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Cardiovascular biological evaluation of medical devices — Guidance for absorbable implants

Évaluation biologique cardiovasculaire des dispositifs médicaux — Directives pour les implants absorbables

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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. www.iso.org/directives

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The committees responsible for this document are ISO/TC 194, *Biological evaluation of medical devices* and ISO/TC 150/SC 2, *Cardiovascular implants and extracorporeal systems*.

Cardiovascular biological evaluation of medical devices — Guidance for absorbable implants

1 Scope

The objective of this Technical Report is to provide interim Part-by-Part guidance on potential adjustments to various test methods within the 10993 series to account for the intentional release of soluble components or degradation products from absorbable medical devices. The content is intended to add clarity and present potentially acceptable approaches for reducing the possibility of erroneous or misleading results due to the nature of the absorbable material. All suggestions should be considered as preliminary and subject to change, with final dispositions implemented through direct modification to the respective parts of ISO 10993. Thus, interim adoption of any of the described adjustments requires an accompanying written justification.

2 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

2.1
absorb
<biomaterials> action of a non-endogenous (foreign) material or substance passing through or being assimilated by cells and/or tissue over time

2.2
degradation product
<byproduct> any intermediate or final result from the physical, metabolic, and/or chemical decomposition of a material or substance

2.3
degrade
to physically, metabolically, and/or chemically decompose a material or substance

2.4
leachable
substances that can be released from a medical device or material during clinical use

Note 1 to entry: In absorbable 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 10993-12:2012, 3.10 modified — Note 1 to entry has been added.]

3 General considerations

Biological evaluation is the assessment of the ability of a device, device component, or a material to be present in the body without creating an adverse systemic impact and/or local effect on the surrounding cells and/or tissue. Biological evaluation of an absorbable material should be conducted in accordance with ISO 10993-1:2009 and other relevant parts (see ISO 10993-1:2009, Table A.1).

NOTE 1 General guidance regarding evaluation of devices in accordance with ISO 10993 series can be found in ISO/TR 15499.

By design, polymeric, ceramic, or metallic absorbable materials inherently produce relatively low molar mass degradation products when *in vivo*. The relatively elevated presence of these same products within the culture media can potentially impact the results of some biocompatibility tests. For example, in rare

cases if the degradation rate of an absorbable material is sufficiently rapid, elevated concentrations of one or more of the intended products could alter the pH and/or osmolality of an *in vitro* test system. Since the *in vivo* condition provides the combined presence of perfusion and carbonate equilibria, when evaluating intentionally degradable (i.e. absorbable) materials it can be considered acceptable, if necessary, to adjust the *in vitro* test solution pH and/or osmolality to bring the cell culture into a physiologic range – provided there is documented evidence this(these) factor(s) is(are) the potential source of an adverse result and post-adjustment testing within a physiologic range produces a successful result. Such adjustment of pH (using a buffer-appropriate acid or base) and/or osmolality (via dilution) to better approximate the *in vivo* environment helps to mitigate the presence of expected degradation products, functionally allowing the test solution to be evaluated for other causation.

Any pH or osmolality adjustment shall be justified. If under standard test conditions an adverse result is obtained, one should consider the cell type, cell media, culture conditions, and degradation products when determining the amount of osmolality adjustment to be used, if any. For example, with magnesium alloys evaluated with an human osteoblast cell type, it may not be appropriate to dilute the culture medium to less than 105 % of normal osmolality.

NOTE 2 Minimum value of 105 % derived from review of experimental results obtained from 10993 to 12 extraction of magnesium and magnesium alloy samples see Reference.[23]

To directly address these and other absorbable-specific method concerns, a list of relevant testing precautions for each relevant part of ISO 10993 has been compiled and is presented in Clause 6. All suggestions should be considered as preliminary and subject to change, with final dispositions implemented through direct modification to the respective parts of ISO 10993. Thus, interim adoption of any of the described adjustments requires an accompanying written justification. As a part of any justification, both local and systemic effects should be considered, as local pH and osmolality changes could result in toxicities that are clinically relevant.

Degradation products may be released into the media/tissue or reside in the degrading implant. Released degradation products that are generated either prior to product use (i.e. during processing or shelf-life) or during degradation should be characterized (e.g. chemical identity, quantity, and toxicity). Identification of the degradation products may be derived from chemical analyses of the implant or through a theoretical analysis. Literature data for implants manufactured from absorbable materials with an established history of safe clinical use (e.g. PGA) at the intended location may be helpful in identifying expected degradation products and potential toxicities - if one can demonstrate that equivalent manufacturing processes were used. A toxicological risk assessment using information from chemical analyses of degradation products over time, in conjunction with toxicity data from the literature may be sufficient to support an omission of biocompatibility testing from various stages of material degradation (either during device storage or in clinical use).

