Evaluation of Medical Devices for Genetic Toxicity: A Global Perspective

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ETHICON

Evaluation of Medical Devices for Genetic Toxicity

Agenda

- What is different about evaluating medical devices
- Determination if genetic toxicity evaluation is needed
- ISO 10993-3 (2014) - Requirements (Risk Based Approach, Chemical Characterization, Tests, Test Sample Preparation, Reports)
- ISO TR 10993-33 - Guidance on Tests to Evaluate Genotoxicity – Supplement to ISO 10993-3
- Challenges using ISO 10993-3 – Globally accepted but subject to interpretation by national regulatory agencies

What is different about evaluating medical devices

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What is different about evaluating medical devices

- How do you get this trocar - medical device on to an Ames plate?

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What is different about evaluating medical devices

- Reliance on using extracts for *in vitro* toxicity and short term *in vivo* toxicity tests
  - Use of both polar and non-polar solvents for extraction
  - Guided by ISO 10993-12
  - For hazard identification, exaggerated extraction required
  - Often use a single top dose when testing

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What is different about evaluating medical devices

- Extracts are usually complex mixtures containing anywhere from 0 to over 100 individual chemicals and/or elements
  - There can be upwards of 30 different materials that have patient contact in a single device.
  - Formulation Concerns: additives, colorants, mold releases, and lubricants
  - Manufacturing processes: cleaning, solvent welding, anodization, and passivation
  - Animal source materials

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What is different about evaluating medical devices

- Reliance on “Medical Grade” materials
  - Lack of a definition (buyer beware)
  - Need for careful screening of suppliers
  - Often have master files or provide biocompatibility information
  - Usually test every lot
- Manufacturing grade materials
  - Require additional controls
  - May require lot testing

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What is different about evaluating medical devices

- Quality agreements with suppliers (patient contacting components)
  - Will provide at least 6 months notice of any change in formulation
  - Process changes to be reviewed prior to implementing
  - Manufacturing equipment kept clean

Determination if a genetic toxicity evaluation is needed

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Determination if a genetic toxicity testing is needed

- Determination of the risk associated with the medical device.
  - Determine the contact category of the device using ISO 10993-1
  - Using the table in Annex A (ISO 10993-1) find the risks associated with the assigned contact category
  - Consider if there are additional risk associated with the device (literature, chemical characterization)
    - » Presence of carcinogens, mutagens, reproductive toxicants (CMRs)
    - » If present, *CMRs must be assessed even if these endpoints are not specified in Annex A*

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From ISO10993-1

Table A.1 — Evaluation tests for consideration

Medical device categorization by			Biological effect							
Category	Contact	contact duration (see 5.3) A – limited (≤ 24 h) B – prolonged (> 24 h to 30 d) C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Haemocompatibility
Surface device		A	X [a]	X	X					
		B	X	X	X					
		C	X	X	X					
	Mucosal membrane	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
	Breached or compromised surface	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
External communicating device	Blood path, indirect	A	X	X	X	X				X
		B	X	X	X	X				X
		C	X	X		X	X	X		X
	Tissue/bone/dentin	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Circulating blood	A	X	X	X	X				X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X
Implant device	Tissue/bone	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Blood	A	X	X	X	X	X		X	X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X

[a] 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.

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Determination if a genetic toxicity testing is needed

- Device contact categories when genetic toxicity should be evaluated
  - **Greater than 24 hours to 30 days:**
    - » externally communicating devices with tissue, bone or dentin, or circulating blood contact
    - » implant devices with tissue, bone or circulating blood contact
  - **Greater than 30 days:**
    - » *mucosal membrane,*
    - » *breached or compromised surface*,
    - » externally communicating devices with *indirect blood contact*; or tissue or bone contact: or direct blood contact,
    - » implant devices with tissue, bone or circulating blood contact

ISO 10993-3 (2014) - Standard

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ISO 10993-3 (2014) - Standard

- ISO 10993-3 Biological Evaluation of Medical Devices Part 3: Tests for the evaluation of genotoxicity, carcinogenicity and reproductive toxicity was revised and issued in 2014

- New
  - Use of risk assessments and chemical characterization to assess the potential for genetic toxicity
  - Additional guidance on the strategies, test preparation and test requirements,
  - Majority of these requirements will not have a significant impact.
  - Additional guidance for performing and reporting tests (ISO TR 10993-33 - ***Informative***)

