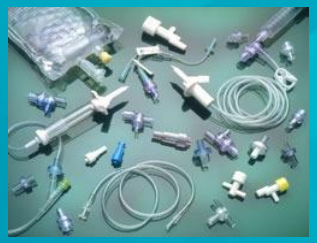
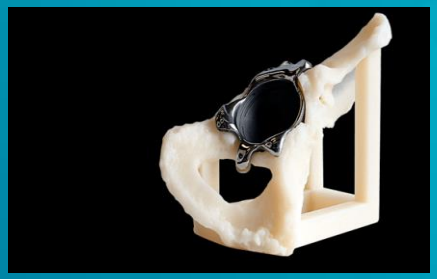
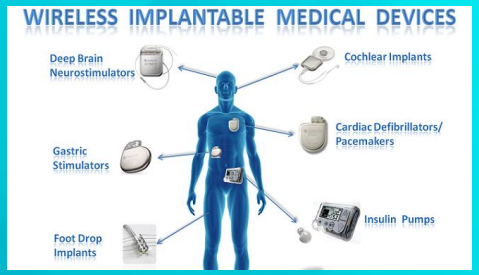








Discussion of a Developing ISO Standard:

Biological evaluation of medical devices — Part 18: Chemical Characterization of Materials

John Iannone, Director, Extractables/Leachables & Impurities, AMRI
Dennis Jenke, Chief Executive Scientist, Triad Scientific Solutions, LLC

What is a Medical Device?

A **medical device** is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to **affect the structure or** any **function** of the body of man or other animals, and which **does not achieve** any of its primary intended purposes **through chemical action** within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

What is a ”Safe” Medical Device?

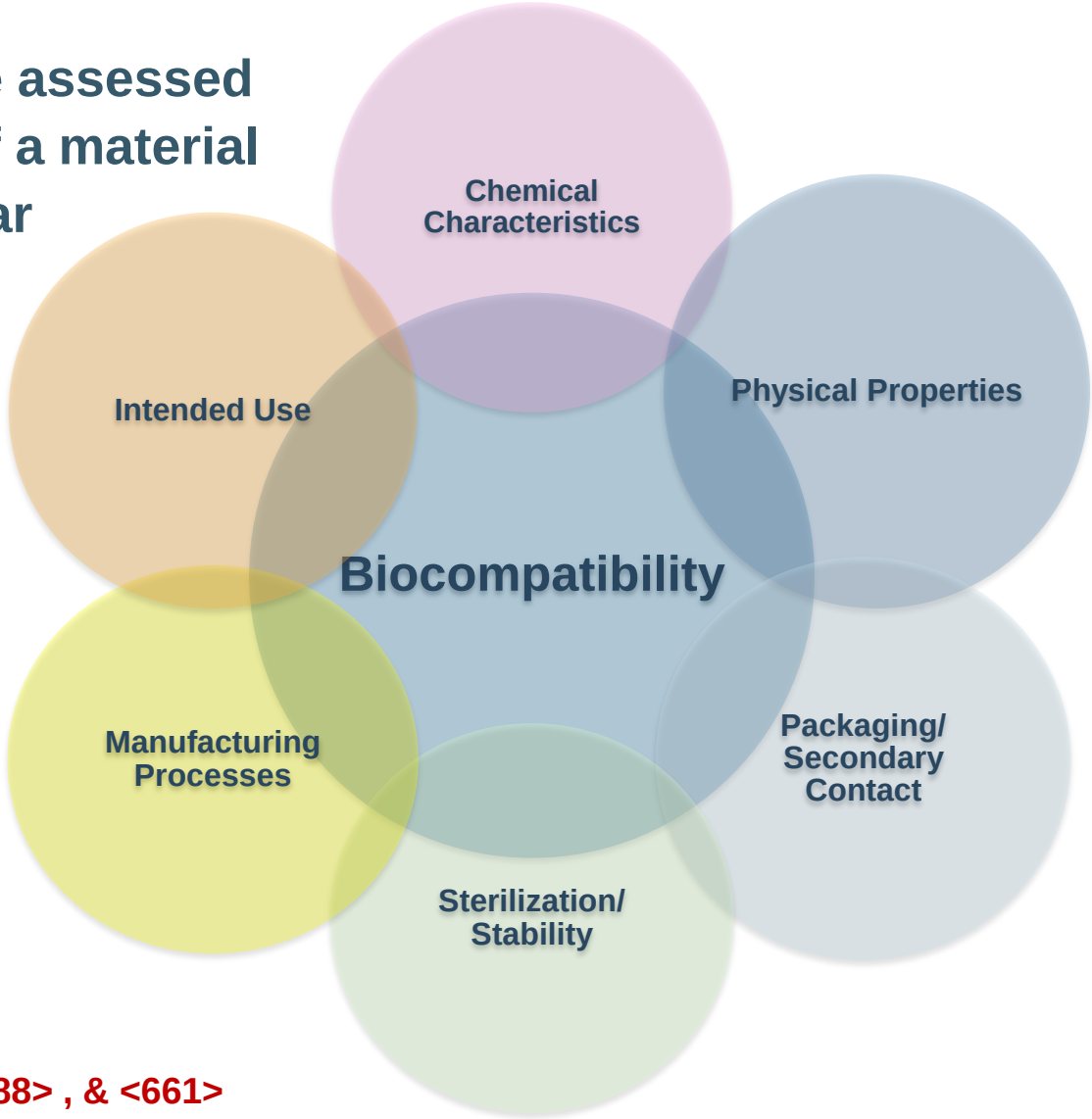
“Essential principles of safety and performance of medical devices”

