*भारतीय मानक*

***Indian Standard***

**IS 18984 : 2024**
**ISO/TS 20721 : 2020**

# सर्जरी के लिए प्रत्यारोपण — अवशोषित करने योग्य धातु प्रत्यारोपण के मूल्यांकन के लिए सामान्य दिशानिर्देश और अपेक्षाएँ

# Implants for Surgery — General Guidelines and Requirements for Assessment of Absorbable Metallic Implants

ICS 11.040.40



भारतीय मानक ब्यूरो
BUREAU OF INDIAN STANDARDS
मानक भवन, 9 बहादुर शाह ज़फर मार्ग, नई दिल्ली - 110002
MANAK BHAVAN, 9 BAHADUR SHAH ZAFAR MARG
NEW DELHI - 110002
www.bis.gov.in www.standardsbis.in

**October 2024** **Price Group 8**

Orthopaedic Instruments, Implants and Accessories Sectional Committee, MHD 02

NATIONAL FOREWORD

This Indian Standard which is identical to ISO/TS 20721 : 2020 ‘Implants for surgery — General guidelines and requirements for assessment of absorbable metallic implants’ issued by the International Organization for Standardization was adopted by the Bureau of Indian Standards on the recommendation of the Orthopaedic Instruments, Implants and Accessories Sectional Committee and after approval of the Medical Equipment and Hospital Planning Division Council.

The text of ISO standard has been approved as suitable for publication as an Indian Standard without deviations. Certain conventions are, however, not identical to those used in Indian Standards. Attention is particularly drawn to the following:

a) Wherever the words ‘International Standard’ appear referring to this standard, they should be read as ‘Indian Standard’; and

b) Comma (,) has been used as a decimal marker while in Indian Standards, the current practice is to use a point (.) as the decimal marker.

The Committee responsible for the preparation of this standard has reviewed the provisions of following mentioned International Standards and has decide that they are acceptable for use in conjunction with this standard:

| *International Standard/ Other Publication* | *Title* |
|---|---|
| ISO/TS 37137-1 | Biological evaluation of medical devices — Part 1: Guidance for absorbable implants |
| 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 |

For the purpose of deciding whether a particular requirement of this standard is complied with the final value, observed or calculated, expressing the result of a test or analysis shall be rounded off in accordance with IS 2 : 2022 ‘Rules for rounding off numerical values (*second revision*)’. The number of significant places retained in the rounded off value should be the same as that of the specified value in this standard.

# Contents

Page

# 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.

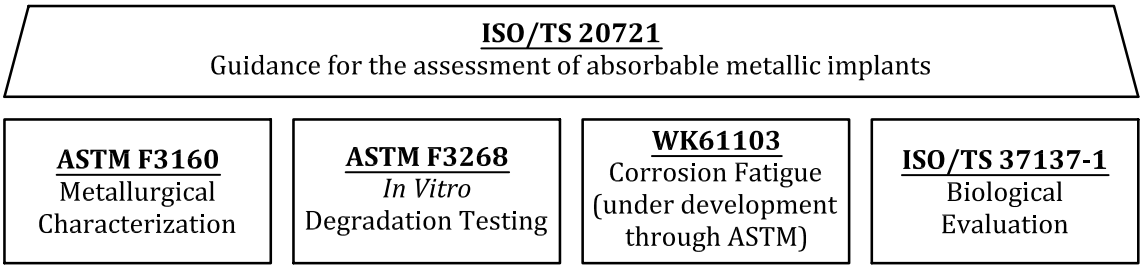


**Figure 1 — Interrelation of standards specific to absorbable implants**

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.

*Indian Standard*

# 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.

The formation of hydrogen or hydroxide can also affect the pH of the local tissue. This pH shift can have an effect on local tissue and alter the rate and mechanism of metallic conversion.

Completion of this first stage conversion of metal into degradation products can be confirmed for *in vitro* and *ex vivo* samples by various analytical methods including optical metallography, energy-dispersive X-ray analysis in scanning electron microscopy (SEM/EDX), or X-ray microtomography (μCT).

### 4.3.3 Subsequent degradation reactions

As the body contains a complex combination of electrolytes, the metal compounds first formed during metal conversion can be further reacted into secondary and ternary compounds. These reactions are dependent on the specific environment surrounding the implant and can differ depending on the implant site.

