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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 (see 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).

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.

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

This second edition cancels and replaces the first edition (ISO/TS 17137:2014), which has been technically revised.

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.

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 metabolism, assimilation, and/or excretion (elimination). Such implants can be either surgically or interventionally introduced 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 should be considered as a supplement to ISO 14630, which specifies general requirements for the performance of non-active surgical implants. This document 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. 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 12417-1.

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, the reader might find it useful to consider a number of other international standards (see Bibliography).

Cardiovascular implants and extracorporeal systems — Cardiovascular absorbable implants

1 Scope

This document outlines design evaluation guidelines 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 meant to supplement device-specific standards by providing guidelines specific for absorbable implants and/or components

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 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 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 of this document.

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 dated references, only the edition cited applies. 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 (all parts), *Sterilization of health care products — Radiation*

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, *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, *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/TR 37137, *Cardiovascular biological evaluation of medical devices —Guidance for absorbable implants*

ASTM F640, *Standard Test Methods for Determining Radiopacity for Medical Use*

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 http://www.electropedia.org/

3.1
absorb
absorption
<biomaterials> action of a non-endogenous (foreign) material or substance or its degradation products passing through or being assimilated by cells and/or tissue 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).

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 physical and/or mechanical 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 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) 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) 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, with ASTM F3160 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, 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 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 could 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, shall apply, with the following information to be supplied as part of the label(s):

a) name or trade name of the device;

b) expiration date (indication of shelf-life) and the recommended storage conditions;

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) a warning against the use of the device if the package’s sterile barrier is damaged;

h) a written and/or “Do not resterilize” symbol warning against re-sterilizing and/or reusing the device, if applicable;

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

j) 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:

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 implant or components thereof;

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;

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 function and 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 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, -2, -3 shall apply, including the Part 1 provision 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 could 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 could 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 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.

ISO/IEC Guide 51, ISO/IEC Guide 63, ISO 10993-1, and ISO 11135 (see Clause 2 and the 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.

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 performance evaluation 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 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 environmental factors. It should be noted that aging can be accelerated when multiple aging processes are involved. One should carefully define the combined effect of accelerated aging in establishing the protocol for these aging process validations.

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.

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 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 62366-1. Intended (correct) use errors (e.g. unable to deliver device past tortuous anatomy that was not excluded in the IFU).

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

4.7.3 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.

4.7.4 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 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.

