ISO 10993

Standard for Biocompatibility

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Outline

• Definition of Medical Device
• Definition of Biocompatibility
• Impact of some different administration routes
• Interlinked standards
• The ISO 10993 standard parts
• Biological evaluation within a risk based approach
• Chemical Characterization
• New Technologies – Nano
• When the standard does not fit
• Conclusion
• Future directions
"Medical device" means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception
Definition - Medical Device – cont.

...and which **does not** achieve its principal intended action in or on the human body by **pharmacological, immunological or metabolic means**, but which may be assisted in its function by such means.'
Definition - Medical Device
Definition - Biocompatibility

“…the ability of a material to perform with an appropriate host response in a specific application” Williams, 1987.

Material is biologically compatible by not eliciting a local or systemic response from a living system or tissue.
Biocompatibility

• Toxicity – chemicals leaching out from the device
• Mechanical effects – heat due to movement of a hip implant
• Reactions due to contamination, such as, endotoxines
• …..

The leachates of a device, or the device itself, should not produce adverse local, systemic, tumorigenic, reproductive, or developmental effects.
Structure of Skin
Topical Cream

- Medical Device?
- Pharmaceutical?
- Cosmetics?
Biological Evaluation of Respiratory Gas Pathways
Background to ISO 10993
Background to ISO 10993

- Tripartite Biocompatibility Guidance (US, UK and Canada) 1987
  FDA Blue Book Memorandum G87-1.
- In 1989 a meeting was held in Pforzheim with the aim to standardise biological evaluation of medical devices. The Technical Committee ISO TC194 "Biological evaluation of medical devices” was established.
Background to ISO 10993

✓ ISO 10993-1 (1992) - Guidance on selection of tests
✓ ISO 10993-1 (since 2007) - Evaluation and testing within a risk management process
The ISO 10993 Standard Series

Prepared by Technical Committee ISO/TC 194 and by Technical Committee CEN/TC 206 in collaboration

ISO/TC 194 committee
  • 24 "participating countries"
  • Representatives of different interests
  • Usually meet once per year (Sept 2016 USA)
  • Acceptance of new standard requires approval of ≥ 75%

Continuous developing, update:
ISO website: http://www.iso.org
CEN website: http://www.cen.eu/
Interlinked Standards

- **EN ISO 13485:2016** Medical Devices – Quality management systems – Requirements for regulatory purposes

- **EN ISO 10993-1:2009** Biological evaluation of medical devices
  - Part 1 Evaluation and testing within a risk management process

- **EN ISO 14971:2012** Medical devices – Application of risk management to medical devices

- **EN ISO 14155:2011** Clinical investigation of medical devices for human subjects – Good clinical practice
Interlinked Standards

13485

14971

14155

10993
The ISO 10993 Standards Series

- Structured way to evaluate biological safety of medical devices
- Categorisation
  - Contact with the patient
  - Duration of the contact
  - Suggests tests to be considered

How does my product affect the human body?
Evaluation Strategy
ISO 10993-1 Biological Evaluation of Medical Devices Part 1: Evaluation and testing within a risk management process

Animal Welfare
Part 2: Animal Welfare requirements

Sample preparation
Part 12: Sample preparation and reference materials

Materials Characterization
Part 18: Chemical characterization of material
Part 19: Physico-chemical, morphological and topographical characterization
Part 17: Establishment of allowable limits for leachables

Degradation products
Part 9: Framework for Identification of degradation products
Part 13, 14, 15: Identification and quantification of polymeric, ceramic, metallic degradation products

Test Methods
Part 3: Genotoxicity, Carcinogenicity and Reproduction and Development
Part 4: Hemocompatibility
Part 5: Cytotoxicity
Part 6: Implantation and local effects
Part 10: Irritation and Sensitization
Part 11: Systemic Toxicity
Part 16: Toxicokinetic study design for leachables and degradation products
Part 20: Principles and methods for immunotoxicity testing

Sterilization Residuals
Part 7: Ethylene oxide sterilization residuals

SYMBIOTEQ
ISO 10993-1 Evaluation and Testing within a Risk Management Process

1. Identification of biological hazards of the device
2. Estimation, evaluation and control of risks
3. Control of the efficacy of the control measures

Assessment of biocompatibility of the FINAL device
ISO 10993-1 Evaluation and Testing within a Risk Management Process

Tests only when necessary!

SYMBIOTEQ
ISO/TR 15499 Guidance on the Conduct of Biological Evaluation within a Risk Management Process

Technical report - marriage between ISO 10993-1 and ISO 14971
Risk Assessment

RISK = SEVERITY x PROBABILITY of HARM
ISO 10993 – Biological Endpoints

- Cytotoxicity
- Irritation
- Sensitization
  - Acute Systemic Toxicity
  - Subacute and Subchronic Systemic Toxicity
  - Pyrogenicity
  - Genotoxicity
  - Implantation Reactivity
  - Hemocompatibility
  - Biodegradation
  - Immunotoxicity
  - Chronic Toxicity
  - Carcinogenicity
  - Reproductive and Development Toxicity
ISO 10993 – Biological Endpoints

- Class I
- Class Is, Im
- Class IIA
- Class IIB
- Class III

Risk vs. Requirement
Risks connected with...

