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Implants for surgery — General guidelines and requirements for assessment of absorbable metallic implants

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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).

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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*.

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

This document provides a general introduction to the field of absorbable metals. It outlines design considerations which differ from non-absorbable metals and provides a detailed description of the absorption process.

Metallurgical evaluation of absorbable metals is discussed, with reference to ASTM F3160 and commentary on the impact of composition and production processes on final performance.

In vitro degradation corrosion testing is discussed, with reference to ASTM F3268 and commentary on the importance of environmental conditions in the tests.

Both *in vitro* and *in vivo* biological assessment are discussed, with reference to several parts of the ISO 10993 series, ISO/TS 37137-1[1)] and the under-development ISO/TR 37137-2[2)].

NOTE ISO/TS 37137-1 applies to all absorbable materials, including metals and polymers. ISO/TR 37137-2 is specific to absorbable magnesium-based materials.

The interrelation of the absorbable-specific reference documents can be viewed in Figure 1.

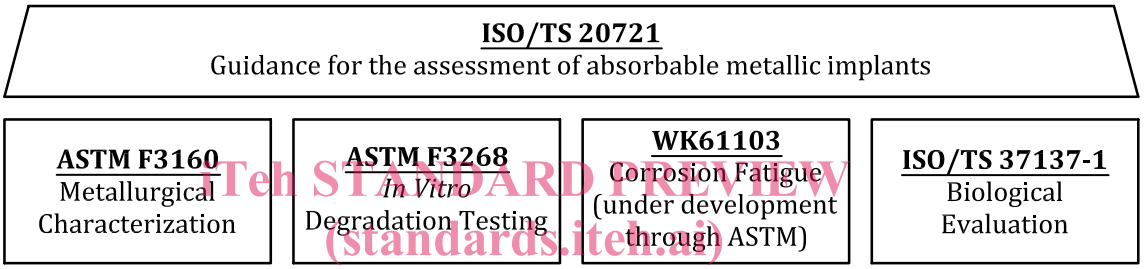

Figure 1 — Interrelation of standards specific to absorbable implants

The guide can be useful to both material suppliers and implant manufacturers.

Absorbable polymers used in conjunction with absorbable metals, either for performance modification or drug delivery, are not addressed. However, it is expected that a polymer coating, absorbable or non-absorbable, can influence absorption and performance of the underlying absorbable metal. ASTM F2902 addresses absorbable polymers.

Some existing standards address specific absorbable implants (e.g. ISO/TS 17137 addresses absorbable cardiovascular implants) made of either polymer or metal.

1) Under preparation. Stage at the time of publication: ISO/TS/CD 37137-1:2020.

2) Under preparation. Stage at the time of publication: ISO/TS/CD 37137-2:2020.

Implants for surgery — General guidelines and requirements for assessment of absorbable metallic implants

1 Scope

This document established the currently recognized approaches and special considerations needed when evaluating the *in vitro* and *in vivo* performance of absorbable metals and implants fabricated, in whole or in part, from them. This document describes how the evaluation of these metals can differ from those utilized for permanent non-absorbable implantable implants (or subcomponents), in that absorbable metal implants (or subcomponents) are — by design — intended to be absorbed in their entirety by the host.

This document provides guidance regarding the materials considerations, *in vitro* degradation/fatigue characterization, and biological evaluation of medical implants made of absorbable metals. The provided content is intended to deliver added clarity to the evaluation of these materials and implants to increase awareness of critical factors and reduce potential for generation of erroneous or misleading test results.

While this document and the herein described referenced standards contain many suggested alterations or modifications to currently practiced procedures or specifications, the provided content is intended to complement, and not replace, current conventions regarding the assessment of implantable implants.

This document covers the evaluation of absorbable metal specific attributes in general and is not intended to cover application or implant specific considerations. Thus, it is important to consult relevant implant and/or application specific standards.

This document does not apply to non-absorbable or non-metallic components (e.g. polymeric coatings, pharmaceuticals, non-absorbable metals) used in conjunction with absorbable metal implants.

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/TS 37137-1, *Biological evaluation of medical devices — Part 1: Guidance for absorbable implants*[3)]

ASTM F3160, *Standard guide for metallurgical characterization of absorbable metallic materials for surgical implants*

ASTM F3268, *Standard guide for in vitro degradation testing of absorbable metals*

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) Under preparation. Stage at the time of publication: ISO/TS/CD 37137-1:2020.

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

Note 1 to entry: Annex A provides further clarification regarding the nomenclature of absorb, degrade and related terms.

[SOURCE: ISO 10993-6:2016, 3.1, modified — Note 1 to entry added.]

3.2
degrade
physically, metabolically, and/or chemically decompose a material or substance

[SOURCE: ISO/TS 37137-1:2020, 3.4]

3.3
degradation product
byproduct
intermediate or final result from the physical, metabolic, and/or chemical decomposition of a material or substance

[SOURCE: ISO/TS 37137-1:2020, 3.3]

3.4
implant
implantable medical device
medical device which can only be removed by medical or surgical intervention and which is intended to:

— be totally or partially introduced into the human body or a natural orifice, or

— replace an epithelial surface or the surface of the eye, and

— remain after the procedure for at least 30 days

[SOURCE: ISO 13485:2016, 3.6, modified — alternative term “implant” added.]