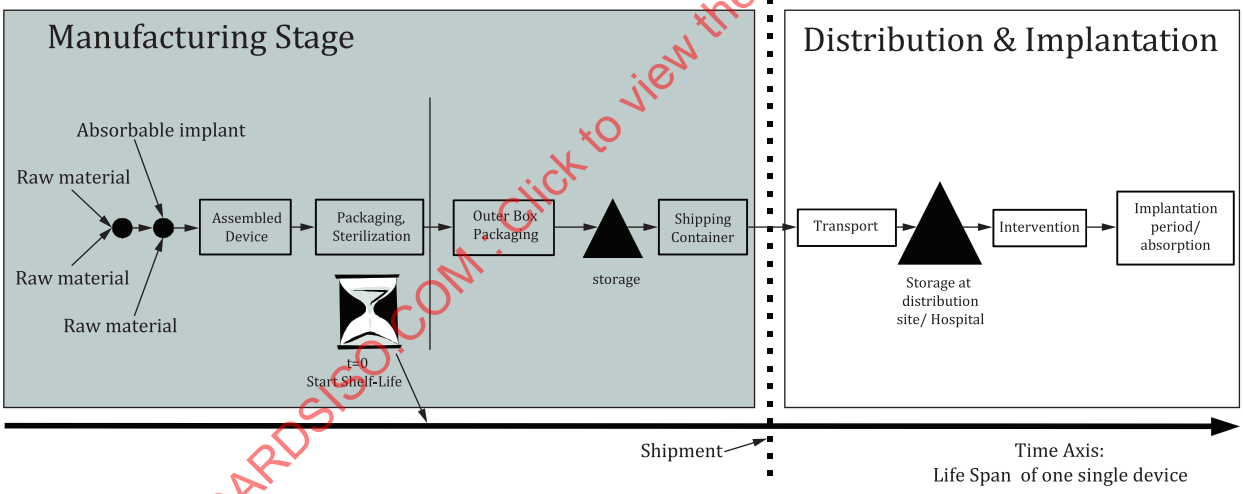

Figure 1 — Life span of one single device/implant

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 from their initial pre-implanted

state and at select time points during degradation until measurement of the partially degraded implant becomes impractical. An overview of the assessment guidance provided herein is as follows:

— 4.6 covers shelf-life and product aging considerations (covered previously).

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

— 5.2 guides product assessment at timeframes 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).

— 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).

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

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

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

— 5.7 covers absorbable-specific concerns when conducting a clinical evaluation.

