Preclinical Medical Device Safety Evaluation in 2022

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History

- Use of medical devices dates back to ancient Egypt
- Concerns about safety is more recent
- Began with use of plastics in drug and fluid containers in the 1950s
- John Autian
  - Expanded the range of testing, adding bioassay type tests
    - cytotoxicity, irritation, sensitization, implantation, acute systemic toxicity
  - Potential harm to patients from chemicals transferred from device to surrounding tissues and distributed systemically
  - Extraction from devices by polar and nonpolar fluids at exaggerated concentrations was used for conducting the tests

History Continued…

- At the same time:
  - It was recognized that nature and duration of exposure determine potential risks
  - A matrix of testing requirements was developed to facilitate which tests are relevant
  - Standards were set to determine volume of extraction proportionate to surface area direct or indirect contact
- From these considerations a set of guidances were drawn out

History Continued…

- First “version” was in the “Tripartite agreement”
- US FDA developed the G95 “Blue Book” guidance from this
- Modifications arose (and continue to be made)
- ISO developed and promulgated the 10993-1 guidance and many subsequent updates
  - Current version is 2020
- The current principal limitation is that not all prescribed tests are called out in 10993-1
- Respiratory exposure guidances not addressed at all

Regulations

- ISO-10993-1 (2020) and subsidiary guidances shown on following slides.
- Respiratory devices need to fulfill testing requirements shown in 10993-1, plus an additional requirement covered in ISO 18562 (parts 1-4)
- Some required tests described in separate guidances
  - Example: material mediated pyrogenicity in the USP
- Critical: Nature of patient contact and duration of exposure.

ISO 10993-1

Medical device categorization by			Endpoints of biological evaluation															
Nature of Body Contact		Contact Duration	Physical and/or chemical information	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Material-Mediated Pyrogenicity[a]	Acute systemic toxicity[b]	Subacute toxicity[b]	Subchronic toxicity[b]	Chronic toxicity[b]	Implantation effects[b,c]	Hemocompatibility	Genotoxicity[d]	Carcinogenicity[d]	Reproductive/developmental toxicity[d,e]	Degradation[f]
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – long term (>30 d)																
Surface Medical Device	Intact skin	A	X[g]	E[h]	E	E												
		B	X	E	E	E												
		C	X	E	E	E												
	Mucosal Membrane	A	X	E	E	E												
		B	X	E	E	E		E	E			E						
		C	X	E	E	E		E	E	E	E	E		E				
	Breached or compromised surface	A	X	E	E	E	E	E										
		B	X	E	E	E	E	E	E			E						
		C	X	E	E	E	E	E	E	E	E	E		E	E			

ISO 10993-1

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Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – long term (>30 d)																
Externally communicating medical device	Blood path, indirect	A	X	E	E	E	E	E					E				
		B	X	E	E	E	E	E	E				E				
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
	Tissue/bone/dentin	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Circulating blood	A	X	E	E	E	E	E					E	E			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

ISO 10993-1

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Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – long term (>30 d)															
Implant medical device	Tissue/bone[	A	X	E	E	E	E	E						E			
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Blood	A	X	E	E	E	E	E				E	E	E			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