NOTE 3 Guidance regarding the identification and assessment of chemical degradation products and leachables can be found in ISO 10993-9 and ISO 10993-17.

Since absorbable materials are intended to degrade, potential exists for generation of transient particulate matter as the device breaks down. While an understanding of the potential clinical impact of such degradation is needed, a separate biocompatibility assessment of the absorbable particulates alone may not be necessary if the particles are both produced and absorbed at a rate that is similar to other materials of the same chemistry with a history of safe use in the intended clinical application. However, formulation chemistry as well as particle size could affect biological responses, so additional information and/or testing may be necessary to establish sufficient equivalency to support omission of full biocompatibility testing. Guidance regarding the determination of whether identification and/or quantification of particulates are needed can be found in ISO 10993-9:2009, Annex A.

4 Sterilization considerations

While biological evaluation can be conducted on any component at any stage in the manufacturing process, finished product evaluation needs to be conducted on sterilized finished devices or test samples that are representative of the final device. Evaluations should be conducted following terminal sterilization at a level that meets or exceeds anticipated commercial exposure. While higher sterilization

durations and intensities are generally considered as providing a more stringent evaluation, caution should be undertaken when sterilizing under harsher conditions (i.e. higher radiation dose) as more and different chemical by-products may be produced. If the final sterilized device is not used for testing, a rationale shall be provided that includes:

a) a description of all manufacturing differences between the test article and the final, sterilized device;

b) data that demonstrates that all differences between the test article and the final device do not impact their chemistry or degradation kinetics.

NOTE If potentially significant differences exist between the test article and final device (e.g. surface properties or device geometry when hemocompatibility testing), some test end points can be affected. In such situations, use of a test article cannot be representative of a final device.

5 Drug-device combination product considerations

For devices that include an active pharmaceutical ingredient (API), the presence of a pharmaceutical can affect the biological response. As such, separate testing of both the finished device including the API and devices constructed excluding any drug component should be considered. In addition, any potential for interaction between the pharmaceutical ingredient(s) and the as-manufactured or degrading absorbable component(s) should be both understood and assessed for its impact on device biocompatibility and the drug component itself.

Any pH or osmolality adjustment shall be justified. If under standard test conditions an adverse result is obtained, one should consider the cell type, cell media, culture conditions, and degradation products when determining the amount of osmolality adjustment to be used, if any. For example, with magnesium alloys evaluated with a human osteoblast cell type, it may not be appropriate to dilute the culture medium to less than 105 % of normal osmolality.

NOTE 1 Minimum value of 105 % derived from review of experimental results obtained from 10993 to 12 extraction of magnesium and magnesium alloy samples see Reference.[23]

NOTE 2 Additional guidance regarding evaluation of drug-device combination products can be obtained in ISO/TS 12417, which was developed for vascular medical devices.

Biological evaluation of identifiable and already previously well characterized chemical components, such as degradation products from some intentionally absorbable materials or APIs in drug-device combination products, may be optionally substituted with an appropriate toxicological evaluation. Such a justification might be generated through a chemical characterization of device extracts in conjunction with a biological risk assessment for the specifically identified chemicals, if the risk assessment considers:

a) How *in vitro* chemical extraction studies reasonably characterize the degradation and accumulation of chemicals *in vivo*;

b) Whether toxicity data are available from the literature to explore the biological response to multiple chemicals present from the same device;

c) Results from a subset of final product testing where surface properties and geometry may impact the toxicological profile of an absorbable device. For example, hemocompatibility testing might be needed if the surface properties and/or device geometry could impact the test results.

Devices that include API's can potentially impact the results with misleading positives when extracted at the recommended extraction ratio detailed in ISO 10993-12. Use of a direct dilution of the sample or a partition of the overall device evaluation may be considered.

6 Part listing and description of absorbable related issues in addition to the relevant parts of ISO 10993 series "Biological evaluation of medical devices"

6.1 ISO 10993-1:2009, Evaluation and testing within a risk management process

a) 5.3 c) and throughout ISO 10993 series

1) Supplemental Information:

i) Within the ISO 10993 series, the term PERMANENT is perceived as including CHRONIC or PERSISTENT implants that are physically present longer than 30 d. Since typically at least a limited amount of an absorbable material and/or its degradation byproducts can be expected to persist in the body past 30 d, such devices should be evaluated using the PERMANENT implant test criteria.

