TECHNICAL SPECIFICATION

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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

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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 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.

Additional guidance on considerations for performing genotoxicity tests can be found in ISO 10993-3 and ISO/TR 10993-33.

8.5 ISO 10993-4, selection of tests for interactions with blood

In vitro haemolysis tests can be affected by pH and osmolality related issues that might not be clinically relevant. If under standard test conditions an adverse result occurs in the *in vitro* haemolysis test, one can consider additional testing to assess whether the failure is the result of pH or osmolality effects. Measurements of extract pH and osmolality should be provided. Additionally, testing of multiple extract dilutions (to the point at which the extract is non-haemolytic) with pH/osmolality extract measurements can be considered. Testing of extracts after pH and/or osmolality adjustment can be considered in repeat testing; however, any pH or osmolality adjustment shall be justified in the biological risk assessment and detailed information on the extract adjustment shall be provided (see Clause 4).

Supplemental simulated use implantation studies are often of critical importance for assessing degradation effects on various aspects of haemocompatibility (e.g. thrombogenicity).

8.6 ISO 10993-5, tests for *in vitro* cytotoxicity

When an adverse result occurs under standard cytotoxicity testing, the following potential investigational methods can be considered by the risk assessor to help understand the initial results:

— Dilution: Extracts from absorbable materials can be diluted (a range of dilutions should be used including the 100 % neat extract), provided they include the relevant degradation products. When using dilutions of the extract, it is often useful to compare the IC_{50} to IC_{50} values for control materials.

— Sequential extract: Conduct separate sequential extracts representing different stages in the material's overall degradation. Test extracts prepared to reflect different stages of degradation can be evaluated independently. Given the variety of materials and clinical applications, it is up to the user to determine which time frames are appropriate.

— Pre-degradation: Use a pre-degraded material with a defined temperature and duration of the degradation or the extraction to deliver a controlled degradation test specimen that reflects an appropriately partitioned stage of degradation. For absorbable materials, extraction at temperatures above 37 °C can lead to non-representative changes in degradation mode and should, if possible, be avoided. Caution should be exercised for polymers extracted at temperatures that are near either a glass transition or melting temperature. Additionally, absorbable metals can potentially develop differing either corrosion chemistry or modes (e.g. pitting, crevice), or both at elevated temperatures.

— The manipulation of the extract to address pH or osmolality issues should be avoided in any of the preceding investigation routes unless utilized in the context of Clause 4.

— Any adverse cytotoxicity findings can be studied further using histological assessment of the local response in implantation studies (see ISO 10993-6). The selection of implantation test methods shall be explained and justified in the biological risk assessment.

8.7 ISO 10993-6, Tests for local effects after implantation

ISO 10993-6 incorporates information for assessment of absorbable medical devices. Simulated use implantation studies are of critical importance for assessing local biological responses and absorption of absorbable medical device materials.

Both tissue properties and clinically relevant loading conditions shall be considered. In the evaluation for local effects after implantation, consideration should be given for the analysis of organs (e.g. draining lymph nodes) that are exposed to the degradation products. Justification for the organs selected for evaluation shall be provided in the biological risk assessment.

The material used as a control should be a commercially available absorbable material whose clinical acceptability and biocompatibility characteristics are generally accepted. The composition and absorption rate of the control material should be as similar as possible to the medical device under test. ISO 10993-6:2016, 5.3.3 should be noted.

When a scientific justification is provided for ending the study before full absorption, evidence that a steady-state biological tissue response has been achieved shall be provided. Additionally, *in vitro* degradation characterization through complete degradation can support ending the implantation study prior to complete absorption if an *in vitro-in vivo* correlation (IVIVC) for degradation can be established. Where the device has different rates of absorption at different stages of clinical use, the different absorption rates need to be considered in the local effects assessment or a rationale provided (e.g. PLLA initially having steady rate of absorption followed by sudden increase in absorption might be seen a number of years post-implantation).

8.8 ISO 10993-7, ethylene oxide sterilization residuals

The release kinetics for EO can be affected by the degradation of the absorbable material. When estimating the average daily exposure of EO residuals for medical devices, the daily EO/ethylene chlorohydrin (ECH) concentration should be derived using the experimentally determined release profile rather than dividing by a default number of days unless other calculations can be justified.

8.9 ISO 10993-9, framework for identification and quantification of potential degradation products

The user shall consider ISO 10993-9 when assessing absorbable medical devices and the evaluation shall be included in the biological risk assessment.

