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**Biological evaluation of absorbable  
medical devices —**

**Part 1:  
General requirements**

*Évaluation biologique des dispositifs médicaux résorbables —*

*Partie 1: Exigences générales*

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## Foreword

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

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

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

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

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

This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices*.

A list of all parts in the ISO 37137 series can be found on the ISO website.

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

## Introduction

Absorbable implants are intentionally designed to degrade and therefore release degradation products into the patient, a feature making these products fundamentally different from other medical devices that are not intended to be absorbed by the patient's body.

The provided content is intended to describe potential approaches to perform biological evaluation of absorbable implants to support the safety of such absorbable medical devices.

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# Biological evaluation of absorbable medical devices —

## Part 1: General requirements

### 1 Scope

This document specifies the requirements for the evaluation of absorbable medical devices during a biological risk assessment based on ISO 10993-1, including a clarification of the terms "absorb", "degrade" and other related terms (see [Annex A](#)).

### 2 Normative references

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

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

### 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/>

NOTE For further discussion of utilized terminology and for a list of potential terms to be included in a literature search see [Annex A](#).

#### 3.1

##### **absorb**

##### **absorption**

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

[SOURCE: ISO 10993-6:2016, 3.1]

#### 3.2

##### **degradation product**

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

#### 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 or simulated clinical use

Note 1 to entry: In absorbable medical 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).

[SOURCE: ISO 10993-12:2020, 3.9 modified — Note 1 to entry has been added.]

### 3.5 final product

medical device or medical device component that has been subjected to all manufacturing processes for the “to be marketed” medical device including packaging and if applicable, sterilization

Note 1 to entry: The final medical device or sterilized finished medical device has the same meaning as the final product in this document.

[SOURCE: ISO 10993-1:2018, 3.8 modified — Note 1 to entry has been added.]

## 4 General considerations

Biological evaluation is the assessment of a medical device, medical device component, or a material to determine if either the medical device material or the medical device design, or both is likely to result in an unacceptable adverse systemic and/or local effect on the surrounding cells and/or tissues. Biological evaluation of an absorbable material shall be conducted in accordance with ISO 10993-1, and other relevant parts of ISO 10993. Any modifications to the methods specified in the ISO 10993 series of standards shall be justified in a written biological risk assessment.

Degradation products can be released into either the extraction media or tissue, or both or remain in the degrading implant. Released degradation products that are generated either prior to product use (i.e. during manufacturing, processing or shelf-life) or during product use should be characterized (e.g. chemical identity, quantity, toxicity, and particulates (see 8.19) as applicable).

Identification of the degradation products may be derived from chemical and physical analyses of the implant or through a theoretical judgement. Literature data for implants manufactured from absorbable materials with an established history of safe clinical use (at the intended anatomical location) can be helpful in identifying expected degradation products and potential toxicities if there is an adequate scientific rationale for the applicability of the referenced data.

Differences in processing might impact the biocompatibility of the final product. Simply demonstrating identical composition is not sufficient since many other factors (e.g. sequence distribution of copolymers, crystallinity, degree of purity, grain size and crystal structure for metals, oxidation level of cellulose derivatives, molecular weight, mode of sterilization) can influence absorbable material performance and biocompatibility. A finished device biological risk assessment using information from chemical analyses of the absorbable material(s) and its(their) degradation products, in conjunction with toxicity data from the literature, can support some of the biological end points described in ISO 10993-1 if a scientifically sound justification can be provided for their clinical relevance.

Additionally, standard extraction conditions and biocompatibility tests are not designed to assess biological responses to absorbable devices throughout degradation. Testing at different stages of device degradation can be needed to demonstrate safety, as absorbable devices are constantly changing in the physiological environment and may present different adverse biological responses at different stages of degradation.

By design, most polymeric, ceramic, or metallic absorbable materials inherently produce relatively low molar mass degradation products *in vivo*. Since the presence of these degradation products within the extraction media can potentially impact the results of some biocompatibility tests and 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 degradation products could alter the pH and/or osmolality of an *in vitro* biological test system. Since the *in vivo* condition can provide the combined presence of perfusion and carbonate equilibria, such *in vitro* results might not reflect the *in vivo* response.

If under standard test conditions an adverse result occurs in an *in vitro* assay, one can consider the test system and degradation products when deciding if repeat testing may be useful in the context of the overall biological risk assessment. Extract adjustments (e.g. dilution, pH, osmolality) can be used as part of the overall biological risk assessment strategy to determine the cause of the test failure which may inform the overall interpretation of results. Testing of multiple extract dilutions can be used to determine the point at which the extract passes the *in vitro* assay which may allow for the adverse response to be viewed in the context of other currently marketed absorbable devices (e.g. similar materials, intended use, and biocompatibility observations, such as cytotoxicity). As described above, testing extracts after pH and/or osmolality adjustment can be useful; however, any extract adjustment shall be justified in the biological risk assessment, as pH and osmolality changes can result in adverse local and/or system effects that are clinically relevant. A justification for extract adjustment shall include scientific evidence (e.g. clinically-relevant animal study, chemical characterization, literature references) to support the relevance of the adjusted extract for the overall biological risk assessment evaluation.