Some metal components undergo multiple corrosion reactions before reaching a final stable entity, which is either removed from the body or remains as a stable molecule contained in the body. The fate of each element of an alloy is dictated by local electrolytic environment in which the corrosion reactions take place, and can involve the formation of metal hydroxides, oxides and subsequent reactions into phosphates and carbonates.

The final degradation products of absorbable metals can be oxide-, phosphate- and calcium-based compounds such as apatite. These compounds are highly stable in the body and only removed by long term biological metabolic pathways.

### 4.3.4 Elemental impact on absorption

When alloying elements are used in an absorbable metal, their impact on the microstructure shall be considered with respect to the absorption process. Alloying elements can be in solution in the matrix, or in the form of intermetallic compounds, depending on relative solubilities and process history.

Different components of the metal, or chemically inhomogeneous regions of the metal, can convert into the degradation products at different rates. For example, intermetallic phases can corrode faster or slower than the matrix depending on their galvanic relationships[33][34]. In some cases, this relationship can be exploited during implant design to exert some control over the corrosion rate.

After most of the metallic conversion and subsequent oxide transformation processes have occurred, alloying elements in the form of intermetallic phase fractions (if more noble than the matrix) can remain at the implant site for a much longer time. It is therefore important to consider if components of the alloy can form more stable phases and how long they can reside in the body until converting to oxide or other degradation products and are absorbed. If sufficiently small, stable phases can be taken up by phagocytosis. If the residue time is expected to be long, the effect of their presence in the biological system should be considered.

### 4.3.5 Biological absorption

As the absorbable metal is converted to degradation products, the degradation products gradually disappear from the implantation site by dissolution, cellular absorption, transport, or other mechanisms. Consequently, the major components of an absorbable metal should consist primarily of metallic elements that can be either metabolized or excreted by the human body. The degradation products should be similarly well tolerated. Further, absorbable metal implant degradation should occur at a rate that is well-tolerated by the body both locally and systemically.

Appropriate means to conduct a biological evaluation of this degradation process are described in Clause 7.

### 4.3.6 Mechanical loss

An inherent feature of absorbable metals is eventual loss of mechanical support; the key concern in ensuring this does not happen prematurely. Thus, the rate and mode of degradation needs to be

adequately matched to the healing of the tissue at the implant site such that the site can accommodate implant failure.

Generally, absorbable metal corrosion occurs in varying degrees of uniformity. Uniform corrosion, where material erodes homogenously from exposed surfaces, is more predictable and in general preferable. Non-uniform corrosion leads to earlier and less predictable mechanical loss and can occur in one of three ways. Stress corrosion cracking is a phenomenon wherein the interactive effects of stress and corrosion lead to cracks even at relatively low stresses. Corrosion fatigue is related to stress corrosion cracking but incorporates cyclic rather than static loads. Finally, pitting corrosion occurs when local sections of the surface are corroded more rapidly than surrounding areas, forming cavities, which lead to loss of cross-sectional area and stress concentrations.

Evaluation of the potential for stress corrosion cracking and corrosion fatigue should be completed early in the design cycle to screen for susceptible materials. These phenomena could impact the performance of the implant.

NOTE 1 Further discussion of corrosion fatigue can be found in the guidance document under development as WK61103 by the ASTM F04.15.03 Absorbable Metals Task Group.

NOTE 2 Refer to [35] for a review of corrosion fatigue of magnesium alloys.