During degradation, it can be appropriate to control pH to a clinically relevant range, especially if pH can affect the rate of degradation or the mixture of the degradation products. The risk assessor should consider the potential impact of pH on this end point and provide both unadjusted and adjusted test data if necessary.

8.10 ISO 10993-10, tests for skin sensitization

No additional considerations beyond ISO 10993-10 for skin sensitization testing are recognized at this time.

NOTE If validated *in vitro* alternatives become available to address this end point, and are qualified for use with absorbable medical devices, they are preferred.

8.11 ISO 10993-11, tests for systemic toxicity

For implantable absorbable materials, assessment of systemic toxicity by implantation at a clinically relevant site in the animal model is recommended (if systemic toxicity is relevant for the medical device category in ISO 10993-1:2018, Annex A). In simulating the intended clinical use of the device in an animal model, the local tissue and systemic responses, the device degradation, metabolism, and systemic distribution should be evaluated. The material mass-to-body weight ratios should be relevant to the intended clinical exposure.

Therefore, it is recommended the mass or surface area of the medical device, according to the weight of the animal (medical device mass in g per kg body weight or medical device surface area in cm^2 per kg body weight), is representative of the intended maximum or exaggerated clinical exposure when expressed per body weight. Multiple device implants can be used to ensure the animals are exposed to exaggerated conditions.

The impact of mechanical loading and tissue environment on degradation and the related biological response should be addressed in a well-designed effectiveness or functionality study which should be included in the considerations of the biological risk evaluation. The test period(s) shall be relevant to the intended degradation and absorption time for the medical device.

Justification for the organs selected for review of systemic effects shall be provided.

To ensure patient safety, the risk of a pyrogenic response originating from Gram-negative bacterial endotoxin or other sources of pyrogens (such as material-mediated pyrogen) should be addressed for absorbable implants, consistent with ISO 10993-11:2017, Annex G.

8.12 ISO 10993-12, sample preparation and reference materials

With absorbable materials, the general risk of invalid test results increases as solvent characteristics and extract conditions depart from physiologic relevance.

a) Since solvent selection, presence of proteins, and electrolyte composition (if applicable) can affect (i.e. increase, decrease, eliminate) the rate of absorbable medical device degradation during extraction, the user should understand the relative impact the selected solvent system will have on both the degradation rate and the test result.

b) Since an absorbable sample's degradation mode/mechanism can be affected by the extraction solvent (including shifts in pH), the user should evaluate whether the resulting degradation products are theoretically likely to be compositionally representative of what occurs under physiologically relevant conditions.

c) With absorbable materials, consideration should be made regarding the potential for solvent-induced physiologically irrelevant degradation.

Regarding extraction duration and/or temperature, extraction parameters can accelerate degradation of an absorbable material and can potentially generate overwhelming amounts of degradation products that can affect the test result. In effect, extraction for 24 h or 72 h might concentrate degradation products that *in vivo* could be both buffered and broadly perfused over that same duration. With absorbable materials, extraction temperature(s) should to be selected with consideration of the specific thermal limitations of the material. If adjustments from standard conditions are used, they shall be documented and justified as described in Clause 4.

NOTE Although elevated concentrations can be unlikely to occur under *in vivo* conditions, when a failed test occurs in an *in vitro* test system, such elevated concentrations might suggest potential toxicity of the degradation product.

For polymeric absorbable materials, extraction above *in vivo* temperatures that are near or above the glass transition temperature can lead to changes in the polymer properties (e.g. degradation) that are not representative of clinical conditions and should be avoided. For absorbable metals, elevated extraction temperatures can introduce new and potentially unrepresentative corrosion mechanisms. Thus, for some absorbable polymers and metals, the standard extraction temperatures listed in ISO 10993-12 (except 37 °C) might not be applicable. When evaluating absorbable medical devices, extraction of partially (pre)degraded materials and their related degradation products can be considered.

8.13 ISO 10993-13, identification and quantification of degradation products from polymeric medical devices

The user shall consider ISO 10993-13 when assessing absorbable polymers and the evaluation shall be included in the biological risk assessment.

8.14 ISO 10993-14, identification and quantification of degradation products from ceramics

The user shall consider ISO 10993-14 when assessing absorbable ceramics and the evaluation shall be included in the biological risk assessment.

8.15 ISO 10993-15, identification and quantification of degradation products from metals and alloys

The user shall consider ISO 10993-15 when assessing absorbable metals/alloys and the evaluation shall be included in the biological risk assessment.