A justification shall include the potential impact of the extract adjustment on extract chemistry to support that the adjusted extract is representative of the device. Any extract adjustments shall be well-described, including the initial pH or osmolality measurements, extract adjustment procedure (e.g. chemical, chemical concentration, volume added), and final pH or osmolality measurements. Appropriate control group(s), per ISO 10993-12, shall be included to address the potential impact of any extract adjustments on the *in vitro* results.

If particulates form during sample preparation, the particulates shall neither be filtered, centrifuged or allowed to settle prior to introducing the sample to the *in vitro* test system. If particulates cause interference in the original testing, repeat testing with particulate removal can be considered if justified in the biological risk assessment. For *in vivo* testing, particulates shall neither be filtered, centrifuged or allowed to settle prior to introducing the sample, except in cases where animal welfare concerns preclude intravascular injection of extracts containing particulates.

Ultimately the biological risk assessment shall consider all pertinent data from, e.g., testing, prior experience, literature; and present a coherent scientific justification explaining how the data interrelate and demonstrate the safety of the absorbable device with a reasonable level of scientific evidence (see ISO 10993-1:2018, Clause 7).

Degradation products from some intentionally absorbable materials can be chemical components (which could include active pharmaceutical ingredients [APIs] in drug-device combination products) that have previously been identified, characterized, and had biological evaluation performed. For these materials, the biological evaluation can be performed in accordance with ISO 10993-17. The evaluation of local effects can require additional data.

Since absorbable materials are intended to degrade, transient particulate matter may be present as the medical device breaks down. The particle size, morphology, generation rate, and mobility can all affect biological response and should be considered in the biological risk assessment.

Rate of absorption through the device lifetime needs to be understood to accurately assess the biological safety. Different rates of absorption need to be identified and the conditions that could potentially impact the rate need to be considered (e.g. change in pH, temperature, tissue environment, material phase change). An understanding of the potential clinical impact of degradation is needed and the effect of degradation on the potential for adverse effects (systemic and local) shall be discussed in the biological risk assessment.

NOTE 1 Guidance regarding the identification and assessment of chemical degradation products and leachables can be found in ISO 10993-9, ISO 10993-13, ISO 10993-14, ISO 10993-15, ISO 10993-17 and ISO 10993-18. Guidance regarding aspects of the biological evaluation of particulate nanomaterials can be found in ISO 10993-22.

NOTE 2 pH adjustment can change the osmolality, depending on the extract contents and what is used for adjustment. If it can be justified that the dilution will reduce the osmolality without affecting the pH, pH adjustments can be done prior to osmolality adjustments.

## 5 Test article considerations

Final product evaluation should be conducted on sterilized finished medical devices or test samples that are representative of the final medical device.

If the final product is not used for testing, a rationale shall be provided that includes:

- a description of all differences between the test article and the final product;
- data that demonstrate that all differences between the test article and the final product do not impact their chemistry or degradation kinetics.

## 6 Sterilization considerations

The sterilization methods and conditions should be carefully considered and justified prior to biological testing. For irradiation sterilization, caution should be undertaken when medical devices are sterilized using a higher radiation dose. With an increased dose, different chemical degradation products can be produced in substantial amounts, or non-toxic chemicals can be degraded into toxic species. Conversely for other sterilization methods, toxicity might increase with increased exposure time/duration (e.g. penetration of ethylene oxide [EO] residuals).

## 7 Drug-device combination product considerations

For medical devices that include an API, the presence of a pharmaceutical can affect the response in a biocompatibility assay. As such, separate testing of the medical device both with and without the API should be considered, but might not be necessary. In addition, available information on the API alone, as well as any potential interaction between the pharmaceutical ingredient(s) and the as-manufactured absorbable materials or degradation product(s) should be evaluated for their impact on medical device biocompatibility and degradation.

APIs can potentially impact the results of biocompatibility assays with drug-induced positives when extracted at the recommended extraction ratio(s) detailed in ISO 10993-12. Use of a range of dilutions of the sample or a partition of the overall medical device evaluation may be considered as part of the overall risk management process if the API is expected to be toxic for the particular end point being studied. Use of a range of dilutions may not allow medical device biocompatibility to be adequately assessed if the API mode of action directly impacts the specific biocompatibility test (e.g. when performing cytotoxicity testing on a medical device that includes a cytotoxic API). In these instances, additional testing of a finished medical device constructed without the API is recommended.

NOTE 1 For vascular device-drug combination products, additional guidance can be obtained in ISO 12417-1.

NOTE 2 Additional tests can be appropriate to study the chemical and biological interaction with the drug, *in vivo* drug migration, toxicological profile, degradation products, and controlled release of the drug (therapeutic dose) to determine toxicological profile and pharmacological safety and efficacy.

## 8 Evaluation of absorbable medical devices in the context of the ISO 10993 series

### 8.1 General

Clause 8 provides clarification on the biological evaluation of absorbable medical devices and is intended to be used in conjunction with the respective part of the ISO 10993 series.