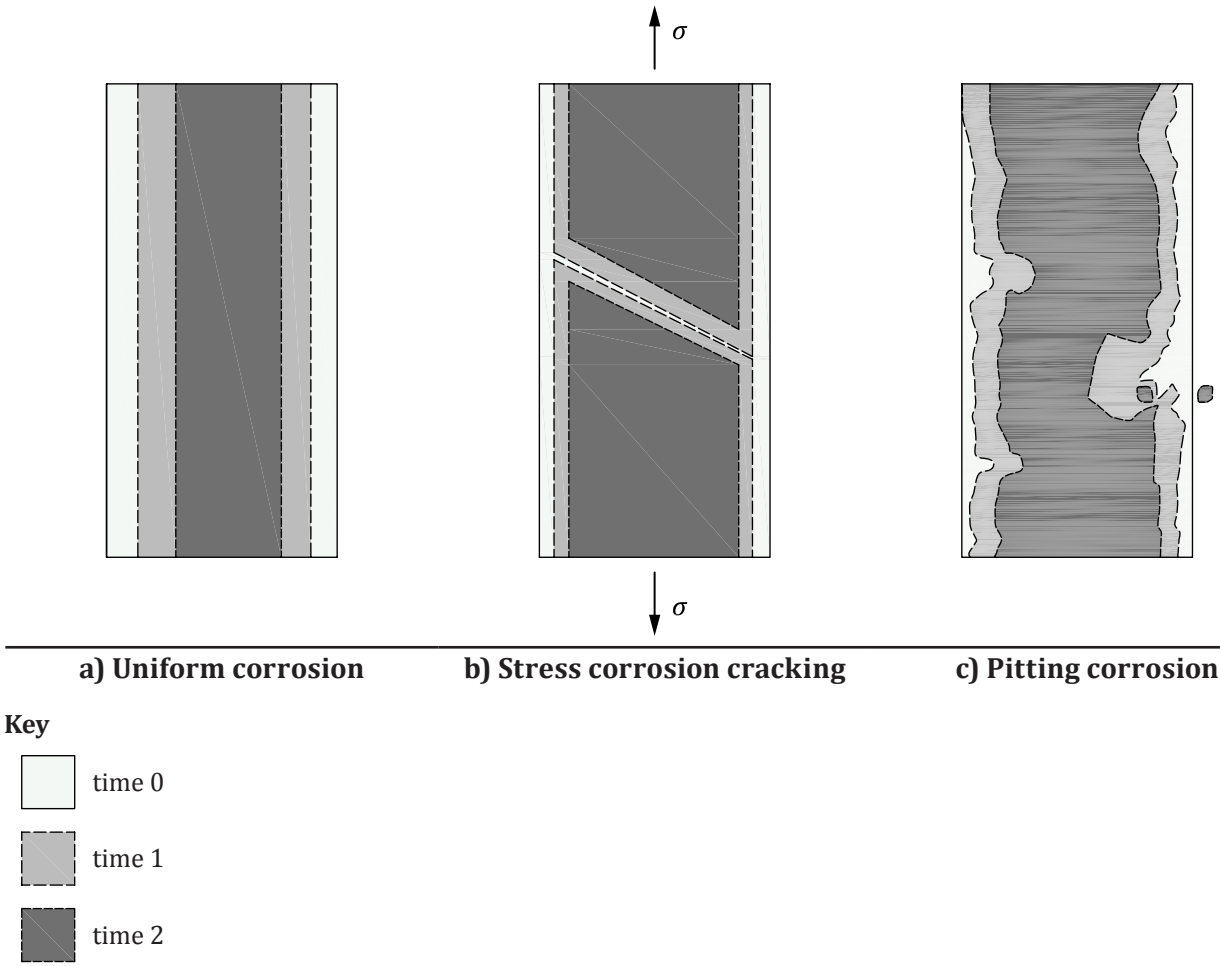


**Figure 2 — Metal corrosion modes**

While uniform corrosion leads to a relatively predictable rate of mechanical loss, stress corrosion cracking or pitting corrosion can cause premature mechanical loss, as illustrated in Figure 2.

# 5 Metallurgical and manufacturing considerations

## 5.1 General

In evaluating and characterizing the metallurgical aspects of an absorbable metal, the guidance of ASTM F3160 shall be considered.

Further discussion of key criteria is provided in 5.2 and 5.3.

## 5.2 Composition

The nominal concentrations of intentionally added alloying elements shall be specified and acceptable tolerance ranges shall be established to ensure consistent performance within the same lot and across multiple lots of material. Further, maximum levels of allowable impurities should be specified.

NOTE ASTM A751, ASTM B954, and ASTM E536 provide methods for quantitative assessment of alloy constituent levels in iron-based, magnesium-based, and zinc-based alloys, respectively.

## 5.3 Production process

### 5.3.1 General

The production processes used for an absorbable metal have significant influence on its microstructure and therefore mechanical and corrosion properties. Known major parameters influencing the performance of absorbable metals are discussed in 5.3.2 to 5.3.7.

### 5.3.2 Raw material purity

All raw materials contain impurities. In some cases, these can be substantially removed during the melting practice, but some amount remains in the material and the implant. Impurities known to have an impact on the overall implant performance and safety should be assessed, and a threshold specified in the production of absorbable materials. Refer to 4.2.1.4 for additional information.

