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CLEANLINESS OF ORTHOPAEDIC IMPLANTS ACCORDING TO ISO 19227: DIFFERENCES AND GAPS COMPARED TO ISO 10993-18

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INTRODUCTION

The evaluation of the cleanliness and biological safety of an orthopaedic implant is a central part of the conformity assessment procedure for market approval. There are two documents describing the cleanliness: ISO 19227 coming from the cleaning processes development and validation and ISO 10993-18 describing the chemical characterisation of medical device materials for the biological evaluation.

In this work, we have taken a closer look at the differences and gaps with regard to the evaluation of the cleanliness of implants focussing on organic and inorganic impurities.

ISO 19227:2018

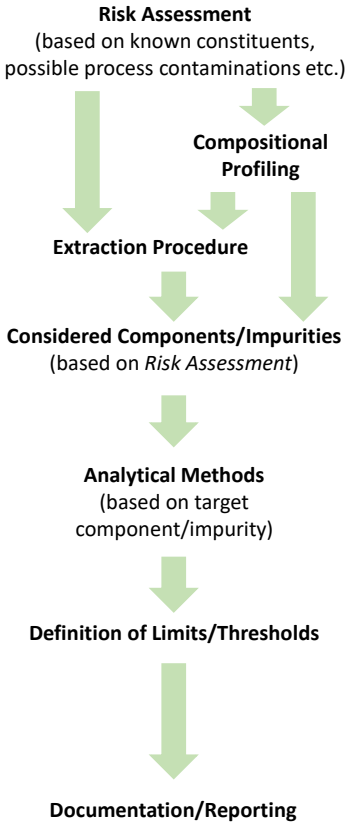
Implant for surgery – Cleanliness of orthopedic implants – General requirements

- Requires *exhaustive extraction (referring to ISO 10993-12) of organic + inorganic impurities.*
- *Organic impurities*
- *Inorganic impurities* (refers to ICH Q3D and therefore to USP 232/233)
- Total Organic Carbon (TOC) for water soluble impurities
- GC or FTIR for Total Hydrocarbons (THC), soluble in nonpolar solvents

Threshold Concept: *mixed*

- Dose-based concept for **inorganic impurities** (by referencing ICH Q3D and ISO 10993-17).
- Specific value of 0.5 mg/implant for TOC and THC for **organic impurities** (proposed as a *starting point*). Independent of chemical composition, toxicity, carcinogenicity etc.

We think that it is inappropriate to set a speficic limit of 0.5 mg/implant as the size, complexity, manufacturing and cleaning process of implants as well as the chemical composition of the impurities can be diverse.



ISO 10993-18:2020

Biological evaluation of medical devices – Chemical characterization of medical device materials within a risk managment process

- Information from the *Compositional Profiling* (supplier or direct chemical testing) can be sufficient for toxicological risk assessment.
- Differentiates between *exhaustive*, *exaggerated*, *simulated extraction.*
- *Organic impurities (VOC, sVOC, nVOC)*
- *Polymers*
- *Inorganic impurities, metals + alloys*
- *Ceramics*
- A wide range of analytical methods are proposed, depending on the target components/impurities as well as required detection limits to achieve corresponding *AETs* (which are based on the risk assessment).

Threshold Concept: *dose-based*

- Introduction of an *Analytical Evaluation Threshold* (*AET);* check eq. 1.
- Conversion of a dose-based threshold (*TTC*, *SCT* etc.) to a concentration-based threshold *AET.*
- Applicable for all *Considered Components/Impurities.*

Surface contamination (cleanliness) can be considered and evaluated as part of the chemical characterization.

$$AET\left(\frac{\mu g}{mL}\right) = \frac{DBT\left(\frac{\mu g}{d}\right) \cdot \frac{A}{B\,(mL) \cdot C(d^{-1})}}{UF} \qquad (1)$$

DBT : Dose based threshold (e.g. TTC or SCT); For potentially mutagenic impurities DBT = TTC= 120 µg/d (see ICH M7).
A : Number of medical devices used for generating the extract
B : Volume of the extract
C : Clinical exposure to the medical device or number of devices a user would be exposed to in a day under normal conditions
UF : Uncertainty factor

DISCUSSION & CONCLUSIONS

- Both standards mention the importance of a risk assessment based on the analysis of the contaminants.
- **ISO 10993-18** offers direct chemical testing of the implant within a Compositional Profiling process (e.g. XPS analysis of the implant's surface without going through the often more costly extraction procedure).
- The specific limit value of 0.5 mg/implant of total hydrocarbon and organic carbon (THC & TOC) in **ISO 19227** is problematic in two ways:
  a.) No consideration of the implant characteristics (e.g. 0.5 mg impurity on a small screw vs. a large hip implant)
  b.) No consideration of the chemical-toxicological nature of the impurity (e.g. highly toxic or even carcinogenic vs. less toxic impurity)
  Such an approach may lead manufacturers to a false sense of security if they follow this example.
- **ISO 10993-18** faces these limitations by taking over the *Analytical Evaluation Threshold (AET)* concept:
  - Concentration threshold below which extractables or leachables identification is not required (derived from a toxicological risk assessment).
  - AET concentration is calculated from a dose-based threshold (e.g. TTC of 1.5 µg/day for carcinogenic substances according to ISO/TS 21726).
  - Limit concentrations are calculated (even individually for known, specific impurities) based on the medical product's intended use.

Based on these points, we suggest that the chemical characterisation of orthopaedic implants should be performed according to ISO 10993-18. Surface contamination is then considered and evaluated as part of the chemical characterisation. If the toxicological assessment shows that the surface contamination is problematic, the cleaning process should be improved in accordance to ISO 19227.

References

ISO 19227:2018-03: *Implants for surgery - Cleanliness of orthopaedic implants – General Requirements.*
ISO 10993-18:2020-01: *Biological evaluation of medical devices – Part 18: Chemical characterization of medical device materials within a risk management process.*
ISO 10993-17:2009-08: *Biological evaluation of medical devices – Part 17: Establishment of allowable limits for leachable substances.*
ISO/TS 21726:2019-02: *Biological evaluation of medical devices - Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents.*
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<232>: *Elemental Impurities – Limits, in: United States Pharmacop. Natl. Formul. (USP 38-NF 33), United States Pharmacopeia Convention, 2012: pp. 245-248.*