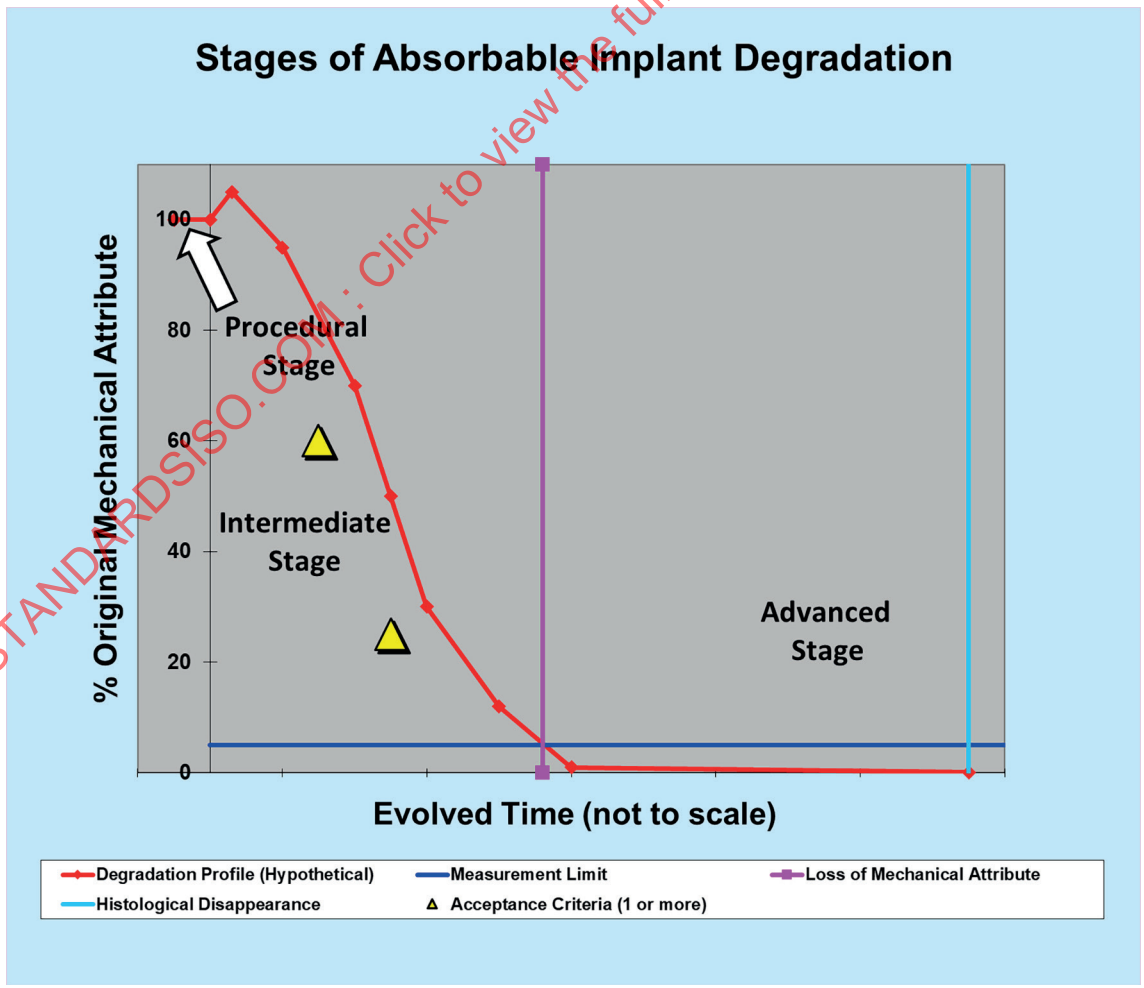

Figure 2 — Schematic representation of stages in the degradation of an absorbable implant

Degradation of the implant should be characterized *in vitro* at multiple time points that encompass the timeframe 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 (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 for how the degradation profile may compare to select acceptance criteria are shown. 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 may retain its dimensions when surrounded by tissue *in vivo*.

5.1.2 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)];

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 in some cases 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 can be found in ISO 10993-9 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, magnetic resonance imaging (MRI), ultrasound, optical coherence tomography (OCT)] on the material and/or implant (e.g. effects of magnetic fields);

f) Consideration should also be made regarding potential for interaction with other commonly used implants;

g) 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 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 Specification may 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 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 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.

5.1.3 Summary of *in vitro* evaluation steps

Briefly, this clause 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 (mechanical, chemical, physical, etc.) 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 5.2 – *in vitro* procedural assessment. During this stage, the absorbable device would be subjected to unpackaging and preparation per IFU (5.2.1). In order to simulate advancement to the treatment site, this assessment may include utilizing an anatomically relevant simulated use model (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 (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, this clause refers to the period post-placement where exposure to the physiological

environment leads to intentional degradation of the implant. 5.3 - *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 *in vitro* procedural evaluation

5.2.1 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 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.

5.2.2 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.

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 (issued: April 18, 2010) https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071863.htm

— ISO 25539, *Cardiovascular implants – Endovascular devices*

— ASTM F2394, *Standard Guide for Measuring Securement of Balloon Expandable Vascular Stent Mounted on Delivery System*

— ASTM F2606, *Three-Point Bending of Balloon Expandable Vascular Stents and Stent Systems*

— 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*

— AAMI TIR42, *Evaluation of particulates associated with vascular medical devices*

— 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*

Regarding imaging evaluation methods:

— ASTM F640, *Standard Test Methods for Determining Radiopacity for Medical Use*

— ASTM F2119, *Test Method for Evaluation of MR Image Artefacts from Passive Implants*

5.2.3 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 5.2.1. 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 this clause 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 and procedurally manipulated and/or deployed 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 for absorbable metals and ASTM F1635 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).

For some anticipated *in vivo* environments, physiological loading conditions from vessels (e.g. axial, pulsatile, torsional, bending) should be considered in *in vitro* degradation studies.

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. All simulated degradation studies and their subsequent evaluations shall be performed on implants after sterilization, unless otherwise justified.

5.3.2 Sample conditioning

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.

5.3.2.1 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.

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

5.3.2.3 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).

5.3.2.4 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 relevant mechanical and/or performance properties 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 timeframe for this increase in magnitude to occur will be nearly immediate (i.e. upon deployment), as could be expected with biodegradable metal implants, to days, as could be the case for full hydration of some polymers. It may be desirable for some mechanical attributes (e.g. strength) to characterize this initial increase in value 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, e.g. 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 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 (such as the passive mechanical support provided by tissue coverage/ingrowth, cell and blood interactions, etc.). 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/chemical degradation evaluation

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 Mw (see following subclause).