- Ingoing materials
- Processing chemicals
- Components leaching from the device
- Degradation products
- Products due to biodegradation
- Physical properties: size (particle), design, hydrophobicity/hydrophilicity; surface morphology, porosity
Materials

- Polymeric materials – may contain unreacted monomers, initiator fragments, stabilizers... e.g. formaldehyde, a known carcinogen
- Metals – release ions e.g. nitinol can release nickel
- Ceramics – processing components
- Different structures – porous materials
- Bioabsorbable materials
Materials – USP/DMF/ASTM

• USP – Biological reactivity tests
• Material Standards (e.g. ASTM) – Metals, alloys, ceramics
• DMF – Device Master File, may have relevant data
1. Raw materials – processing, additives (colours), coatings, processing aids
2. Components – assembling, contaminants
3. Device – sterilisation, packaging, distribution, storage

Patient

Post Market Surveillance
Biological Evaluation Process

1. Intended Use
   - Biological Risks

2. Material Characterization

3. Perform Testing

4. Evaluate Risks

5. Apply Required Risk Controls

Available Existing Data?

   No

   Existing Data Sufficient for risk evaluation?

      Yes

      Summarize within a Biological Evaluation Report

      No
Biological Evaluation Plan

Your plan

Reality
Final Device

In its "as-used" state

Impact of Sterilization - often missed!
Biological Evaluation – Process

Post Market Surveillance
Is the confirmation that the assumptions made are correct
Common Pitfalls in Biological Evaluations

- Lack of coherent risk management process.
- Risk analysis does not identify all the relevant hazards and risk control measures.
- Biocompatibility assessment sees purely as ”the tests”.
- Biocompatibility inadequate assessed; ”a competitor has the same material”, ”this material has been used safely for years”.
- No evidence that the author of the biological evaluation holds appropriate knowledge and experience, in accordance with EN ISO 10993-1.
ISO 10993

Standard for Biocompatibility
ISO 10993-1

ISO 10993-1 – Evaluation and testing within a risk management process
<table>
<thead>
<tr>
<th>Category</th>
<th>Contact</th>
<th>Cytotoxicity</th>
<th>Sensitization</th>
<th>Irritation or intracutaneous reactivity</th>
<th>Systemic toxicity (acute)</th>
<th>Subchronic toxicity (subacute toxicity)</th>
<th>Genotoxicity</th>
<th>Implantation</th>
<th>Hemocompatibility</th>
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*The crosses indicate data endpoints that can be necessary for a biological safety evaluation, based on a risk analysis. Where existing data are adequate, additional testing is not required.*
ISO 10993-2 Animal Welfare Requirements

- R3 (Replacement, Reduction, Refinement)
ISO 10993-3


• Risk based approach för genotox test
• They are used to detect compounds that induce genetic damage, either directly or indirectly. This is necessary because such compounds can be carcinogenic or may create germ line mutations (which can cause human disease)
ISO 10993-33


Overview of differences in various regulatory bodies regarding genotoxicity testing.
ISO 10993-4 interactions with blood
ISO 10993-5  Cytotoxicity
ISO 10993-5

Three basic types of cytotoxicity test:
1. Elution test – extracts (cell culture medium including serum, 37°C/24h)
2. Direct contact test
3. Indirect contact test
   a) Filter diffusion
   b) Agar diffusion – cells covered by an agar layer and then the device (extract) is placed on top
ISO 10993-5 - Interpretation

• Devices that fail the **cytotoxicity** test may cause biocompatibility problems in people, e.g. irritation, hemolysis, etc.

This is often, but not always the case!
ISO 10993-6 Tests for Local Effects after Implantation

- In general, the test sample is implanted into the tissues most relevant to the intended clinical use of the material (e.g., subcutaneous tissue, intramuscular, or bone).
- The biological response is determined via macroscopic and histopathological responses as a function of time comparing responses of the test sample to those obtained at the control sample or sham-operated sites.
The choice of EO sterilization should be justified!
ISO 10993-9/-13/-14/-15/-16

All about degradation of materials…

Part 9: Framework for Identification of degradation products
Part: 13, 14, 15: Identification and quantification of polymeric, ceramic, metallic degradation products
Part 16: Toxicokinetic study design for leachables and degradation products
ISO 10993-10
ISO 10993-11 – systemic toxicity

System tox (acute, sub-cronic, chronic tox)

Pyrogen –implants, devices in blood contact, cerebrospinal and when labeled pyrogen free

Endotoxin (in vitro) – LAL test routine batch control
ISO 10993-12 – Sample preparation and reference materials