### 5.3.3 Metal melting practice

As absorbable materials are eventually exposed to the body, careful consideration to the environment of the melting operation should take place to avoid contaminants. Melting practice can be optimized to minimize impurities from the molten metal prior to casting. Improper melting practice leads to inconsistent material and subsequent implant performance.

### 5.3.4 Metal casting

Various methods can be used to solidify, or cast, metals. The microstructure of a cast metal is governed primarily by the alloy chemistry and the cooling rate. For absorbable metal implants which are produced from cast materials, proper control of the cooling rate is crucial. Most implants, however, are fabricated from metals which are thermo-mechanically processed after casting. This subsequent thermomechanical processing, rather than the casting, dictates the microstructure of the final material.

### 5.3.5 Metal thermo-mechanical processing

Processes such as extrusion, rolling, forging, and drawing are regularly used to simultaneously modify the microstructure and produce a semi-finished product for input to subsequent manufacturing steps. All thermo-mechanical processing impacts the microstructure and therefore is critical in determining the performance of the absorbable metal and implant. Parameters which effect the microstructure should be evaluated for impact on absorbable metal performance and controlled accordingly. In some cases (e.g. zinc alloys), it might be necessary to evaluate the stability of the microstructure under normal storage conditions[32].

Thermo-mechanical processing can introduce processing aids or contaminants to the material. Methods where lubrication is used, such as extrusion or drawing, can lead to residual lubrication on or within the material. Careful consideration should be used when choosing the type of lubrication and when designing cleaning and monitoring steps. Contamination can occur from the equipment used in the mechanical processing. Wear of tooling is common and the effect on the performance of the material should be considered.

#### 5.3.6 Surface considerations

Changes in surface finish effectively change the surface area, increasing or decreasing the corrosion rate. Characterization and control of the surface condition is recommended for consistent performance.

#### 5.3.7 Implant cleaning, sterilization, packaging, storage, and handling

As with all medical implants, implants formed from absorbable metals are generally cleaned, sterilized, packaged, stored, and handled prior to and/or during implantation. The influence of these processes on total implant performance should be considered.

NOTE References [30] and [31] provide information on the impact of sterilization techniques on magnesium alloys.

## 6 Evaluation of *in vitro* degradation characteristics

### 6.1 General

When evaluating the *in vitro* degradation characteristics of an absorbable metal, the guidance provided in ASTM F3268 shall be considered.

NOTE An additional document on corrosion fatigue (WK61103) is currently under development by the ASTM F04.15 subcommittee.

### 6.2 Additional considerations

*In vitro* degradation testing in simulated body fluid is an important first step to understanding the corrosion behaviour of absorbable metals and implants fabricated from absorbable metals. However, it is not yet a substitute for *in vivo* testing. The use of a simulated body fluid alone does not fully replicate the complex environment (e.g. proteins, electrolytes, cells, stress, pH) of specific regions of the body. Both immersion and electrochemical test methods are suitable for comparing different absorbable metal compositions and lot-to-lot variability, but they cannot be expected to provide accurate estimates of *in vivo* corrosion rates.

Corrosion conditions of the *in vitro* experiment shall be closely controlled and monitored to achieve reproducible results across varying time points and laboratories. Conditions that affect the experiment are electrolyte composition, environmental gas exchange with the electrolyte, environmental gas pressure, changes in composition of the electrolyte during the experiment, biological contamination, temperature control of the experiment, pH and changes of pH of the electrolyte during the experiment, electrolyte movement over the surface of the test piece, and accumulated corrosion products. The use of a suitable reference material as an experimental control is highly recommended.

The addition of application-relevant applied mechanical loads (whether static or dynamic) during corrosion testing is often worthwhile to assess susceptibility to stress corrosion cracking or corrosion fatigue, as discussed in 4.3.6.

Various methods to evaluate the results of *in vitro* corrosion tests are described in ASTM F3268. Methods include mass loss, hydrogen gas evolution, measurement of corrosion products, metal ion release, or volume loss via imaging methods (e.g. ultrasonography, microtomography, or magnetic resonance imaging). The analysis can be somewhat complicated by the build-up of non-metallic corrosion products on the remaining metallic sample.

The mechanically relevant implantation period can be considered complete when the metallic volume of the absorbable metal has been fully converted into corrosion products.

With sufficient *in vitro* and *in vivo* data, an *in vitro – in vivo* correlation factor can be calculated.