8.16 ISO 10993-16, toxicokinetic study design for degradation products and leachables

Absorbable materials are intentionally designed to degrade in the patient and expose the patient to chemical degradation products. Consideration of the toxicokinetics of these degradation products is essential and shall be included in the biological risk assessment. Data or primary literature references supporting toxicokinetic and/or ADME evaluations shall be provided in the biological risk assessment.

8.17 ISO 10993-17, establishment of allowable limits for leachable substances

The user shall consider ISO 10993-17 when assessing absorbable medical devices and the evaluation shall be included in the biological risk assessment.

An absorbable material, its extracts, and/or its degradation products can be expected to be absorbed and potentially excreted by the body over a definable period of time. As the degradation profile is likely to be nonlinear, the use of mathematical averaging to estimate daily exposure might not be representative of the worst-case exposure (e.g. bolus release). Normalization to the 30 d and the 25 000 d (68 years) maximum exposure durations is inappropriate. Thus, determination of the maximum allowable limit should be derived using maximum daily exposure estimates and shall consider maximum number of medical devices per patient, per procedure, and cumulative use (if applicable).

8.18 ISO 10993-18, chemical characterization of materials

The scope of ISO 10993-18 states that it does not address the identification or the quantification of degradation products. However, the general concepts listed in the document can be useful for the biological risk assessment.

Since ISO 10993-18 states that it does not address degradation products and includes test conditions that could either accelerate or change either their composition or their quantities, or both, either the standard's applicability or the ability to provide results that adequately differentiate between inadvertent and intentional degradation products, or both, should be reviewed prior to assessing absorbable materials, medical devices, or medical device components. For instance, chemical extractions typically go beyond exhaustive conditions to total dissolution, and additional concerns such as intermediate chemistry during absorption process, crystallinity, sequence distribution and oxidation state are often important for proper characterization of absorbable medical device materials.

8.19 ISO/TS 10993-19, physico-chemical, morphological and topographical characterization of materials

The user shall consider ISO/TS 10993-19 when assessing absorbable medical devices and their degradation products, including particulate matter, and the evaluation shall be included in the biological risk assessment. Since absorbable materials are intended to degrade, a potential exists for generation of transient particulate matter as the medical device breaks down. An understanding of the potential clinical impact of such degradation (e.g. for intravascular implants, embolization leading to coronary or cerebral infarction should be considered) is needed. Formulation chemistry as well as particle size could affect biological responses and shall be discussed in the biological risk assessment. Justifications shall be provided by individuals with necessary knowledge and experience.

NOTE Some transient particulate matter can have very long degradation time, for example large hydroxyl apatite crystals that can be a part of some degradable bone substitutes can degrade very slowly.

8.20 ISO/TS 10993-20, principles and methods for immunotoxicology testing of medical devices

The user is directed to ISO 10993-1:2018 6.3.2.15 regarding the potential need for immunotoxicology testing. If appropriate, the user shall use ISO/TS 10993-20 when performing immunotoxicology testing of absorbable medical devices and the evaluation shall be included in the biological risk assessment.

8.21 ISO/TR 10993-22, guidance on nanomaterials

Since absorbable materials are intended to degrade, transient particulate matter can be present as the medical device breaks down. ISO/TR 10993-22 can be used for the evaluation of nano-objects generated as products of degradation. The criteria for determining the acceptability of the material for the intended purpose shall be reported in the biological risk assessment.

8.22 ISO 10993-23, tests for irritation

8.22.1 General

The user shall follow the recommendations in ISO 10993-23 when assessing absorbable medical devices and the evaluation shall be included in the biological risk assessment.

8.22.2 Tests for irritation

Absorbable materials can often cause pH changes in extracts and this should be measured before testing in animals, as described in ISO 10993-10:2010, 6.2.

If data are available to demonstrate that these pH extremes are not relevant to the clinical application, then adjustment of the extract pH to better reflect actual physiological conditions per clinical use within the intended *in vivo* condition can be considered so the extract can be studied for the potential presence of other irritating chemicals. In this situation, it is crucial to provide justification (i.e. clinically-relevant implantation study) to demonstrate that such corrosion or irritation will not occur per clinical use. It is also critical that the extract adjustment is well-documented and justified in the biological risk assessment (see Clause 4).

For implantable materials, the intracutaneous reactivity test is recommended. If validated *in vitro* alternatives become available to address this end point, and are qualified for use with absorbable medical devices, they are preferred.