Guidance regarding methods for the determination of the physical mass lost from a retrievable degrading implant can be found in either ASTM F1635 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 - *Guide for in vitro Degradation Testing of Absorbable Metals*. Aside from describing potential experimental approaches, this standard 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 at minimum of two (2) 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 could include mass loss, particulate evaluation, or other physical evaluations such as systematic imaging at selected time points. Chemical evaluation of degradation (e.g. via 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 - 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.

5.3.5.1 Material and degradation product evaluation

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. Degradation products that are released into the surrounding media or tissue should be evaluated per ISO 10993-1. 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.

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 gel permeation/size exclusion chromatography (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 highly aggressive and/or corrosive solvents 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 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 Bibliography. 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.

Corrosion/degradation - 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 or ASTM F3044) 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 - *Guide for in vitro Degradation Testing of Absorbable Metals*.

The biological evaluation of the particulate matter and/or soluble degradation products 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.

5.3.6 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 (Figure 2 – Procedural Stage). Since it is expected that the radiopacity of the device may 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.

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. 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. General guidance regarding MRI safety can be found in the US-FDA Guidance entitled: "*Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment*", issued on December 11, 2014 and available online at: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM107708.pdf

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 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 ISO 10993-1:2009, Table A.1).

By design, most polymeric, ceramic, or metallic absorbable materials will inherently produce low molar and/or atomic mass degradation products when *in vivo*. 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/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 products could alter the pH and/or osmolality of an *in vitro* test system. 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. In such situations, it may be appropriate to adjust the *in vitro* test solution pH and/or osmolality to bring the extraction vehicle into a physiologic range – and to then repeat the *in vitro* biological test to document evidence this(these) factor(s) is(are) the mechanism of an adverse result. In such situations, the use of animal models to demonstrate the safety of the product are often an important follow-up to confirm that the pH and/or osmolality changes caused by the presence of expected degradation products do not represent patient safety risks. To directly address these and other absorbable-specific method concerns, a list of relevant testing precautions for each of the 10993 parts is presented in ISO/TR 37137 and shall be considered.

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 stages of the Advanced Stage and after most of the implant's mechanical strength has been lost and molar mass is very low to undetectable by GPC methods (see Pistner). 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 could affect biological responses, which should be discussed in the risk assessment.

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 a rate that is similar to that of other materials of the same chemistry with a history of safe use in the intended clinical application.

5.4.2 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.

5.4.3 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 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 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.

5.5 *in vitro-in vivo* correlation

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 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;

— 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 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 *in vivo* pre-clinical evaluation

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

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 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 and with consideration for the test animal's body mass with respect to the intended patient population;

b) evaluate appropriate haematological and biochemical laboratory parameters;

c) 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;

d) assess local biological responses (e.g. vascular trauma, thrombus deposition, inflammation, endothelialization, necrosis, neointimal proliferation, aneurysm formation);

e) 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 may be device or procedure related;

f) 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 objectives. Animal studies are designed to demonstrate safety. Animal studies are not designed for demonstrating either efficacy or effectiveness. However, a pre-clinical 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.

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.

5.6.3 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 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, including multiple assessments during the intermediate stage, leading to final disappearance of the implant or absorbable component. Consideration needs to be made regarding the impact that normal physiological temperature of the test species may have on the degradation rate of the implant. 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.

In an attempt to pre-clinically assess risk of late events (e.g. thrombus) generated by implant degradation and/or collapse, a retrieval time point should be selected at which the device 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 3x 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 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 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 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 assessment 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 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 pre-clinical laboratory practices.

5.6.4 Data collection

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 5.7.3. General guidance also is provided in 10993-6.

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 cardiovascular absorbable implants as detailed in 5.6.3 also being included.

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 testing requirements of this Technical Specification 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 [Ref. Bergsma (1995), Waksman (2017), Stone (2017), Keriakes (2017), Wang (2018)]. 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 non-clinical 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 may have contributed to these results. Although there is not enough statistic 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.