ISO 10993-1

-[a]Refer to ISO 10993-ww: 2017, Annex F
-[b]Information obtained from comprehensive implantation assessments that include acute systemic toxicity, subacute toxicity, subchronic toxicity, and/or chronic toxicity may be appropriate if sufficient animals and timepoints are included and assessed. It is not always necessary to perform separate studies for acute, subacute, subchronic, and chronic toxicity.
-[c]Relevant implantation sites should be considered. For instance, medical devices in contact with intact mucosal membranes should ideally be studied/ considered in contact with intact mucosal membranes.
-[d]If the medical device can contain substances known to be carcinogenic, mutagenic, and/or toxic to reproduction, this should be considered in the risk assessment.
-[e]Reproductive and developmental toxicity should be addressed for novel materials, materials with a known reproductive or developmental toxicity, medical devices with relevant target populations (e.g. pregnant women), and/or medical devices where there is the potential for local presence of deice materials in the reproductive organs.
-[f]Degradation information should be provided for any medical devices, medical device components or materials remaining within the patient, that have the potential for degradation.
-[g]X means prerequisite information needed for a risk assessment.
-[h]E means endpoints to be evaluated in the risk assessment (either through the use of existing data, additional endpoint-specific testing, or a rationale for why assessment of the endpoint does not require an additional data set). If a medical device is manufactured from novel materials, not previously used in medical device applications, and no toxicology data exists in the literature, additional endpoints beyond those marked “E” in this table should be considered. For particular medical devices, there is a possibility that it will be appropriate to include additional or fewer endpoints than indicated.
-[i]Tissue includes fluids and subcutaneous spaces. For gas pathway devices or components with only indirect tissue contact, see device specific standards for biocompatibility information relevant to these medical devices.
-[j]For all medical devices used in extracorporeal circuits.

ISO 10993 Standards

- ISO 10993-1:2018 Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process
- ISO 10993-2:2006 Biological evaluation of medical devices Part 2: Animal welfare requirements
- ISO 10993-3:2014 Biological evaluation of medical devices Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
- ISO 10993-4:2017 Biological evaluation of medical devices Part 4: Selection of tests for interactions with blood
- ISO 10993-5:2009 Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity.
- ISO 10993-6:2016 Biological evaluation of medical devices Part 6: Tests for local effects after implantation
- ISO 10993-7:2008 Biological evaluation of medical devices Part 7: Ethylene oxide sterilization residuals
- ISO 10993-8:2001 Biological evaluation of medical devices Part 8: Selection of reference materials (withdrawn)
- ISO 10993-9:2019 Biological evaluation of medical devices Part 9: Framework for identification and quantification of potential degradation products
- ISO 10993-10:2021 Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization
- ISO 10993-11:2017 Biological evaluation of medical devices Part 11: Tests for systemic toxicity
- ISO 10993-12:2021 Biological evaluation of medical devices Part 12: Sample preparation and reference materials (available in English only)
- ISO 10993-13:2010 Biological evaluation of medical devices Part 13: Identification and quantification of degradation products from polymeric medical devices

ISO 10993 Standards

- ISO 10993-14:2009 Biological evaluation of medical devices Part 14: Identification and quantification of degradation products from ceramics
- ISO 10993-15:2009 Biological evaluation of medical devices Part 15: Identification and quantification of degradation products from metals and alloys
- ISO 10993-16:2018 Biological evaluation of medical devices Part 16: Toxicokinetic study design for degradation products and leachables
- ISO 10993-17:2002 Biological evaluation of medical devices Part 17: Establishment of allowable limits for leachable substances
- ISO 10993-18:2020 Biological evaluation of medical devices Part 18: Chemical characterization of medical device materials within a risk management process
- ISO/TS 10993-19:2020 Biological evaluation of medical devices Part 19: Physico-chemical, morphological and topographical characterization of materials
- ISO/TS 10993-20:2006 Biological evaluation of medical devices Part 20: Principles and methods for immunotoxicology testing of medical devices
- ISO/TR 10993-22:2017 Biological evaluation of medical devices Part 22: Guidance on nanomaterials
- ISO 10993-23:2021 Biological evaluation of medical devices Part 23: Tests for irritation
- ISO/TR 10993-33:2015 Biological evaluation of medical devices Part 33: Guidance on tests to evaluate genotoxicity — Supplement to ISO 10993-3
- ISO 18562 (parts 1-4)

