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MEDICAL RESEARCH ORGANIZATION

The New ISO 10993-1:2018 – What Now?

August 27th, 2018

Agenda

- History and the ever Expanding Universe
- Review changes to the standard
  - Overview of what changed/remained the same in main clauses of the standard
  - Look at new additions to the standard
- Consider how these changes may impact past and future evaluation strategies

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History

- Tripartite Agreement in Mid 80's
- ISO 10993
- Blue Book-G95-1 The FDA's response to ISO 10993
- Major Revision to ISO 10993 in 2009
- FDA response in 2012 (finalized in 2016)
- Major Revision to ISO 10993 in 2018

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Foreword of ISO 10993-1:2018

- Provides a summary of main changes – most notable items mentioned
  - Annex A changed
  - ISO TR 15499 added as Annex B
  - Additional definitions
  - Non-contacting and transitory device categories added
- Other clauses in the standard also changed

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Clause 1: Scope

- Devices making patient contact remain in scope
- "User's body" also in scope for devices intended for protection – gloves/masks
- Hazards due to breakage also in scope
  - May expose new or novel materials
  - Previously mechanical failure not in scope

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Clause 3: Terms and definitions

- Numerous additional definitions added
  - Biological risk, biological safety, material characterization, physical and chemical information, risk analysis, risk assessment, risk evaluation, toxicological hazards, etc
  - Definitions provide framework for the concept of evaluation presented in the standard
  - Important to go back to the definitions when a term/concept is used in text of the standard

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Clause 4: General principles

- There were 8 - now 11
- Original 8 remain with some modifications
- Principles 1 and 2 remain essentially the same
  - Principle 1 continues to stress that biological evaluation is part of a planned activity
- Principle 3 now includes packaging materials as part of the evaluation
- Principles 4 and 5 remain consistent with prior version but other sections of standard they reference are modified

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Clause 4: General principles cont'd

- Principle 6 essentially the same but points to Annex A which has changed
- Principle 7 is new
  - Safety evaluation covers the whole life cycle of a medical device

  This will be an interesting point for FDA/Notified Bodies/Device Manufactures? When does it end?
- Principle 8 is new
  - Evaluate re-usable devices for maximum number of validated processing cycles
    - How? What's required?
    - Principle 9-Changes requiring retesting

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Clause 4: General principles cont'd

- Principle 11 (4.11) is new
  - Standard shall not mandate a need for new testing of previously evaluated devices
  - Compliance – justification for omission of any such testing
  - History of safe clinical use can be leveraged to meet the standard
  - Any changes as outlined in Principle 9 require evaluation per the current standard

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Clause 5: Categorization of medical devices

- General (5.1):
  - Keep devices with different exposure evaluated separately

- Nature of body contact
  - Non-contacting devices added
  - Surface contacting/skin
    - The “NOTE” is new
    - Address items made of common materials that contact a user’s ungloved or gloved hand
    - Leverage data supporting the safety of the material

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Clause 5: Categorization of medical devices cont'd

- Nature of body contact
  - Externally communicating
    - Indirect contacting devices that deliver fluids to bone or tissue now defined here
- Duration of contact
  - Permanent now called "Long-term"
  - Transitory contacting devices defined
    - Not listed as a category in Annex A
    - Use less than a minute assuming nothing is left behind
    - "…not require testing to address biocompatibility"

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Clause 6: Biological evaluation process

- Significant changes
  - Physical and chemical information requirement - modified
  - Gap analysis – new section
  - Annex A, Table A.1 – modified

- Physical and chemical information

  Step 1 in biological evaluation process - was referred to as material characterization now is part of the material characterization process

  "knowledge regarding formulation, manufacturing processes, geometric and physical properties and type of body contact and clinical use that is used to determine whether any additional biological or material characterization testing is needed"

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Clause 6: Biological evaluation process cont'd

- Physical and chemical information
  - Still indicates that at a minimum, characterization shall address the constituent chemicals of the medical device and possible residual process aids or additives used in its manufacture
  - Data should address two rows of questions in Figure 1