Medical devices should be designed and manufactured in such a way that, when used under the conditions and for the purposes intended and, where applicable, by virtue of the technical knowledge, experience, education or training of intended users, they **will not compromise** the clinical condition or **the safety of patients, or the safety and health of users or, where applicable, other persons**, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.

GHTF.SG1.N0020R5. Essential Principles of Safety & Performance of Medical Devices. The Global Harmonization Task Force. 30-June-1999.

What does that mean?

Biocompatibility is the assessed biological response of a material or device in a particular application.



Source: USP Workshop on <87> , <88> , & <661>

What is a ”Safe” Medical Device?

Evaluation Strategy

ISO 10993–1:2009 *Biological Evaluation of Medical Devices: Part 1: Evaluation & testing within a risk management process*.

Test Methods

Part 5:	Cytotoxicity
Part 10:	Irritation & hypersensitivity
Part 11:	Systemic toxicity
Part 3:	Genotoxicity, carcinogenicity and reproductive toxicity
Part 6:	Implantation and local effects
Part 4:	Blood compatibility
Part 16:	Toxicokinetic study design for leachables and degradation products
Part 20:	Principles and methods for immunotoxicology testing

Animal Welfare

Part 2: Animal welfare requirements

Reference Materials

Part 8:	Selection of reference materials
Part 12:	Sample preparation and reference materials