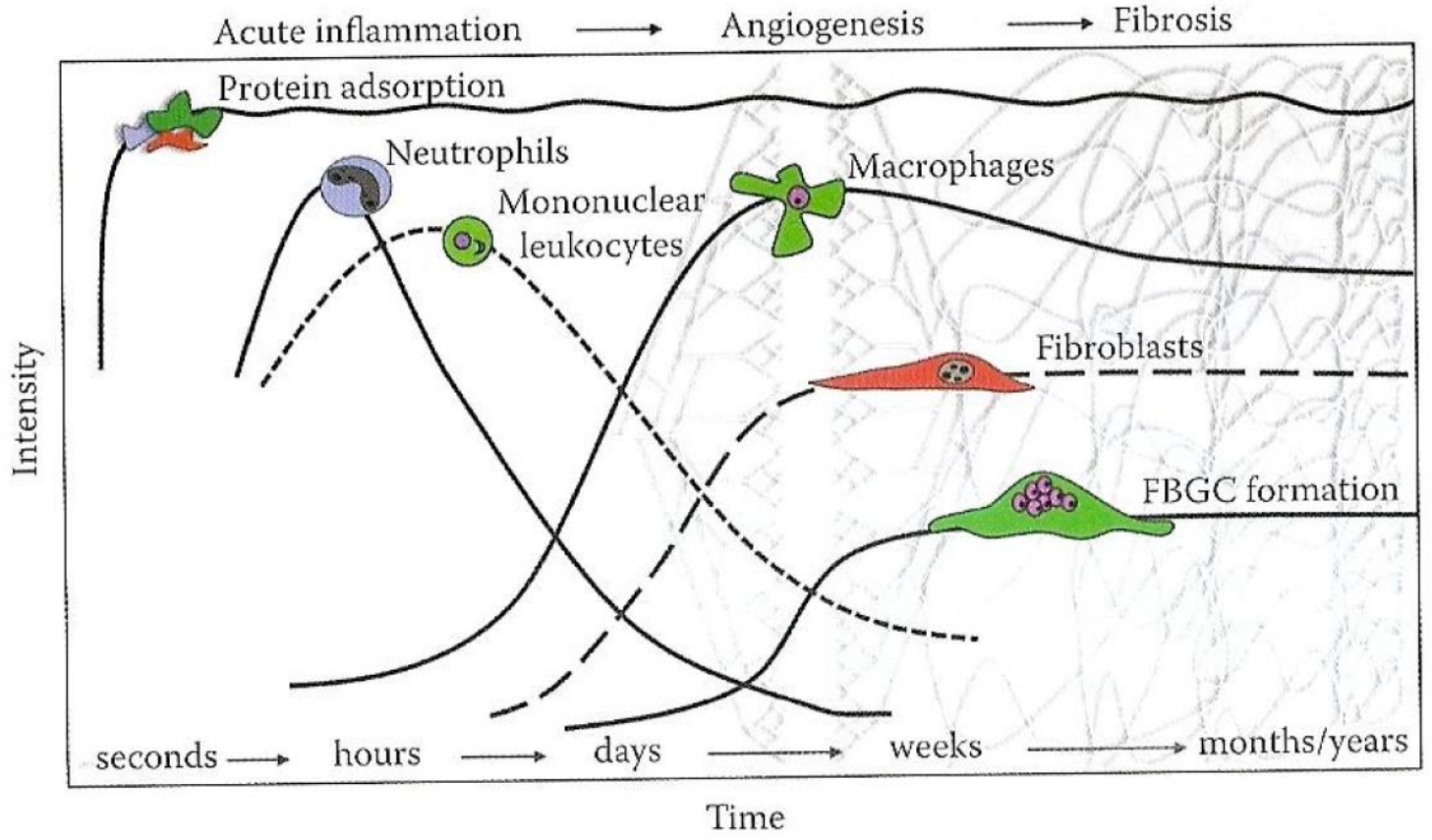
Not Everything is a Nail

- Pharmaceutical toxicology is primarily chemical toxicology, influenced by the long history thereof
- Biotechnological toxicology is primarily immunotoxicology, with aspects of chemical and cellular/organ function toxicity included
- Medical device toxicology has significant aspects which are not chemical or (adaptive) immune system based
- GMP vs GLP (to meet GLP Requirements)
- Biocompatibility testing for devices must be completed before any clinical testing or use is undertaken.
- Nonclinical testing for drugs is done incrementally over the process of development.