6.2 ISO 10993-2:2006, Animal welfare requirements

a) No identified adjustments/allowances/compensation for absorbable devices

6.3 ISO 10993-3:2003, Tests for genotoxicity, carcinogenicity and reproductive toxicity

a) Clause 4 – Genotoxicity Tests

1) 4.4 – Test Methods

i) Supplemental information to 4.4.1:

I) When evaluating absorbable materials using *in vitro* genotoxicity methods, the potential is present for artefactual positive results due to inadequately controlled pH, osmolality, or high levels of cytotoxicity within the culture media [see OECD Guideline 473(1997), Clauses 4, 14 and 38 and OECD Guideline 476(1997), Clauses 3, 14 and 36]. Since absorbable materials carry potential for at least partial dissolution during extraction, the test sample's mass may be monitored to ensure that sample concentration within the extract not does not exceed either the 5 mg/ml or 0.01M OECD limits for the chromosome aberration or mouse lymphoma test or the 5 mg/plate limit for the bacterial reverse mutation test. If extraction results in a higher concentration, dilution of the test liquid to no less than 80 % of the respective concentration limit is acceptable. Lower concentrations may be utilized if evaluated as part of a range of concentrations per OECD guidelines. The sample's cell culture may then be monitored for the presence of abnormal pH and/or osmolality for later consideration in the event of a positive result.

NOTE Significant discussion regarding the effects of abnormal pH and osmolality on genotoxocity testing is available in the ICPEMC report "Genotoxicity under extreme culture conditions," which provides a table showing the chemical-dependent nature of the impact of high osmolality on mammalian cell toxicity and chromosomal aberrations see Reference.[21] Additional guidance regarding appropriate follow-up to a positive *in vitro* genotoxicity test can be found in the internationally authored review article in Reference:[22]

6.4 ISO 10993-4:2002, Selection of tests for interactions with blood

a) Annex C.6 – Haemolysis Testing – General Considerations

1) Supplemental Information:

i) This subclause provides a brief description of direct and indirect haemolysis methods. In indirect methods, such as ASTM F756, extracts from absorbable materials can optionally be either diluted or partitioned into various stages of degradation to address byproduct

driven haemolysis. Thus, as a specific component of ISO 10993-12 and/or other more central 10993 Clauses/subclauses and/or parts, absorbable materials can be either:

Extracted once per the appropriate conditions for the test and the extract then adjusted to maintain test vehicle (i.e. solution) pH and/or osmolality

or

conduct separate sequential extracts representing different stages in the material's overall degradation that, without further adjustment, result in acceptable test vehicle (i.e. solution) pH and/or osmolality.

Any pH or osmolality adjustment shall be justified. If under standard test conditions an adverse result is obtained, one should consider the cell type, cell media, culture conditions, and degradation products when determining the amount of osmolality adjustment to be used, if any. For example, with magnesium alloys evaluated with a human osteoblast cell type, it may not be appropriate to dilute the culture medium to less than 105 % of normal osmolality.

NOTE Minimum value of 105 % derived from review of experimental results obtained from ISO 10993-12 extraction of magnesium and magnesium alloy samples, see Reference. [23]

If accelerated strategies are used to simulate real-time degradation, evidence should be provided to demonstrate that the resulting degradation products are compositionally representative of what occurs under physiologically relevant conditions.

6.5 ISO 10993-5:2009, Tests for *in vitro* cytotoxicity

a) Clause 4 – Sample and control preparation

1) 4.1 – General: "The test shall be performed on a) an extract of the test sample and/or b) the test sample itself. Sample preparation shall be in accordance with ISO 10993-12. Negative and positive controls shall be included in each assay."

i) Supplemental Information:

I) For absorbable devices, cytotoxic assessment can be conducted through *in vitro* evaluation the extract. Extracts from absorbable materials can be either diluted or partitioned into various stages of degradation to address degradation product driven cytotoxicity. Thus, as a specific component of ISO 10993-12 and/or other more central 10993 Clauses/subclauses and/or parts, absorbable materials can be either:

Extracted once per the appropriate conditions for the test and the extract then adjusted to maintain culture medium pH and/or osmolality

or

conduct separate sequential extracts representing different stages in the material's overall degradation that, without further adjustment, result in acceptable culture medium pH and/or osmolality.

Any pH or osmolality adjustment shall be justified. If under standard test conditions an adverse response is obtained, one should consider the cell type, cell media, culture conditions, and degradation products when determining the amount of osmolality adjustment to be used, if any. For example, with magnesium alloys evaluated with an human osteoblast cell type, it may not be appropriate to dilute the culture medium to less than 105 % of normal osmolality.

NOTE Minimum value of 105 % derived from review of experimental results obtained from ISO 10993-12 extraction of magnesium and magnesium alloy samples, see Reference [23].

II) For absorbable devices, it is allowed to limit temperature and duration of the extraction to deliver a controlled degradation that reflects an appropriately partitioned stage of degradation.