4 Absorbable metal considerations

4.1 General

Implants fabricated from absorbable metals are expected to degrade gradually while retaining sufficient mechanical properties over time to achieve a clinically successful end point. As these implants degrade by corrosion, their degradation products should be released at a rate which is acceptable to the host both locally and systemically. Generally, absorbable metals are primarily composed of one of three main nutrient elements: magnesium, iron, or zinc. Various alloying elements are commonly added to each of these base materials to improve properties like strength, ductility, fatigue resistance, or corrosion resistance. In some cases, non-metallic coatings or components can be added to the absorbable metal to augment the total implant performance.

In contrast, non-absorbable metallic implants (or subcomponents) intended to permanently replace a missing, lacking, destroyed, or diseased physiological function, or to support healing process are intentionally resistant to corrosion. Since the corrosion rate of such implants is extremely slow to negligible, such alloys can include toxic or harmful elements which are not expected to significantly leach into the body but rather remain within the implant. In some cases (e.g. metal on metal hip implants), wear particles of these corrosion-resistant alloys can be generated and can lead to negative outcomes due to their non-absorbing nature. Since most current standards have been developed with such permanent implants in mind, these standards need to be carefully evaluated for their suitability as test methods for absorbable metals.

4.2 Design considerations

4.2.1 Composition

4.2.1.1 General

All components of the absorbable metal are intended to be directly or indirectly exposed to the body tissue where the potential for an adverse biological response can occur. Informed decisions shall be made on the toxicity profile of the materials including potential impurities and their resultant degradation products. As the implants progress through the corrosion process, they produce a series of degradation products including ions, oxides, hydroxides and gases (see Reference Zheng 2014). Further, metallic particles can be released from the implant during the corrosion process which can result in transient mechanical and biological impacts in addition to the degradation products mentioned previously.

Components of the absorbable metal native to the host, such as magnesium, iron, or zinc, can simply be incorporated in the body's various biological processes, with excesses removed by natural homeostasis mechanisms. However, in some physiological circumstances, the components and degradation products can have long residence periods in either the initial implant site or a remote tissue after transport. A general understanding of what happens to the implant's resulting degradation products during its absorption lifecycle is important.

4.2.1.2 Base element

It is recommended to use metals considered native to the body, examples of which are iron, magnesium, or zinc.

Assessment for biocompatibility of the base element shall be done according to 7.2.

4.2.1.3 Alloying elements

Alloying elements are intentionally added to the base element to improve properties like tensile strength or corrosion rate. These elements can account for a significant portion of the alloy, and thus require a high level of scrutiny. Unlike the base elements which are easily removed by the body, the alloying elements are often not nutrient metals, and can sometimes have longer residence times in the implant-site tissue. They can also be transported by the body to other tissues for further processing. It is important to consider the degradation pathways, residence locations and residence durations of these alloying elements.

Assessment for biocompatibility of the alloying elements and their compounds (metal phases and intermetallic compounds) shall be done according to 7.2.

4.2.1.4 Impurities

Impurities are those elements that are not purposely added to the alloy but are introduced through raw material impurities and/or processing. Within this context, impurities include, but are not limited to, trace elements, contaminant materials, and unintended elements. Impurities should normally be present at very low concentrations. The primary concern with impurities is their impact on implant performance and safety. In the case of magnesium alloys, for example, trace iron, nickel, or copper can dramatically reduce corrosion resistance by forming microgalvanic cells between the anodic magnesium and cathodic impurity. In all metals, inclusions (e.g. oxides, nitrides, intermetallics) exceeding some critical size can also limit implant strength and fatigue life. Proper risk and quality management systems should ensure these impurities are sufficiently low to avoid these negative side effects.

ASTM B107/B107M, ASTM B93/B93M, ASTM B90/B90M, and the ASM Specialty Handbook for Magnesium and Magnesium Alloys contain useful information on impurity limits in common magnesium alloys.

ASTM A36 and ASTM A314 detail impurity limits for some commercially available iron-based materials.

ASTM B86 sets impurity limits for commercially available zinc alloys.

NOTE ASTM B107/B107M, ASTM B93/B93M, ASTM B90/B90M, ASTM A36, ASTM A314, ASTM B86, and ASM Specialty Handbook for Magnesium and Magnesium Alloys cited here are for information only.

4.2.2 Coatings

In some implants, a coating can be initially employed to alter the corrosion behaviour (including the corrosion rate, corrosion uniformity, corrosion mechanisms, and corrosion products) and failure modes. Coatings can take the form of a conversion layer (oxides/passivation) or extraneous materials (e.g. polymers, metals, or ceramics). When designing *in vitro* and *in vivo* tests, it is important to consider and evaluate the impact of any coatings intentionally applied to the implant. Potential interactions between the coating, absorbable metal substrate, and degradation products from the coating and/or the absorbable metal substrate should be considered.