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ISO 10993-3 (2014) – Standard

- Scope - section was revised
  - Includes strategies for risk estimation and risk management to be consistent with ISO 10993-1: 2009
  - Revision is a significant change in approach to identifying potential hazards
- Requirements for Test Strategies (NEW – Section 4.1)
  - Determination if genetic toxicity testing is necessary. Primary purpose is to ensure patient safety and to reduce unnecessary testing
  - Emphasizes the need to perform an extensive analysis of the potential risks

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ISO 10993-3 (2014) – Standard

Section 4.1 con't

- Included is an analysis of the chemical constituents of the device materials, manufacturing process residues and degradation products
  - » Reluctance of material manufactures to provide information
  - » May result in device manufacturer performing chemical characterization to obtain needed information.

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ISO 10993-3 (2014) – Standard

- Requirements for Test Strategies (NEW – Section 4.1)
  - Added to conform ISO 10993-1
  - Assessment of risk shall address the following factors:
    - » Chemical Characterization (ISO 10993-18) shall be performed prior to biological testing (ISO 10993-1 section 4.3)
    - » Literature and other Sources
    - » Structure Activity Relationships
    - » Threshold of Toxicological Concern
    - » Tolerable Intake (ISO 10993-17)
  - Results of risk assessment may find that genetic toxicity testing is unnecessary

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ISO 10993-3 (2014) – Standard

- Genotoxicity tests – Test Battery (Section 5.2.2)
  - A single test battery is now preferred
  - Includes a test for reverse mutations in bacteria and an *in vitro* mammalian cells test for genotoxicity
  - To meet the *in vitro* mammalian cell genotoxicity tests requirement, 1 of 3 tests may be chosen:
    - » An *in vitro* test for chromosomal damage;
    - » An *in vitro* mouse lymphoma tk test; or
    - » An *in vitro* mammalian cell micronucleus test (new)
  - *In vivo* genotoxicity testing is not part of the initial test battery
    - » Should only be considered when relevant factors indicate the need
    - » When there is a need to resolve the results from *in vitro* tests

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ISO 10993-3 (2014) – Standard

- Genotoxicity tests – Follow up evaluation (New Section 5.2.3)
  - If both *in vitro* tests are negative, additional testing is not required
  - If any of the *in vitro* tests indicate the potential for genotoxicity, a step-wise procedure is recommended (but not a requirement)
    - » Identify any confounding factors
    - » Weight of Evidence and Mode of Action
    - » Determine if the extract is a genotoxin
    - » Manage risks if possible or consider performing additional tests
    - » If an *in vivo* test is performed, the test **shall** be selected on the basis of the most appropriate end point
    - » Reinterpret all of the accumulated data

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ISO 10993-3 (2014) – Standard

- Genotoxicity tests – Sample Preparation (Revised 5.3)
  - Text needs to be revised since many scientist have interpreted this section to require the extraction procedure in Annex A
  - Extractions performed per ISO 10993-12
  - Both polar and not non-polar solvents are used for extraction.
  - Polar and non-polar extracts are tested separately
  - Selection of solvents shall be based on their ability to maximize extraction
  - Exaggerated conditions are required and extractions using physiological conditions are not generally acceptable

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ISO 10993-3 (2014) – Standard

- Genotoxicity tests – Sample Preparation (Revised 5.3)
  - Any decision to omit testing with one class of solvent shall be documented and justified
  - An extraction procedure is provided in informative Annex A. However, the procedure may not be accepted by some regulatory agencies (Japan vs. USA)
  - Test article should represent the final state of the medical device including processing.

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ISO 10993-3 (2014) – Standard

- Genotoxicity tests – Added report requirements:
  - Name and certification of the test laboratory,
  - Date of the test, and name and signature of the responsible person
  - A statement of compliance to the appropriate Good Laboratory Practice (GLPs) or if applicable to ISO/IEC 17025
  - Additional information as specified in ISO TR 10993-33 (March, 2015)

ISO TR 10993-33 - Guidance on Tests to Evaluate Genotoxicity – Supplement to ISO 10993-3 (March 2015)

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ISO TR 10993-33 - Guidance on Tests to Evaluate Genotoxicity – Supplement to ISO 10993-3 (March 2015 - Informative)