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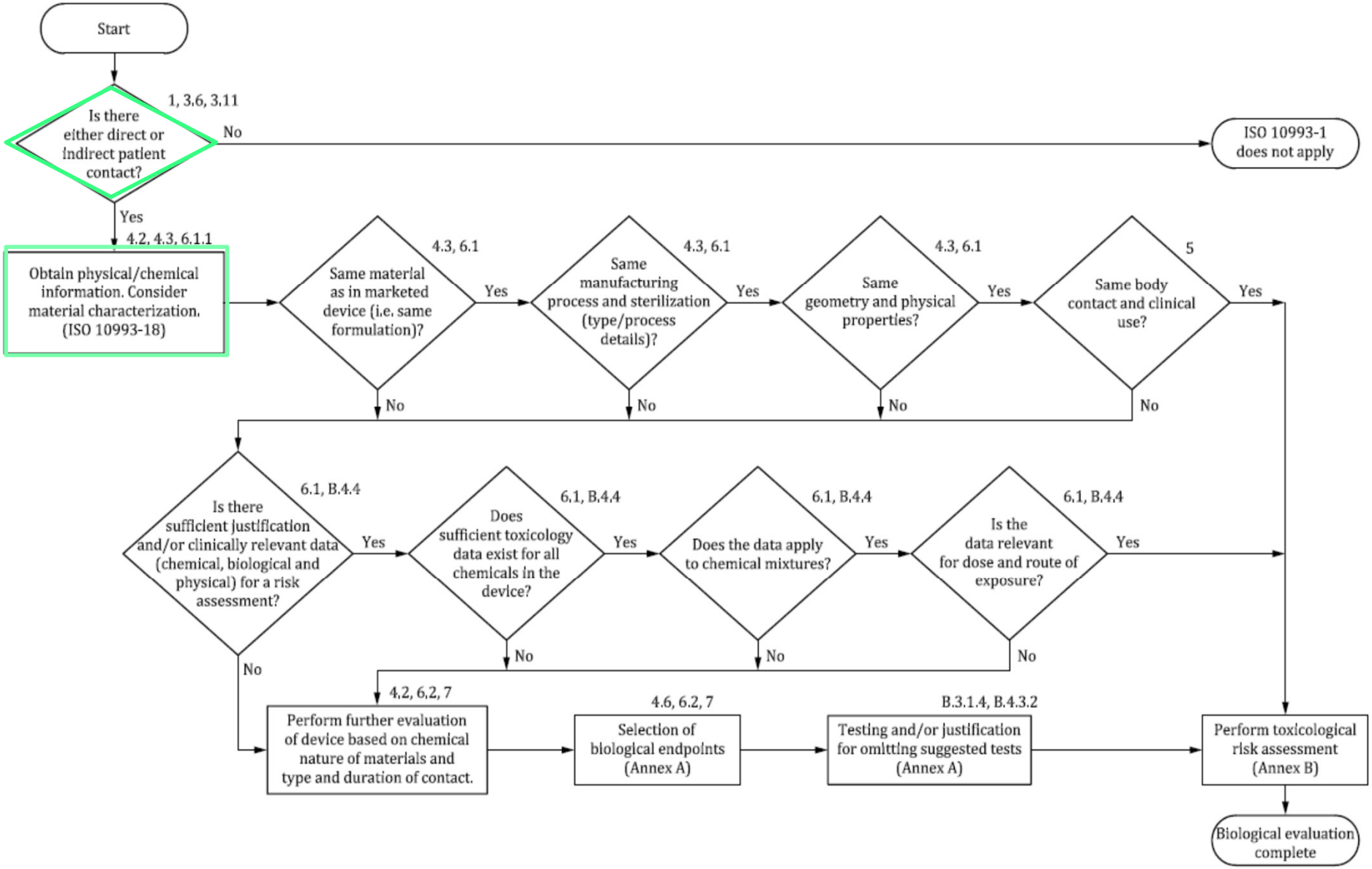
Start
1, 3.6, 3.11
Is there either direct or indirect patient contact?
No
ISO 10993-1 does not apply
Yes
4.2, 4.3, 6.1.1
Obtain physical/chemical information. Consider material characterization. (ISO 10993-18)
4.3, 6.1
Same material as in marketed device (i.e. same formulation)?
Yes
4.3, 6.1
Same manufacturing process and sterilization (type/process details)?
Yes
4.3, 6.1
Same geometry and physical properties?
Yes
5
Same body contact and clinical use?
Yes
No
No
No
No
6.1, B.4.4
Is there sufficient justification and/or clinically relevant data (chemical, biological and physical) for a risk assessment?
Yes
6.1, B.4.4
Does sufficient toxicology data exist for all chemicals in the device?
Yes
6.1, B.4.4
Does the data apply to chemical mixtures?
Yes
6.1, B.4.4
Is the data relevant for dose and route of exposure?
Yes
No
No
No
No
4.2, 6.2, 7
Perform further evaluation of device based on chemical nature of materials and type and duration of contact.
4.6, 6.2, 7
Selection of biological endpoints (Annex A)
B.3.1.4, B.4.3.2
Testing and/or justification for omitting suggested tests (Annex A)
Perform toxicological risk assessment (Annex B)
Biological evaluation complete

