. If non-homogenous degradation (e.g. due to stress concentration) is present and potentially significant, then further investigation of the physical and/or chemical properties in that region may be undertaken.

#### 5.4.2.4 Material composition assessment

The composition of the implant material(s) and any expected sub-components (e.g. reactive chemical byproducts, trace metals/catalysts) shall be identified and their impact on degradation evaluated as guided in ISO 10993-18. The significance of potential alterations to the composition and/or chemical properties of the implant over its lifetime shall be evaluated, the scope of which may include- but is not limited to - molecular weight loss and thermo-mechanical properties [e.g. degree of crystallinity (in the case of polymers)]. Degradation products that are released into the surrounding media or tissue should be characterized [see Section 5.2.1 c)]. Quantification of each expected component is to be undertaken at an analytic level that ensures the final degraded implant will be suitable for the intended application.

#### 5.4.2.5 Other property assessments

##### 5.4.2.5.1 Corrosion/degradation

The biocompatibility of the particulate matter and/or soluble degradation products generated during testing is addressed in 5.6.

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) 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).

##### 5.4.2.5.2 Evaluate clinically using relevant imaging modalities

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

##### 5.4.2.5.3 Radiopacity

The radiopacity of the device shall be characterized, confirming adequate visibility of the device location under fluoroscopic imaging equipment at a time point or points relevant to the device application. Fluoroscopic radio-opacity is required only at placement (Figure 2 - Procedural Stage), with assessment optional during later stages of degradation.

##### 5.4.2.5.4 MRI compatiblity

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. Assessment of magnetically induced displacement force can be found in ASTM F2052. Assessment of magnetically induced torque can be found in ASTM F2213. Assessment of image artefact can be found in ASTM F2119. Recommendations for MRI Labelling can be found in ASTM F2503.

### 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 such correlation steps and/or attributes. In addition, the

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degree of necessary correlation between *in vitro* and *in vivo* measures may vary by implant type and clinical indication.

Correlation may be sought for the following areas:

— degradation time frames and mechanism(s);

— in case of drug components, drug release rate and mechanism.

Absorbable metals will corrode during most *in vitro* tests, the rate of which will vary depending on the test conditions; however, no correlation or preferred method is currently known to exist between *in vitro* tests and *in vivo* results.

Isolation of the explanted partially degraded implant for analytical or physical investigation may 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 may become impractical or impossible with some materials and/or stages of degradation.

## 5.6 Biocompatibility

### 5.6.1 General considerations

Biological evaluation is the assessment of the ability of a device, device component, or a material to be present in the body without creating an adverse systemic impact and/or local effect on the surrounding cells and/or tissue. Biological evaluation of an absorbable material is to be conducted in accordance with ISO 10993-1 and other relevant parts (see 10993-1:2009, Table A.1). General guidance regarding evaluation of devices in accordance with ISO 10993 can be found in ISO/TR 15499.

By design, polymeric, ceramic, or metallic absorbable materials inherently produce low molar and/or atomic mass products when *in vivo*. The relatively elevated presence of these same products within the culture media can potentially impact the results of some biocompatibility tests. For example, if the degradation rate of an absorbable material is sufficiently rapid, elevated concentrations of one or more of the intended products could alter the pH and/or osmolality of an *in vitro* test system. Since the *in vivo* condition provides the combined presence of perfusion and carbonate equilibria, when evaluating intentionally degradable materials it can be considered acceptable, if necessary, to adjust the *in vitro* test solution pH (via addition of HCl or NaOH) and/or osmolality (via dilution) to bring the cell culture into a physiologically relevant condition – thereby allowing evaluation for other causation and provided the correlating effect on the test system is documented within the test report. To directly address these and other absorbable-specific method concerns, a list of relevant testing precautions for each of the 10993 parts has been compiled and is presented in ISO/TR 37137.

Since absorbable materials are intended to degrade, potential exists for generation of transient particulate matter as the implant breaks down. While an understanding of the potential clinical impact of such degradation is needed, a separate biocompatibility assessment of the absorbable particulates alone may not be necessary if the particles are both produced and absorbed at rate that is similar to other materials of the same chemistry with a history of safe use in the intended clinical application. Guidance regarding the determination of whether identification and/or quantification of particulates is needed can be found in ISO 10993-9:2009, Annex A.

### 5.6.2 Sterilization considerations

Evaluations are to be conducted 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 commercial 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 may be produced.

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### 5.6.3 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/TS 12417, 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 or APIs in drug-device combination products, may be optionally substituted with an appropriate toxicological evaluation. Such a justification might be generated through a chemical characterization of device extracts in conjunction with a biological risk assessment for the specifically identified chemicals.

## 5.7 Pre-clinical *in vivo* evaluation

### 5.7.1 Purpose

NOTE See ISO 10993-2 (Animal Welfare), ISO 10993-6 (Local effects after implantation), ISO/IEC 17025 (laboratory quality management), and US-FDA GLP Regulations for additional guidance on appropriate pre-clinical laboratory practices.

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 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. This section should be considered as a supplement to the information provided in ISO 10993-2 (Animal Welfare), ISO 10993-6 (Local effects after implantation).

### 5.7.2 Specific aims

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

a) since traditional fluoroscopy procedures may 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;

b) evaluate appropriate haematological and biochemical laboratory parameters;

c) evaluate the structural integrity and absorption of the cardiovascular implant;

d) assess local biological responses (e.g. vascular trauma, thrombus deposition, inflammation, endothelialization, necrosis, neointimal proliferation, aneurysm formation) and downstream and systemic effects (e.g. embolism, infarction) through an evaluation of histology and pathology of explants and pertinent tissues/organs and whether these may be related to implant degradation and/or drug elution;

e) record adverse events and potential contributing factors (e.g. implant vs. catheter delivery system).