Sterilization Residuals

Part 7: Ethylene oxide sterilization residuals

Degradation Products

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

Risk Assessment

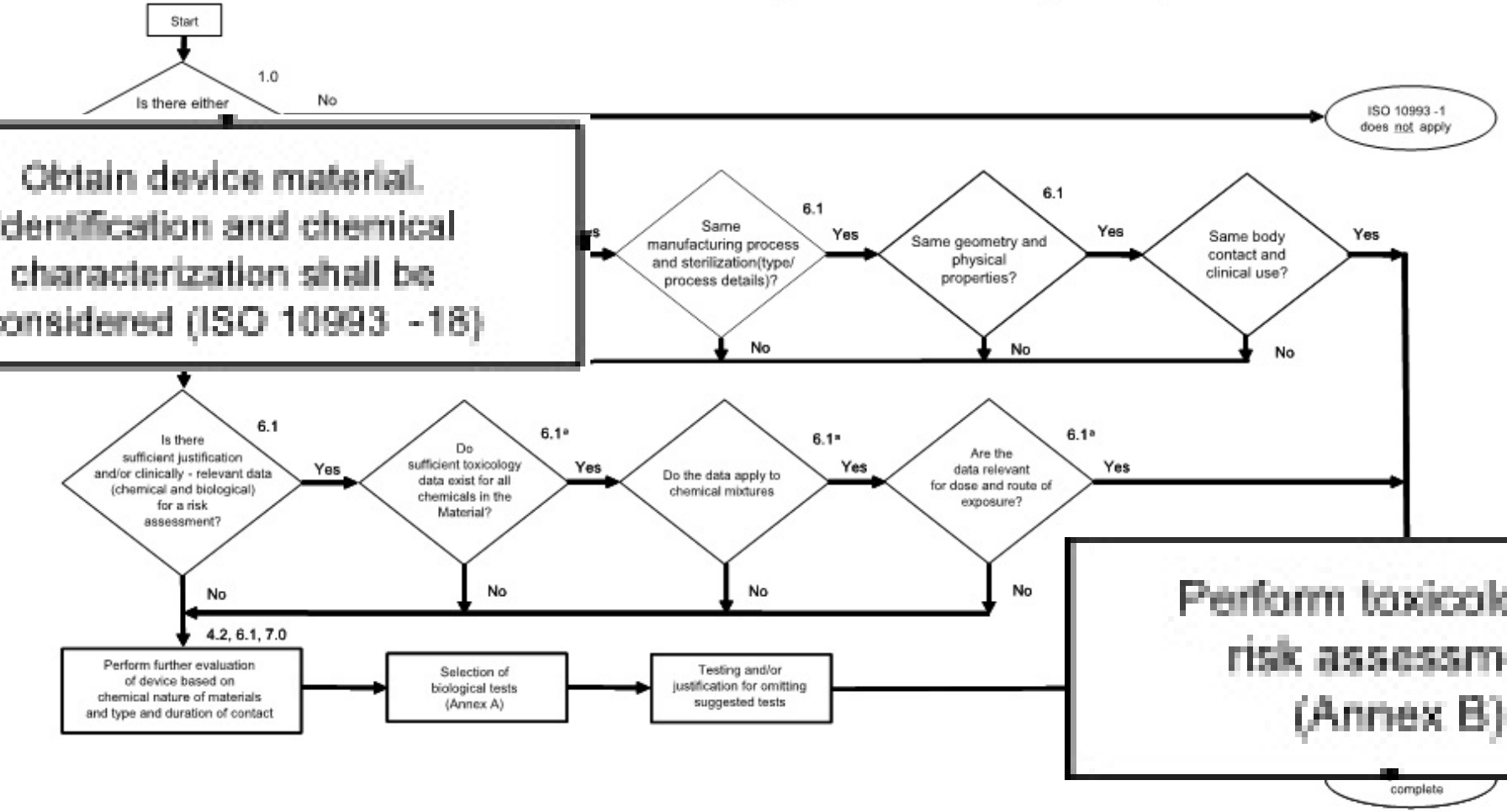
Part 17: Establishment of allowable limits for leachables

Materials Characterization

Part 18:	Chemical characterization of materials
Part 19:	Physico-chemical, morphological and topographical characterization

Role of Chemical Characterization in Biological Evaluation of Medical Devices

Figure 1 — Summary of the systematic approach to a biological evaluation of medical devices as part of a risk management process



Role of Chemical Characterization in Biological Evaluation of Medical Devices

Device Categories				Initial Evaluation										Supplemental				
Category	Body Contact Contact	Contact duration		Cytotoxicity	Sensitivity/Sensitization	Irritation/Intracutaneous Reactivity	Systemic Toxicity (Acute)	Pyrogenicity	Sub acute and/or Sub chronic toxicity	Genetic Toxicity/Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/ Developmental	Biodegradation/ Biodegradable	
Body Surface Contact Device/Surface Device	Skin	less than 24 hours	X	■	■	■											
		24 hours to 30 days	X	■	■	■											
		more than a 30 days	X	■	■	■											
	Mucous/Mucosal Membrane	less than 24 hours	X	■	■	■											
		24 hours to 30 days	X	■	■	■	❍	❍	❍		❍						
		more than a 30 days	X	■	■	■	❍	❍	■	■	❍		❍				
	Breached/Compromised Surface	less than 24 hours	X	■	■	■	❍	❍									
		24 hours to 30 days	X	■	■	■	❍	❍	❍		❍						
		more than a 30 days	X	■	■	■	❍	❍	■	■	❍		❍				
Devices connecting the internal to the external/External communicating device	Blood Vessels/Blood Path Indirect	less than 24 hours	X	■	■	■	■	■				■					
		24 hours to 30 days	X	■	■	■	■	■	❍			■					
		more than a 30 days	X	■	■	❍	■	■	■	■	❍	■	■	■			
	Tissue/Bone/Dentin	less than 24 hours	X	■	■	■	❍	❍									
		24 hours to 30 days	X	■	■	□	□	□	□	■	■						
		more than a 30 days	X	■	■	□	□	□	□	■	■		□	■			
	Circulating Blood	less than 24 hours	X	■	■	■	■	■		❍		■					
		24 hours to 30 days	X	■	■	■	■	■	□	■	□	■					
		more than a 30 days	X	■	■	■	■	■	■	■	□	■	■	■			
Internally implanted devices/Implant device	Tissue/Bone	less than 24 hours	X	■	■	■	❍	❍									
		24 hours to 30 days	X	■	■	□	□	□	□	■	■						
		more than a 30 days	X	■	■	□	□	□	□	■	■		■	■			
	Blood	less than 24 hours	X	■	■	■	■	■	◆		■	■					
		24 hours to 30 days	X	■	■	■	■	■	□	■	■	■					
		more than a 30 days	X	■	■	■	■	■	■	■	■	■	■	■			

