TECHNICAL SPECIFICATION

ISO/TS 37137-1

First edition
2021-03

Biological evaluation of absorbable medical devices —

Part 1: General requirements

Évaluation biologique des dispositifs médicaux résorbables —

Partie 1: Exigences générales

Reference number
ISO/TS 37137-1:2021(E)

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Published in Switzerland

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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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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.

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.

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.

8.2 ISO 10993-1, evaluation and testing within a risk management process

Degradation information (e.g. rate, duration, chemical changes, mechanisms, degradation products) of the absorbable device, component(s), or material(s) shall be provided in the biological risk assessment documentation, including parameters that could affect the degradation process. Expected mechanical changes (under *in vitro* or *in vivo* degradation testing conditions) also need to be understood. A general framework for degradation characterization is provided in ISO 10993-9, with guidance for hydrolysable polymers provided in ISO 13781. Guidance for *in vitro* degradation characterization of absorbable metals can be found in ASTM F3268.

The biological risk assessment of absorbable medical devices shall include all the relevant end points identified in ISO 10993-1:2018, Annex A, with consideration of 8.2 to 8.22, as relevant. In addition, degradation and toxicokinetics are typically required end points. Reproductive and developmental toxicity should be considered and discussed for any absorbable medical devices used in the reproductive system or with potential for systemic distribution in paediatric patients or those of reproductive age.

The biological risk assessment shall be conducted in accordance with ISO 10993-1:2018, Clause 7, by individuals with the necessary knowledge and experience.

Within the ISO 10993 series, LONG-TERM is perceived as including CHRONIC or PERSISTENT implants that are physically present longer than 30 d. If an absorbable material and/or its degradation products are expected to persist in the body longer than 30 d, such medical devices should be evaluated using the LONG-TERM implant test criteria.

8.3 ISO 10993-2, animal welfare requirements

Because *in vitro* models can be susceptible to pH and osmolality related issues, determination of the *in vivo* relevance of such tests often makes the use of animal models more likely to be necessary for absorbable medical devices.

In addition, assessment of the impact of mechanical loading and tissue environment on degradation and associated biological response within a clinically-relevant animal model may be utilized to evaluate device functionality and safety (e.g. chronic toxicity and implantation evaluation). Such studies shall adhere to the basic principles of animal welfare.

8.4 ISO 10993-3, tests for genotoxicity, carcinogenicity, and reproductive toxicity

In cases where the degradation products of an absorbable material are well known, primary literature may be used to evaluate genotoxicity, carcinogenicity, developmental and reproductive toxicity of the degradation products. If degradation products are not known, chemical analysis with literature assessment or genotoxicity testing of extracts may be undertaken.

Since absorbable materials carry potential for either degradation dissolution during extraction, or both, the test extract can be monitored to ensure that the amount added to the cells does not exceed toxicity limits for each assay. If the extract causes significant toxicity, dilution to the respective toxicity limit is acceptable. Lower concentrations may be utilized if evaluated as part of a range of concentrations up to the optimal toxicity limit defined in OECD guidelines for *in vitro* mammalian cell micronucleus test (OECD 487), for *in vitro* chromosomal aberration test (OECD 473), and for *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD 490). The cytotoxicity limits in current OECD guidelines are 55 % ± 5 % for the *in vitro* chromosomal aberration and *in vitro* micronucleus assays and 20 % to 10 % of the relative total growth (RTG) for the mouse lymphoma assay.

Manipulation of the extract to address pH or osmolality issues should be avoided unless utilized in the context of Clause 4. If a novel absorbable material is being evaluated, an *in vivo* test for genetic toxicity should be considered in the genetic toxicity test battery. Either a *mammalian erythrocyte micronucleus test* (OECD 474), *mammalian bone marrow chromosomal aberration test* (OECD 475), or an *in vivo* mammalian alkaline comet assay (targeting organs or tissues other than bone marrow) (OECD 489) should be considered. The choice of assay shall be justified. If the quantities of materials in the test extract are below the threshold of detection of the *in vivo* assay, the test does not need to be performed.