- Provides background information on the selection of genotoxicity tests, recommendations on tests to perform and guidance on the use of *in vitro* and *in vivo* tests in genetic toxicity evaluations

- Specific guidance of how to perform tests (bacterial reverse mutation, *in vitro* chromosomal aberrations, *in vitro* mammalian micronucleus, *in vitro* mammalian gene mutation using mouse lymphoma cells, *in vivo* mammalian erythrocyte micronucleus, and *in vivo* chromosomal aberration tests)

- Provides specific recommendation on the preparations, test conditions, procedures, data collection and reporting

- May need to be revised to be consistent with recent changes to OECD Test Guidelines

Challenges using ISO 10993-3

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Challenges using ISO 10993-3

- Although ISO 10993-3 is globally accepted, there are various national interpretations or exceptions to the standard
- These interpretations or exceptions can result in adding or repeating a test to acquire approval of a submission.
- On June 16, 2016, the FDA issued: Guidance for Industry and Food and Drug Administration Staff: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process“
  - An *in vivo* cytogenetics assay should be considered, for example, for devices containing novel materials.
  - Accepts risk assessments (chemical characterization)

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National Exceptions – USFDA

In July, the FDA revised its list of recognized consensus standards.

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm

1. Clause 4.1, is not recognized.
2. Clause 5.2.3, is not recognized.
3. Clause 5.3, is not recognized.
4. Clause 6.2, Sentence, "One animal species is typically sufficient for testing medical devices." is not recognized (Carcinogenicity).
5. Clause 7.2, Phrase, "or test material", is not recognized (Reproductive Toxicity).
6. Annexes A and B, are not recognized.

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National Exceptions - USFDA

1. Section 4.1 (General):

   Comment: this section is overly complicated and that much of the information is already covered in ISO 10993-1

2. Section 5.2.3 (Follow Up Evaluation):

   Comment: *in vitro* genetic toxicity test performed to current standards would not have to be evaluated for potential false positives and that the resolution of *in vitro* positive results is best resolved by repeating the test or performing another *in vitro* genetic toxicity test.

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National Exceptions – USFDA

3. For section 5.3 – Sample Preparation,

   Comment: the FDA does not accept the alternative extraction procedure which is used in Japan. The FDA also stated that the use of a single solvent without justification is unacceptable.

4. The FDA also does not accept Annex A and Annex B of ISO 10993-3 which are associated with sections 5.2.3 and 5.3.

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National Exceptions – Japan MHLW

- In Basic Principles of Biological Safety Evaluation Required for Application to Market Medical Devices, MHLW recommends a 3-stage decision tree to determine the appropriate extraction procedure to use for genotoxicity tests
  - A similar but not identical decision tree in Annex A of ISO 10993-3 (2014) However, Annex A is unclear about the need to test 2 extracts
  - The Difference is Method C
    - » ISO 10993-3 Annex A - The device is extract per ISO 10993-12
    - » The MHLW recommends:
      1. For the bacterial reverse mutation test, extract using DMSO
      2. For the in vitro mammalian mutagenesis tests, extract using media