Extraction ratio: 3 cm²/ml, 6 cm²/ml, 1,25 cm²/ml, 0,2 g /ml, 0,1 g / mL

Extraction conditions

Choice of solvents

Extraction temperature

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ISO 10993-17, -18, -19

ISO 10993-18: Chemical characterization of materials (guidance for the evaluation of devices and their leachates)
ISO 10993-17: Establishment of allowable limits for leachable substances (guidance for toxicological risk assessment of leachates)
ISO/TS 10993-19: Physico-chemical, morphological and topographical characteristics of materials
Overview of immunotoxicology with particular reference to the potential immunotoxicity of medical devices
Supplemental Tests

- Chronic toxicity – Long-term tests
- Carcinogenicity – Long-term tests for formation of cancerous cells
- Reproductive and development toxicity – Long-term test on the effects of the materials and extracts on the reproductive system and/or development
- Biodegradation – Long-term evaluation of material degradation in the body
Alternative Methodologies

Examples:

• Skin Irritation 3D-Skin Models: Epiderm, EpiSkin, Epics
• Skin Sensitization: KeratinoSens™, Direct Peptide Reactivity Assay (DPRA)

Not validated for medical devices yet!
Chemical Characterization

• Starting point for the biological evaluation – ALL DEVICES
• Extent depending on intended use and material characteristics
• Use of:
  • GC-MS or GC-FID
  • LCMS-MS or HPLC-MS
  • ICP-MS
• Use of:
  • Water
  • Isopropyl alcohol
  • N-hexane
"Dosage alone determines poisoning"

- Mode of Action
- Metabolism
- Surfaces (e.g. Nano)
- ….

PARACELCUS
(Philippus Aureolus
Theophrastus Bombastus von
Hohenheim)
1493 -1541
Material Characterization

The approach of material characterization

• Evaluate changes
• Waive long-term tests
Chemical Characterization - Multiple polymers/materials

- PP
- PE
- PVC
- PC
- PTFE
- Steel
- MABS
- Silicone elastomers
- Rubber elastomers
- Glass
- Adhesive
- Coating
- And more....
Chemical Characterization - Extractables and Leachable relationship

Leachables is a subset of extractables

Extractables = What CAN come out
Leachables = What DOES come out
Chemical Characterization – Allowable Limits

Mixtures!
Chemical Characterization – TTC

- Threshold of Toxicological Concern

- $1.5 \, \mu g/dag \, - \, 10^{-5}$ lifetime risk of cancer (genotoxic impurities)

- Below the TTC - no biological risk to humans?

Technical Report on this for Medical Devices is in development by the ISO/TC194
Toxicity

Complex *in vivo*, *e.g.*

- Direct cellular damage (as cytotoxic materials)
- Physiological effects (as membrane transport)
- Neurotoxicity
- Inflammatory effects
- Specific target organs
Questions

- Do you think the Notified Body will check the biological evaluation?
- The only difference is the sterilization process…
- The device is in contact with all tissues, except brain and kidney…
A nanometer is 1 billionth of a metre, i.e. $10^{-9}$
New technologies – Nanoparticle size

The number of surface molecules present is a function of the particle size. When particle size decreases <100nm, the number of surface molecules increase exponentially.
New technologies – Nano surface interactions
New technologies - Nano

Carbon nanotubes

Zinc nanowires

Iron oxide nanofibre
Chromium and joint replacements

Nanoparticles?
Challenges
Challenges

• Medical devices, such as ventilators, often consist of several materials including different colours
• Looking at the Table....
<table>
<thead>
<tr>
<th>Medical device categorization by</th>
<th>Biological effect</th>
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<tbody>
<tr>
<td>nature of body contact</td>
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<td>Category</td>
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<td>Cytotoxicity</td>
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<td>Haemocompatibility</td>
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³ The crosses indicate data endpoints that can be necessary for a biological safety evaluation, based on a risk analysis. Where existing data are adequate, additional testing is not required.
Challenges - 18562

• Part 1: Evaluation and testing within a risk management process
• Part 2: Test for emissions of particulate matter
• Part 3: Tests for emissions of volatile organic compounds (VOCs)
• Pat 4: Test for leachables in condensate
Future:
• Part 5: Test for emissions of inorganic gases
• Part 6: Test for compatibility with inhalation anaesthetic agents
• Part 7: test for compatibility with inhalation drugs (therapeutics)
Conclusion

- Tricky to have a guidance covering all different types of medical devices
- The ISO 10993 standard series suggest a structured way on how to evaluate biocompatibility
- Chemical Characterization provides key information
- New technologies are challenging and will always be so
Future Directions

1. More emphasis on **Material Characterization**
2. Evaluation and testing within a **Risk Management Process**
3. More focus on competence responsible for the biological evaluation – a **Multidisciplinary Team**!
There are known knowns
These are things we know that we know
There are known unknowns
These are things we know we don’t know
But there are unknown unknowns
These are things we don’t yet know we don’t know

(Based on quote from Donald Rumsfeld)
Thank you!
Symbioteq Conference proudly invites you to:

Biocompatibility of Medical Devices 2017

Gothenburg Sweden

Feature a comprehensive program “from Science to Regulation”
face the challenges in relation to biocompatibility.

We look forward to welcome you to this not-to-be-missed event.

http://symbioteq.com/conferences/