Foreign Body Response

- Much of what happens with devices occurs at (and depends on) the device/tissue interface
- Foreign Body Response (FBR) a time dependent spectrum of innate and adaptive immune responses to a device.
- Time, concentration, and surface characteristics are the most important factors
- Chronicity
- Viscosity, osmolarity and pH are overlooked factors
- Implantation biology

Foreign Body Response



- Source: Gad, S.C., and Gad, S.E., (2015) Biomaterials, Medical Devices, and Combination Products. CRC Press, Boca Raton, FL

Traditional Testing May Not Detect Potential Risk to Patients

- Toxic shock syndrome (TSE 1 and 2)
- Physical degradation as a factor in adverse events (physical degradation of orthopedics)
- Textured breast implants and cancer (BIA-ALCL – breast implant associated anaplastic large cell lymphoma)

What is tested must be the final, ready to market form of the device or the patient contacting component thereof.

Recent CDER Changes – Interpretation

1. Endotracheal tubes (ETTs) are externally communicating devices with tissue contact for biocompatibility testing/assessment purposes.
   - Not clear from FDA yet
   - Are other natural channel/contact devices to be treated the same way?
2. Hyaluronic Acid (HLA) used for injection into joints now regulated by CDER as a drug
   - other liquid injections still devices
3. ICH/CDER drug set of genotoxicity tests now required to comply with genotoxicity testing
   - Ames, mutagenicity, chromosomal abnormalities, AND micronucleus tests

Recent CDER Changes – Interpretation
(Continued…)

4. Subchronic toxicity studies –
   - 28 day, 1-control, 1-dose level study
   - Single gender is acceptable
   - Clinical chemistry, hematology, organ weights and limited (~10 tissue) histopathology
   - Implant or daily extract dosing
5. Colorants – Best case is if they are on the CFR list
   - If not, use literature (if data is available) to qualify

Recent CDER Changes – Interpretation
(Continued…)

6. Heavy metals limits:
   - ICH Q3D – Allowable levels of “elements” (metals and boron)
   - EMA
   - USP

   Each of these provide numerical limits for levels allowed by different exposure routes in drugs, the CDRH also accepts them as applicable to device L&E results.

Recent CDER Changes – Interpretation
(Continued…)

7. Leachables and extractables (L&E) testing must be performed on **all** new devices with potential systemic exposure of (single or cumulative use) 29 days or more.
   - Including those using the 510(k) route
   - Also includes wound dressings or wound healing devices

   Extraction for such must be performed as:
   - Exhaustive extraction (ISO-10993-12, 2013)
   - Chemical characterization ISO-10993-18 (2020)
   - Extraction should be performed at 50°C for 72hrs except when extracting into cell media for cytotoxicity

Respiratory Devices

- ISO 10993-1 and coverage of requirements are not comprehensive.
  - Regulatory requirements posed by pharmacopeia
  - Free-standing guidances for special cases
    - Combination devices, resorbable devices, and devices used to support respiration
  - The matrix and understanding of the science and regulatory requirements will remain in flux
- Two specific issues considered more appropriate for separate guidances:
  - Color additives
  - Biocompatibility of gas pathway devices, discussed in terms of ISO-18562
- Any identified extractable materials must be assessed for risks as per L&E approach (TRA, Toxicology Risk Assessment)

References

Autian, J. (1977) Toxicological evaluation of biomaterials: Primary acute toxicity screening program. *Artificial Organs*. 1:53-60

CDRH (1997). *Premarket Notification (510(k)) Guidance Document for Contact Lens Care Products.*

ISO (2000). ISO 10993-8 Selection and qualification of reference materials for biological tests

ISO (2021). ISO 10993-12 Sample preparation and reference materials

ISO (2017). ISO 18562-1: Biocompatibility of breathing gases

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