# 7 Biological evaluation

## 7.1 General

To assist in developing an appropriate biological evaluation of an absorbable metal implant, guidance regarding utilization of ISO 10993-1 in both the *in vitro* and *in vivo* biological evaluation of absorbable materials and implants can be found in ISO/TS 37137-1[4)].

NOTE 1 "Biological evaluation" refers to the ISO 10993 series of tests and does not include guidance on other pre-clinical implant performance or safety studies.

ISO/TS 37137-1 provides discussion regarding the general considerations needed when biologically evaluating any absorbable implant, be it of a metallic, a polymeric, and/or a biologic-based composition. When evaluating the biological impact of an absorbable metal, the guidance provided in ISO/TS 37137-1 shall be considered.

NOTE 2 More specific guidance for the biological evaluation of absorbable magnesium materials is available in ISO/TR 37137-2[5)].

## 7.2 Biocompatibility of degradation products

Toxicological evaluation of degradation products and impurities should follow the recommendation of ISO 10993-17 and consider the degradation kinetics.

Local and systemic biological responses to degradation products can be evaluated using *in vivo* implantation and/or safety studies.

## 7.3 *In vitro* biological evaluation

In an ideal situation, *in vitro* biological test systems should reflect the physiological environment of the intended implant location. However, this is often not practically possible, and testing using standard *in vitro* biocompatibility methods (e.g. ISO 10993-5 for cytotoxicity) should be used. However, it should be noted that the conventional biological testing will likely only address the implants in their pre-degraded state (e.g. as manufactured).

NOTE 1 Since the release of ionic degradation products is expected during the *in vitro* or *in vivo* corrosion of an absorbable metal, results obtained from *in vitro* cell culture systems with finite pH buffer capacity might or might not reflect the *in vivo* response due to pH changes. Similarly, with static *in vitro* test systems, if degradation product induced osmolality changes occur, this can cause *in vitro* signals of toxicity that might or might not occur during *in vivo* exposure.

NOTE 2 See Reference [36] for further information on *in vitro* biological testing of magnesium alloys. See Reference [27] for further information on safety assessment of elemental impurities.

## 7.4 *In vivo* biological evaluation

### 7.4.1 Biocompatibility end point studies

For most implants, *in vivo* evaluation in an appropriate animal model is needed to provide a level of assurance that the implant performs as expected and does not produce adverse biological response throughout the degradation process. Guidance regarding the appropriate concerns and assessment

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

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

methods when undertaking an *in vivo* biological implantation evaluation can be found in ISO 10993-6 and other relevant parts.

General guidance regarding the special considerations needed when biologically evaluating an absorbable metal or implant in accordance with the ISO 10993 series can be found in ISO/TS 37137-1[6)].

Proper selection of retrieval or analysis time points is important to ensure the collected data are useful. These time points should be matched to the implant type and application and consider the expected tissue response and metal absorption times.

### 7.4.2 Animal safety and implant performance studies

Implant-specific assessments regarding both safety and implant performance are outside the scope of this document, and users should consult other relevant standards for specific requirements.

NOTE ISO/TS 17137, for example, provides guidance on cardiovascular absorbable implants.

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

# Annex A
(informative)

# Nomenclature of absorb, degrade and related terms[7)]

Synthetic implants fabricated from hydrolysable alpha-hydroxy polyesters have been described as "absorbable" since the first polyglycolide based sutures were commercialized in the United States in the 1970s. At that time, both poly(glycolide) (DEXON—Davis and Geck) and poly(glycolide-co-lactide) copolymer (VICRYL—Ethicon) based sutures were classified as "Absorbable Surgical Suture" by the United States Pharmacopeia (USP) and the United States Food Drug Administration (US-FDA), a designation that remains to this day. In contrast with "Nonabsorbable Surgical Suture," synthetic glycolide-lactide and collagen-based sutures undergo hydrolytic and/or enzymatic driven chain scission, generating degradation products that are then absorbed by the body. Since this designation, other terms such as "degradable" and "resorbable" have been used interchangeably to describe absorbable implants, with the prefix "bio-" often applied to all these terms.

Based on historical usage and regulatory precedent, this document preferentially utilizes the term absorb/absorbable/absorption to describe implantable synthetic hydrolysable polymers and devices. These same terms are also applied to natural polymers (e.g. collagen) and metals intended to undergo *corrosion in vivo*, since any degradation by-product – be it proteinaceous or ionic – is inherently absorbed by the host organism. The prefix "bio" is avoided since it is redundant in the context of implant applications.