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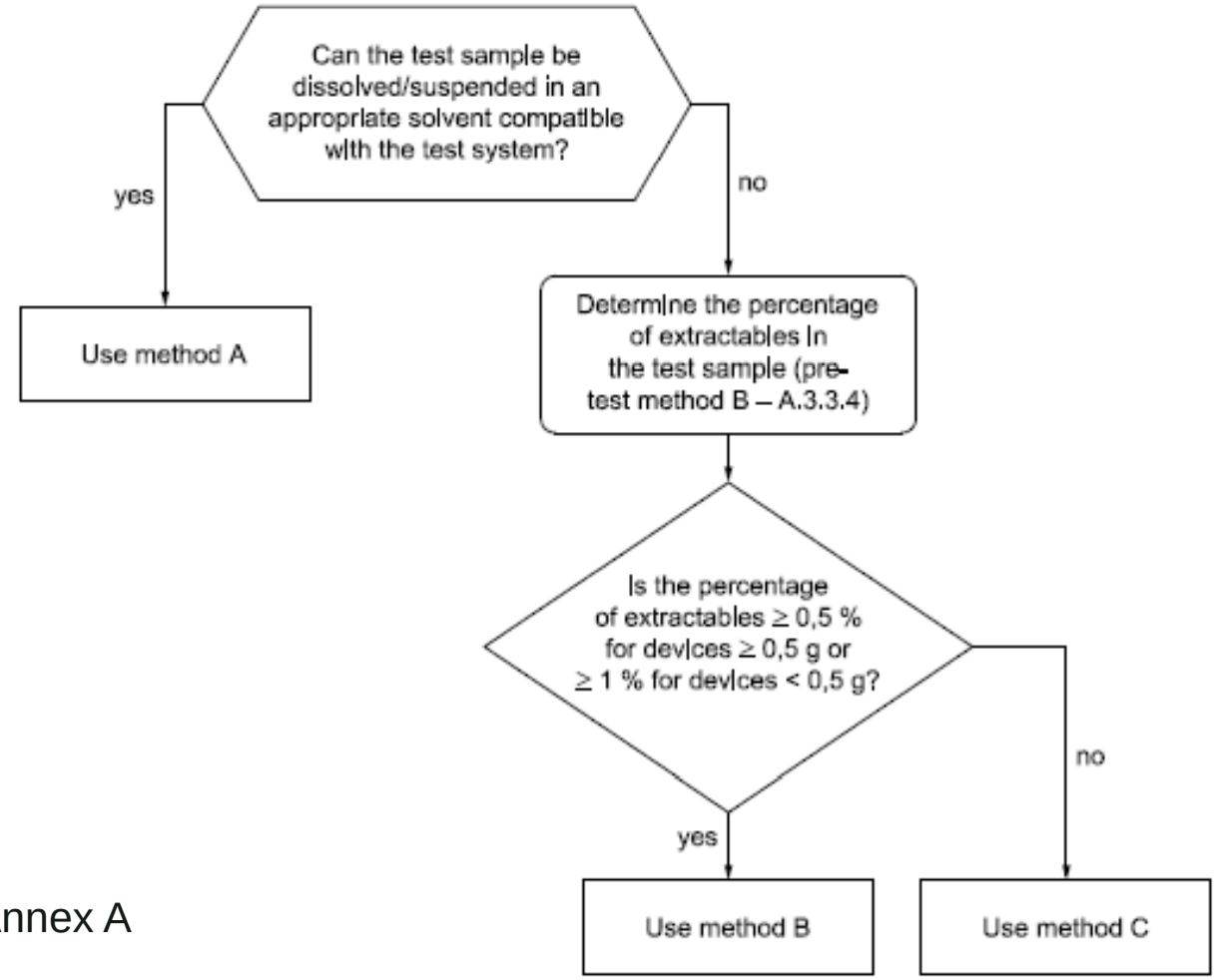

From ISO 10993-3: Annex A

Figure A.1 — Structured approach to select a sample preparation procedure

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National Exceptions – Chinese FDA

- Chinese Food and Drug Administration (CFDA) currently accepts ISO 10993-3 (2003)
  - Not clear if the *in vitro* mammalian cell micronucleus test will be accepted since it is not included in the 2003 version
  - Chemical characterization and risk assessments justifying not performing genotoxicity tests may or may not be accepted.
  - However, CFDA does recognize the current version of ISO 10993-1 (2009) and has made considerable efforts to train reviewers to use the risk management process.
  - Translation issues

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National Exceptions – Europe

There are no exceptions to harmonized standards. Any procedure or method allowed in the standard is acceptable.

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The adequacy of the various sample preparations allowed in ISO 10993-3 is still being debated

- The Debate arose from the concern that various solvents extract chemical entities differentially, and testing of a single extract may not adequately assess the risk
- Is there a need to concentrate the extract?
- Will concentrating the extract exclude some chemicals and create new chemical entities.
- Is the ISO 10993-12 method sufficient for hazard identification?
- Is exhaustive extraction sufficient for hazard identification (FDA Guidance, 2016)

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Summary

- Discussed what is different about evaluating medical devices
- How to determine if genetic toxicity testing is needed
- ISO 10993-3 (2014) - Standard
- ISO TR 10993-33 - Guidance on Tests to Evaluate Genotoxicity – Supplement to ISO 10993-3
- Challenges using ISO 10993-3 – Globally accepted but subject to interpretation by national regulatory agencies
- Because of these challenges, ISO 10993-3 (2014) should be considered a work in progress and further development is warranted

Thank You!