2) 4.2.3.2 – "For polymeric test samples, the extraction temperature should not exceed the glass transition temperature as the higher temperature can change the extractant composition." (in reference to a ISO 10993-12 extraction)

i) Supplemental Information:

I) For absorbable materials, extraction at temperatures above 37°C may lead to undesirable and/or non-representative changes in degradation mode and should, if possible, be avoided unless validated otherwise. 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 corrosion chemistry and/or modes (e.g. pitting, crevice, etc.) at elevated temperatures.

3) 4.2.3.3 – "Any pH adjustment of the extract shall be reported. Manipulation of the extract, such as by pH adjustment, should be avoided because it could influence the result.", and

and

4) Clause 6 – "The culture medium shall be maintained at a pH of between 7,2 and 7,4."

i) Supplemental Information:

I) The pH of the extract and culture are inherently linked and can lead to artefactual test failures (misleading positives) if inadequately controlled (i.e. pH outside the range of 7,2 to 7,4). Since the pH of the extract from an absorbable material is generally more easily monitored than is the culture media, adjustment of the extract can be considered as a means for practical control of culture pH. This approach would be considered as valid only if the product is specifically designed to degrade and its degradation byproducts are known to affect culture pH. **Maintenance of culture pH is perceived as compensation for the robust *in vivo* buffer capacity facilitated by the combined presence of perfusion and carbonate equilibria.**

Any pH or osmolality adjustment shall be justified. If under standard test conditions an adverse response is obtained, one should consider the cell type, cell media, culture conditions, and degradation products when determining the amount of osmolality adjustment to be used, if any. For example, with magnesium alloys evaluated with a human osteoblast cell type, it may not be appropriate to dilute the culture medium to less than 105 % of normal osmolality.

NOTE Minimum value of 105 % derived from review of experimental results obtained from ISO 10993-12 extraction of magnesium and magnesium alloy samples, see Reference [23].

6.6 ISO 10993-6:2007, Tests for local effects after implantation

a) General Note: ISO 10993-6 incorporates a large amount of information for assessment of absorbable devices

b) Clause 3 – Terms and definitions

1) 3.1 – degradation – decomposition of a material [ISO 10993-9:1999, definition 3.1]

and

2) 3.2 – degradation product – product of a material which is generated by the chemical breakdown or decomposition of the material. [ISO 10993-16:1997, definition 3.1]

i) Supplemental Information:

I) Since the above two definitions from ISO 10993-6 are somewhat limiting, the degrade definition provided within this document should be used when assessing the biocompatibility of an absorbable material or device.

c) Clause 5 – Test methods, general aspects

1) 5.1 – "Tissue and implantation site: For degradable/resorbable materials, the implantation site shall be marked in a manner suitable for identification of the site at the end of the designated time periods. The use of a non- invasive permanent skin marker and/or a template marking the placement of the specimen is recommended. In certain circumstances an appropriate negative control may be used as a marker for the location of the implant site. Exceptionally, a sham surgical procedure might be used to evaluate the impact of the procedure on the tissue involved; in these cases the specific justification shall be provided."

i) Supplemental Information:

I) Devices/subcomponents fabricated from suitably biocompatible permanent materials (e.g. gold band) may be utilized to provide an *in situ* mark of the location of *in vivo* placement.

2) 5.3 – Test periods: "In general, it is expected that experiments that go up to or beyond the point of absorption are needed for the evaluation of degradable materials."

i) Supplemental Information:

I) While gross and microscopic evaluation after complete device absorption is highly desirable, *in vivo* degradation profiling of the absorbable material and/or its byproducts to a state of limited visually identifiable histological presence can also be considered acceptable. Thus, in the absence of complete degradation, absorption, and restoration to normal tissue structure and function, the overall data collected may be sufficient to allow characterization of local effects after implantation.

II) If present, an assessment needs to be made regarding the reversibility of any accompanying adverse pathology.

3) 5.5.3 – Implant retrieval and tissue sample collection

i) Supplemental Information:

I) Per ISO 10993-1, systemic effects should be evaluated based on the device and its components, and the toxicology data set already available. Such considerations should be emphasized if an implant's degradation products are not resolved within the histologically assessed area.

II) For absorbable materials, care should be taken to minimize artefacts due to histological processing and handling (further degradation of material, shrinkage, etc).

d) Clause 6 – Test report

1) c) "Retrieval and histological procedure…

i) Apply the following revised (changes underlined) sentence to paragraph c): "For degradable materials, the report shall include, but not be limited to, a description of the degree of degradation (when possible), including material characteristics at explantation (free particles, fibre formation, amorphous gel, crystallinity). Potentially relevant additional