■ = Evaluation required by ISO, FDA and MHLW
□ = Evaluation required by ISO and FDA
❍ =Evaluation required by FDA
◆ =Evaluation required by ISO

Objectives of 10993-18

The **requirements specified** are **intended to yield** the following **information,** which will be of value in **assessing** the **biological response of** the **materials** as represented in the final product**:**

- The **identities** and **quantities**, as appropriate, of the **materials of construction** of the medical device (**device configuration**).
- The **identities** and **quantities**, as appropriate, of the **chemical substances** intentionally and unintentionally present in each material of construction (**material composition**).
- The **identities** and **quantities**, as appropriate, of **chemical substances** used in the device's **manufacturing process** including processing aids and residues.
- The **potential** of the medical **device** and/or its materials of construction to **release chemical substances** to which the **patient** could be **exposed** to during clinical conditions of use.

Scope of 10993-18

This document specifies a framework for the characterization of a device through:

- the **identification** of its materials of construction (**device configuration**),
- the **characterization** of the materials of construction via the identification and quantification of their chemical constituents, both intentionally and unintentionally present (**material composition**),
- the **characterization** of the device for **chemical substances** that were introduced during **manufacturing** (e.g., mold release agents, DEHP contaminants), and
- the **assessment** of the **potential** of the device, or its materials of construction, to **release chemical substances** under **clinical use conditions**.

Applicability of 10993-18 (1)

ISO 10993 series of standards is **applicable** when the material or device has **direct or indirect** tissue **contact** with a patient **.**
(see ISO 10993-1 for categorization by nature of body contact)

Part 1 also describes **instances** in which **direct or indirect contact** with a ***clinician's body should be considered*;**

> that is, if the device is intended to protect the clinician (e.g., surgical gloves, masks and others).
>
> throughout this part, *references to patient contact shall be understood to include contact with the clinician for devices intended to protect the clinician.*

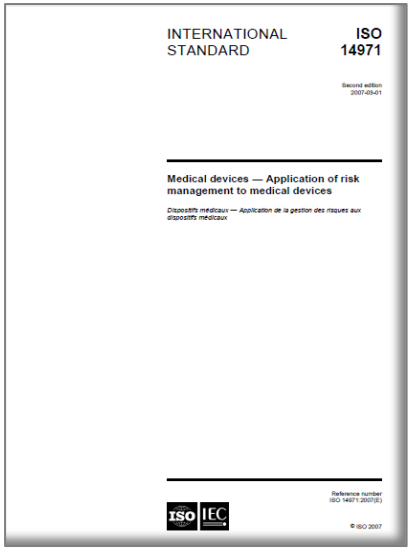
Applicability of 10993-18 (2)

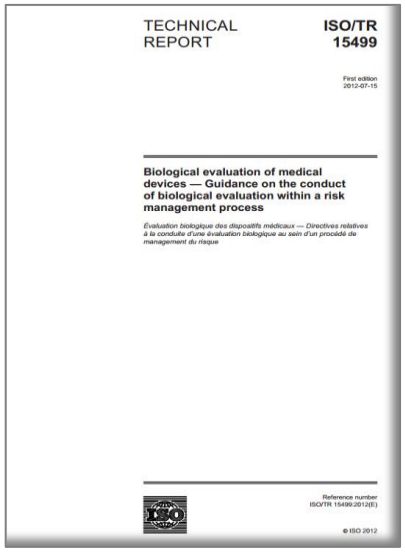
This document is intended for suppliers of materials and manufacturers of medical devices, to support a biological evaluation.