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Clause 6: Biological evaluation process cont'd

- Gap analysis and selection of biological endpoints
  - Assess available information
    - General principles
    - Annex A
    - Literature search (Annex C)
  - Determine gaps between data available and risks identified and fill gaps with obtainable data as needed
    - Justifications possible to address gaps?
    - Testing needed?
      - Chemical characterization testing of device extracts?
      - Biological testing?

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Clause 6: Biological evaluation process cont'd

- Biological testing
  - Concept and use remains consistent
  - Include appropriate level of testing where needed to address gaps in your dataset
  - Material mediated pyrogenicity indicated as its own endpoint
  - Implantation – emphasizes combing this into systemic studies an/or large animal studies to address multiple endpoints
  - Genotoxicity – chemical identification of impurities/extractables/leachables may be needed with positive results
  - 6.3 refers to Annex A, Table A.1

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Table A.1 — Endpoints to be addressed in a biological risk assessment

Medical device categorization by			Endpoints for biological evaluation														
Nature of body contact		Contact duration															
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – Long term (>30 d)	Physical and/or chemical information	Cytotoxicity	?	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]
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		
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[i]	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[j]			
		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		

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Medical device categorization by			Endpoints of biological evaluation														
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Implant medical device	Tissue/bone [i]	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		
	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		

[a] Refer to ISO 10993-11:2017, 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 device 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 tissue 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.

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Clause 6: Biological evaluation process cont'd

- Annex A summary
  - Physical and chemical information added as prerequisite
  - Additional biological endpoints added to the table
  - Additional points of evaluation for some categories of devices
  - Justification for addition of the endpoints presented

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Summary

- New Contact Category Added
- Big Three of Testing is now Big Five (Added MMP and Risk Assessment)
- Reach an overall conclusion of the biological safety of the device
- Written Plan to address all endpoints to be considered
- Consider Life of Device
- Consider Breakage and Exposure

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Cleanliness-ISO 19227

- Cleaning is an essential step to achieve biocompatibility and to control the microbiological load required for sterilization
- Are contaminants coming from the previous manufacturing steps? YES => include a cleaning process
- Replaced by ISO 19227 « Implants for surgery – Cleanliness of orthopedic implants – general requirements »
  - In-process cleaning = performed between 2 manufacturing steps in order to remove the contamination coming from previous manufacturing steps
  - Final cleaning = before the implant is protected against further contamination before distribution
- ASTM F3127-16 « Validating Cleaning Processes Used During the Manufacture of Medical Devices »

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Risk Management Process

- ISO 14971 “Medical Devices: Application of Risk Management to Medical devices”
- Identify contaminants, determine test methods and acceptance criteria, before assessing the performances of a cleaning process
- ISO 19227 lists some questions to be addressed (not exhaustive):
  - What are the potential contaminants in contact with the implants during the manufacturing steps preceding each cleaning?
  - What are the risks associated to these contaminants?
  - What are the potential interactions between the contaminants and the implant material?
  - Are there previous critical in-process cleaning or other operations for removing these potential contaminants from the surface?
  - What are the potential contaminants brought by the cleaning steps?
  - Are the test methods selected for the validation of the cleaning process able to assess the level of the potential contaminants to be limited on the implants, taking into account the detection limit, quantitation limit and accuracy of the method?
  - What are the acceptance criteria for each cleaning family?
  - Following validation, what process control requirements are required to maintain cleanliness during manufacturing?
  - What process changes would require revalidation of product cleaning effectiveness?

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Questions?

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