"Resorb" and its derivatives are avoided since they are accepted medical terms routinely utilized to describe natural resorption processes present in dynamic tissue, such as osteoclastic driven bone remodeling.

"Degrade" and its various derivatives are avoided when referring categorically to either an implantable device or a raw material since common utilization is routinely applied broadly to include other natural processes unrelated to medical device use that cause materials to either intentionally or unintentionally break down into chemical and/or particulate matter. However, use of the term "degrade" and its derivatives is considered acceptable when specifically referring to breakdown processes (e.g. chain scission, corrosion) within the absorbable material or implantable device (e.g. "The absorbable implant degrades through hydrolysis." or "During extrusion, absorbable polyglycolide is prone to thermal degradation.").

Since a variety of alternative terms to absorbable have been historically utilized interchangeably both within and across surgical disciplines (but intermittently with inferred differentiation), the user of this document is cautioned that effective searches of the published literature should include all potential terms used to describe an absorbable implant or material. These include, but are not limited to:

— absorbable and its derivatives;

— bioabsorbable and its derivatives;

— degradable and its derivatives;

— biodegradable and its derivatives;

— resorbable and its derivatives;

— bioresorbable and its derivatives.

---

7) Adopted and modified with permission from ASTM F2902-16, X4. Copyright ASTM International. The most current edition can be obtained from www.astm.org.

# Bibliography

[1] ISO 643, *Steels — Micrographic determination of the apparent grain size*

[2] ISO 10993 (all parts), *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

[3] ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

[4] ISO 11737-1, *Sterilization of health care products — Microbiological methods — Part 1: Determination of a population of microorganisms on products*

[5] ISO 11737-2, *Sterilization of health care products — Microbiological methods — Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process*

[6] ISO 11737-3, *Sterilization medical devices — Microbiological methods — Part 3: Guidance on evaluation and interpretation of bioburden data*[8)]

[7] ISO/TS 17137, *Cardiovascular implants and extracorporeal systems — Cardiovascular absorbable implants*

[8] ISO 19227, *Implants for surgery — Cleanliness of orthopedic implants — General requirements*

[9] ISO/TS 37137-2, *Cardiovascular biological evaluation of medical devices — Guidance for absorbable implants — Part 2: Standard guide for absorbable metals*[9)]

[10] ANSI AAMI ST72, *Bacterial endotoxin — Test methods, routine monitoring and alternatives to batch testing*

[11] ASTM A36, *Standard specification for carbon structural steel*

[12] ASTM A314, *Standard specification for stainless steel billets and bars for forging*

[13] ASTM A751, *Standard test methods, practices, and terminology for chemical analysis of steel products*

[14] ASTM B86, *Standard specification for zinc and zinc-aluminum (ZA) alloy foundry and die castings*

[15] ASTM B107/B107M, *Standard specification for magnesium-alloy extruded bars, rods, profiles, tubes, and wire*

[16] ASTM B93/B93M, *Standard specification for magnesium alloys in ingot form for sand castings, permanent mold castings, and die castings*

[17] ASTM B90/B90M, *Standard specification for magnesium-alloy sheet and plate*

[18] ASTM B954, *Standard test method for analysis of magnesium and magnesium alloys by atomic emission spectrometry*

[19] ASTM E112, *Standard test methods for determining average grain size*

[20] ASTM E340, *Standard practice for macroetching metals and alloys*

[21] ASTM E407, *Standard practice for microetching metals and alloys*

[22] ASTM E536, *Standard Test Methods for Chemical Analysis of Zinc and Zinc Alloys*

---

8) Under preparation. Stage at the time of publication: ISO/TS 11737-3:2020.