4.2.3 Non-absorbable subcomponents

Some subcomponents of absorbable metals can be designed to remain permanently in the body. For example, small tantalum or platinum markers can be added to a vascular scaffold to increase radiopacity and aid in deployment.

4.2.4 Microstructure

The microstructure of an absorbable metal can have a significant impact on nearly all aspects of mechanical performance. It can also impact corrosion behaviour which can impact biological response. Mechanical properties like strength, toughness, and ductility, as well as corrosion rate and corrosion morphology, are strongly tied to the metal's microstructure. In the case of additively manufactured components, understanding porosity can be important as well. Amorphous metals, also known as metallic glasses, do not have the typical crystalline structure found in most metals and requires special consideration. At micro and nano scales, there are five major factors that impact the performance of the material:

a) the size and distribution of grains and subgrains (individual crystallites in metals);

b) crystallographic texture (orientation of grains);

c) presence, type, morphology, size, volume fraction, orientation relative to the matrix/ coherency, chemical composition, structure, and distribution of intermetallic phases, inclusions, or pores;

d) concentration of solute atoms within the phases (matrix phase and intermetallic phases);

e) concentration and distribution of defects (e.g. dislocations, vacancies, interstitials) within the crystal structure.

A metal's microstructure is a function of both its chemistry (base and alloying elements) and its processing history. Therefore, metallic materials with equivalent chemistries but different process histories possess different microstructures. Likewise, metals with identical process history but different chemistries also have different microstructures. Further discussion on processing can be found in 5.3.

Because a consistent microstructure can be critical to an implant's performance, inspection for appropriate retention of the microstructure should be undertaken at appropriate stages in the manufacturing process. ASTM F3160 provides significant information and guidance regarding the metallurgical (and microstructural) characterization of magnesium (Mg), iron (Fe), and zinc (Zn) based metals and alloys. Generally, metallic microstructures are observed by optical (light) or electron microscopy.

NOTE ASTM E407, ASTM E340, ASTM E112, ASTM E1382, ASTM E2627 and ISO 643 provide methods for sample preparation and characterization of the microstructure.

4.2.5 Implant design and functional performance

The absorbable implantable medical implant shall accomplish its intended clinical treatment over a sufficient time period to provide a clinically successful outcome. The implant shall be designed to be absorbed by the body over a finite time and eliminated such that there is no residual complication by the former presence of the implant or significant persistent residuals. The implant shall meet the performance requirements expected for the clinical treatment and maintain sufficient integrity during the tissue healing and remodeling period to not adversely affect the implant site. Additionally, the components of the alloy, their degradation products and intermediates shall result in an acceptable biological response, and the risks associated with local pH changes, gas bubble formation, heat generation, and adverse responses to changes in mechanical properties with degradation shall also be assessed – see 4.2.1, 4.3.5, and Clause 7.

The implant performance at the time of implantation shall meet the applicable requirements. Legal requirements can apply, that define specific implant performance for the implant type. An appropriate level of performance shall be maintained during the healing process as required by the treatment. The degree of performance required at any time point should be informed by any available clinical judgement of the user community.

NOTE 4.3.6 provides guidance for profiling mechanical performance/loss during the absorption period.

4.3 The absorption process

4.3.1 General outline

The physiological environment is a harsh one in which metals tend to corrode. Materials like stainless steel and titanium are intentionally selected for their stability in such an environment. Absorbable metals, however, are intentionally selected to break down by corrosion and be absorbed, in a suitable manner for the application at hand.

Absorbable metals degrade in a three-stage process:

a) Metallic conversion (corrosion) – the metal is either converted into an oxidized state or into an ionic state;

b) Oxide reactions – initial oxide or hydroxide formed in the first stage can further react into complex compounds and can induce formation of additional compounds;

c) Biological absorption/removal – the degradation products can be absorbed, distributed, metabolized, and/or excreted by biological process, or can remain in the tissue.

NOTE See Reference [29] for further reading.

4.3.2 Metallic conversion

Absorbable metals in aqueous solutions corrode with reduction-oxidation (redox) reactions. During the degradation of absorbable metals, the metal is oxidized, and the resulting released metal ions can form compounds with the body's electrolytes. For metals with a low electrochemical potential (e.g. magnesium and zinc), the predominant reduction reaction is the hydrogen evolution reaction wherein water and the electrons generated from the metallic oxidation react into hydroxide and hydrogen gas. Iron has a higher electrochemical potential, and at physiological pH its electrons are consumed in the dissolved oxygen reduction reaction, and generally does not generate a gaseous byproduct.

In many implants, immediately after implantation there is a relatively high corrosion rate until a more passive corrosion layer develops and slows the corrosion rate to a steadier state.

The rate of hydrogen gas creation is directly related to the rate of corrosion. To avoid build-up of gas pockets or bubbles which can impede tissue healing, corrosion rate and gas production rate should be kept below the rate of perfusion of hydrogen through tissue. The small size of hydrogen gas molecules allows for relatively fast diffusion, but specific rates vary based on local tissue types and perfusion level.