Applications of 10993-18 (1)

- Supporting the **overall biological safety** of a medical device (ISO 10993-1 (*including former ISO 15499*) & ISO 14971.

ISO 14971 → ISO/TR 15499 ← ISO 10993


INTERNATIONAL STANDARD
ISO 14971
Second edition
2007-03-01
Medical devices — Application of risk management to medical devices
Dispositifs médicaux — Application de la gestion des risques aux dispositifs médicaux
Reference number
ISO 14971:2007(E)
© ISO 2007


TECHNICAL REPORT
ISO/TR 15499
First edition
2012-07-15
Biological evaluation of medical devices — Guidance on the conduct of biological evaluation within a risk management process
Évaluation biologique des dispositifs médicaux — Directives relatives à la conduite d'une évaluation biologique au sein d'un procédé de management du risque
Reference number
ISO/TR 15499:2012(E)
© ISO 2012


INTERNATIONAL STANDARD
ISO 10993-1
Fourth edition
2009-10-15
Biological evaluation of medical devices —
Part 1:
Evaluation and testing within a risk management process
Évaluation biologique des dispositifs médicaux —
Partie 1: Évaluation et essais au sein d'un processus de gestion du risque
Reference number
ISO 10993-1:2009(E)
© ISO 2009

Applications of 10993-18 (1)

- Supporting the **overall biological safety** of a medical device (ISO 10993-1 (*including former ISO 15499*) & ISO 14971.
- Supporting the overall biological safety of a reprocessed medical device.
- Determining the **level** of **chemical substances** that might be **leached** from a medical device **under** the **conditions** of its clinical use, to **assess** conformance to the **allowable limit** of those substances as derived from health based risk assessment (ISO 10993-17).
- **Screening** of potential **new materials** for **chemical suitability** in a medical device for a proposed **clinical application**.

Applications of 10993-18 (2)

- Establishing **equivalence** of a **proposed device** to a legally **marketed device** with regard to either the device's **configuration** or its **extractables/leachables profiles** and any subsequent relevant evaluations.
- Establishing **equivalence** of a legally **marketed device** ***after changes*** in the **manufacturing process**, (including, but not limited, to changes in the sterilization process), manufacturing sites, suppliers of materials or components, etc.
- Establishing **equivalence** of a **proposed material** of **construction** to a **clinically established material of construction** with regard to either the **material's composition** or its **extractables profiles** & any subsequent relevant evaluations.
- Establishing **equivalence** of a **final device** to a **prototype device** in regards to the use of data secured on the prototype to support the assessment of the final device, specifically **considering** relevant information such as **composition, device configuration** and **extractable profile** obtained for either the device or its materials of construction.

An Important Caveat

… chemical characterization **alone may be insufficient** to **establish** the **equivalence** or **biocompatibility** of materials and devices, and cannot unilaterally substitute for biological testing.

However, **chemical characterization** in combination **with risk assessment** may be a necessary part of judging chemical equivalence and assessing biocompatibility, and **if appropriately conducted** can be used **in lieu** of certain **biocompatibility** tests.

More on this later …

Key Definitions (1)

chemical safety risk assessment

process of establishing that a medical device, when used in its clinically prescribed manner, **is safe**, meaning that there is a negligible risk to the health of potentially affected individuals, **based** on the individual's **exposure** to the device's **chemical constituents**

Key Definitions (2)

Extractables

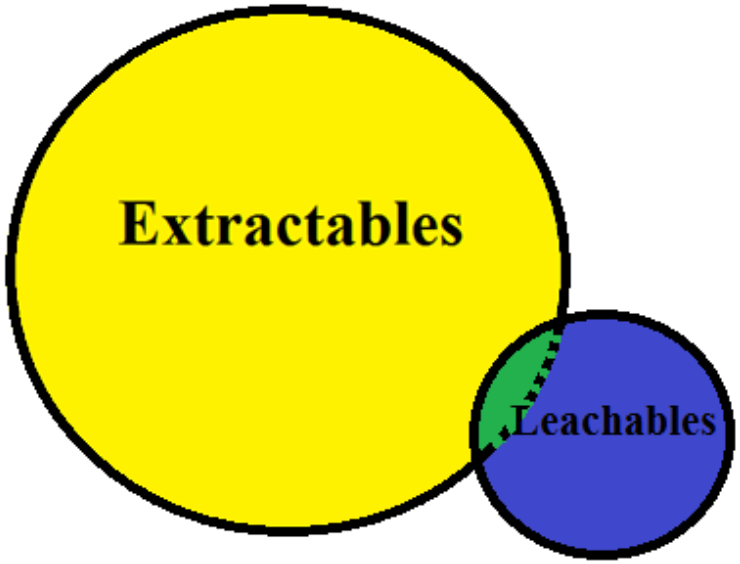
substances that are **released** from a medical device or material of construction when the device or material is extracted using **laboratory extraction conditions** and **vehicles**