More than one study may be used to address the specific aims. Animal studies are designed to demonstrate safety. Animal studies are not designed for demonstrating efficacy. However, a study may

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be designed with specific end points related to the local biological response (e.g. reduced neointimal proliferation, improved rate of endothelialization) that can demonstrate a potential clinical benefit.

When evaluating the *in vitro*/*in vivo* correlation (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. inconsistent quantification and/or sample preparation issues). 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.

### 5.7.3 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 days), or permanently]. Long-term in-dwelling cardiovascular absorbable implants or implants with absorbable components may require additional study follow-up time points. Assessment intervals should be targeted in accordance with the expected pattern of degradation leading to final resolution of the implant or absorbable component. In the absence of complete degradation, the data collected and resulting trend may be sufficient to allow characterization of local effects after implantation, provided that both substantial absorption and the restoration of normal tissue structure and function has been obtained. While gross and microscopic evaluation after complete implant absorption is highly desirable, *in vivo* degradation profiling of the absorbable material and/or its degradation products 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.

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-dependant effects, including the effect of overdosing (e.g. no drug, nominal drug dose, and 3x overdose) unless justification can be provided for omission of this type of testing. Local, regional (down-stream), and systemic toxicities should be assessed.

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

Interpretation of animal study results may be enhanced by the use of at least a small number of control implants for comparison purposes. A rationale should be provided if a control implant is not used in the study. For implanted products, if the matrix 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 may be product compatibility issues that may need to be considered for the animal study design.

In accordance with the specific aims detailed in Section 5.7.2, 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

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shall be specified. In addition, the choice of animal model such as species, gender, age, and whether or not a lesion is created, 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. 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.

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 includes down-stream histopathologic assessments in order to assess potential clinical implications of particulates released from the cardiovascular absorbable implant.

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

Recognition and adherence to appropriate animal husbandry-related precautions may prevent poor outcomes not related to the product. Refer to the Bibliographic references to the US-FDA guidance for cardiovascular animal studies, the Institute for Laboratory Animal Research (ILAR) guide for care of laboratory animals, and the ISO/TS 12417 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 pre-clinical laboratory practices.

### 5.7.4 Data acquisition

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

### 5.7.5 Test report and additional information

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

The test report shall include those detailed in ISO 25539, ISO 5840, and/or other applicable standards with exceptions or additional considerations pertinent to cardiovascular absorbable implants as detailed in Section 5.7.3 also being included.

## 5.8 Clinical considerations specific to absorbable implants

### 5.8.1 Purpose

The purpose of clinical evaluation is to evaluate the performance of the delivery system if applicable, and assess the safety and efficacy 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 testing requirements of this Technical Specification before starting the clinical investigation. Refer to ISO 12417 for absorbable implants with active pharmaceutical ingredients or degradation products considered to be bioactive.

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### 5.8.2 Specific aims

Specific aims of the study shall be stated and can include the following aims 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;

c) evaluation of histology and pathology of any explants and pertinent tissues/organs to discern the effects of material degradation.

### 5.8.3 Clinical-investigation plan

A multicenter study with a statistically justified number of patients shall be performed. General guidelines for patient selection, duration of follow-up, control groups, clinical end points, data reporting and analysis are outlined in ISO/TS 12417. General guidelines for patient monitoring can be found in ISO 14155 and ISO/TS 12417.

The duration of patient follow-up for absorbable cardiovascular implants may 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 for absorption. Specifically, clinical study duration should be guided by bench and animal studies, and should be sufficient to capture clinical events at key time points during and potentially, after complete implant degradation.

A justification shall be required for follow-up intervals but may be based on clinical end points and/or expected degradation times of interest.

Preliminary 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, there could be additive-dose and/or product compatibility issues of the degradation products and/or any drug component that may need to be considered in the clinical study design. In addition, if degradation products are bioactive, pharmacokinetic studies to assess the degradation products may be needed.

### 5.8.4 Data acquisition

In addition to the data acquisition specifications outlined in ISO 14155 and ISO/TS 12417, the following data 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 may be some unanticipated interactions between the absorbable implant and pre- or post-operative medications, especially those that include an active pharmaceutical ingredient (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 degradants and/or API may be observed systemically or at sites distal to the implant site.

### 5.8.5 Final report

In addition to the final report specifications outlined in ISO 14155 and ISO/TS 12417, a rationale shall be provided for selection of patient follow-up intervals and assessments at each time point which may have been chosen based on the degradation profile of the implant.

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### 5.8.6 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 or an equivalent publication. For absorbable cardiovascular implants, post-market surveillance shall consider the expected time course of implant degradation.

## 5.9 Shelf life considerations

### 5.9.1 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.

The ISO/IEC Guide 51, ISO/IEC Guide 63:2012, ISO 10993-1, and ISO 11135-1 (see Bibliography) 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 provides guidance for determination of the appropriate attributes for testing as part of establishment of shelf-life for endovascular devices. Accelerated aging might be appropriate to establish the shelf-life of an absorbable device in a timely manner. AAMI TIR17 contains guidance regarding accelerated aging programs and provides a brief discussion of aging theory. Also, ASTM F1980 provides guidance on accelerated aging parameters and discusses humidity. Absorbable device shelf-life establishment requires special consideration. ASTM F2902 provides guidance regarding shelf-life of absorbable polymeric implants.

### 5.9.2 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 performance evaluation is provided in 4.6.

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. 0,5, 1, and 2 years) are recommended to mitigate risk associated with a failure to meet the requirements at later time points

### 5.9.3 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 confirm the shelf-life established by accelerated aging testing.

The testing plan to establish the desired 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 provides conservative accelerated aging factors. 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

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