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Cardiovascular biological evaluation of medical devices — Guidance for absorbable implants

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Cardiovascular biological evaluation of medical devices — Guidance for absorbable implants

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Foreword

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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*.

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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

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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

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