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

[23] ASTM E1382, *Standard test methods for determining average grain size using semiautomatic and automatic image analysis*

[24] ASTM E2627, *Standard practice for determining average grain size using electron backscatter diffraction (EBSD) in fully recrystallized polycrystalline materials*

[25] ASTM F2902, *Standard Guide for Assessment of Absorbable Polymeric Implants*

[26] U.S. FOOD & DRUG ADMINISTRATION, Biological Response to Metal Implants. Washington, DC. 2019

[27] U.S. FOOD & DRUG ADMINISTRATION, Q3D Elemental Impurities: Guidance for Industry. Washington, DC. 2015

[28] ASM Specialty Handbook: Magnesium and Magnesium Alloys. Materials Park, OH: ASM International, 1999

[29] Zheng YF., Biodegradable Metals, *Material Science and Engineering R,* 2014, **77**, pp. 1-34

[30] Seitz JM., The Effect of Different Sterilization Methods on the Mechanical Strength of Magnesium Based Implant Materials, *Advanced Engineering Materials*. 2011, **13**, pp. 1146-1151

[31] Johnston S., The influence of two common sterilization techniques on the corrosion of Mg and its alloys for biomedical applications. *J. Biomedical Materials Research B*, 2017, **106**, pp. 1907-1917

[32] Jin H., Novel high-strength, low-alloys Zn-Mg (<0.1wt%Mg) and their arterial biodegradation. *Materials Science and Engineering C.* 2018, **84**, pp. 67-79

[33] Cihova M., Biocorrosion Zoomed In: Evidence for Dealloying of Nanometric Intermetallic Particles in Magnesium Alloys. Advanced Materials. 2019, 1903080

[34] Hofstetter J., High-Strength Low-Alloy (HSLA) Mg-Zn-Ca Alloys with Excellent Biodegradation Performance. *JOM*. 2014, **66**, pp. 566-572

[35] Singh Raman R.K., Resistance of Magnesium Alloys to Corrosion Fatigue for Biodegradable Implant Applications: Current Status and Challenges. *Materials*. 2017, **10**, pp 1316-1327

[36] Jung O., Improved *In vitro* Test Procedure for Full Assessment of the Cytocompatibility of Degradable Magnesium Based on ISO 10993-5/-12. *Int. J. Molecular Sciences*. 2019, **20**, pp 255-275

**Bureau of Indian Standards**

BIS is a statutory institution established under the *Bureau of Indian Standards Act*, 2016 to promote harmonious development of the activities of standardization, marking and quality certification of goods and attending to connected matters in the country.



**Review of Indian Standards**

Amendments are issued to standards as the need arises on the basis of comments. Standards are also reviewed periodically; a standard along with amendments is reaffirmed when such review indicates that no changes are needed; if the review indicates that changes are needed, it is taken up for revision. Users of Indian Standards should ascertain that they are in possession of the latest amendments or edition by referring to the website-www.bis.gov.in or www.standardsbis.in.

This Indian Standard has been developed from Doc No.: MHD 02 (25942).

## Amendments Issued Since Publication

| Amend No. | Date of Issue | Text Affected |
|---|---|---|
| | | |
| | | |
| | | |
| | | |

**BUREAU OF INDIAN STANDARDS**

**Headquarters:**

Manak Bhavan, 9 Bahadur Shah Zafar Marg, New Delhi 110002
*Telephones*: 2323 0131, 2323 3375, 2323 9402 *Website*: www.bis.gov.in

| **Regional Offices:** | | *Telephones* |
|---|---|---|
| Central | : 601/A, Konnectus Tower -1, 6th Floor, DMRC Building, Bhavbhuti Marg, New Delhi 110002 | 2323 7617 |
| Eastern | : 8th Floor, Plot No 7/7 & 7/8, CP Block, Sector V, Salt Lake, Kolkata, West Bengal 700091 | 2367 0012<br>2320 9474 |
| Northern | : Plot No. 4-A, Sector 27-B, Madhya Marg, Chandigarh 160019 | 265 9930 |
| Southern | : C.I.T. Campus, IV Cross Road, Taramani, Chennai 600113 | 2254 1442<br>2254 1216 |
| Western | : 5th Floor/MTNL CETTM, Technology Street, Hiranandani Gardens, Powai Mumbai 400076 | 25700030<br>25702715 |

**Branches** : AHMEDABAD, BENGALURU, BHOPAL, BHUBANESHWAR, CHANDIGARH, CHENNAI, COIMBATORE, DEHRADUN, DELHI, FARIDABAD, GHAZIABAD, GUWAHATI, HARYANA (CHANDIGARH), HUBLI, HYDERABAD, JAIPUR, JAMMU, JAMSHEDPUR, KOCHI, KOLKATA, LUCKNOW, MADURAI, MUMBAI, NAGPUR, NOIDA, PARWANOO, PATNA, PUNE, RAIPUR, RAJKOT, SURAT, VIJAYAWADA.

Published by BIS, New Delhi