Leachables

substances that are **released** from a medical device and to a patient **during its clinical use**

Relationship of Extractables & Leachables

Controlled Extraction relevance to clinical application



Overlap **is based on** ***how well*** **Controlled Extraction study** ***models***
Clinically Relevant condition

Key Definitions (3)

Device Configuration

listing of a **device's components (***qualitative*), augmented by a listing of the component's **materials of construction** (*qualitative*) and the **proportion** of each material in each component (***quantitative***)

Material Composition

listing of the **substances** that are **contained** in a material (*qualitative*) and the **amount** of **each substance** in the material (***quantitative***)

Key Definitions – Types of Extractions (4)

Extraction: chemical process performed to **separate a chemical substance** from a test article by **exposing** the **test article** to an **extraction vehicle** under defined and **controlled conditions**

Exhaustive: extraction, accomplished using **multiple extraction steps**, that solubilizes the **total amount** of **extractable substances** present in a test article, as evidenced when the amount of extractables released in a subsequent extraction step is less than 10% of the amount of extractables released in the first extraction step

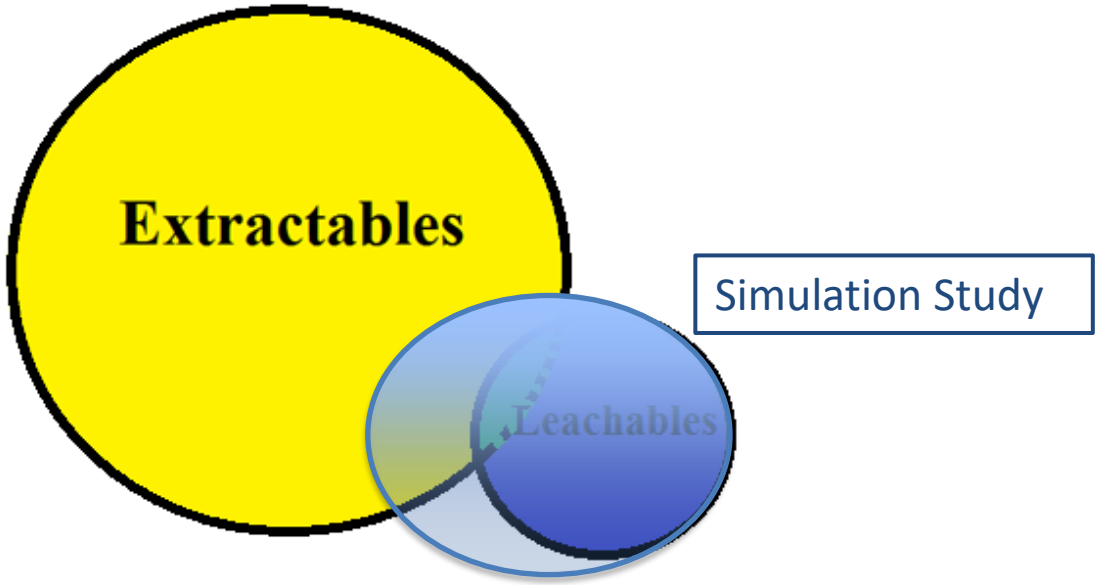
Exaggerated: extraction that is intended to result in a **greater number or amount of chemical constituents** being released as compared to the **amount generated under the clinical conditions** of use but is not expected to result in a chemical change of the substances being extracted

Accelerated: extraction whose **duration is shorter** than the **duration of clinical use** but whose conditions do not result in a chemical change of the substances being extracted

Simulated-use: extraction, performed using an **extraction method** that **simulates clinical use**, which is conducted to evaluate those extractable substances which **could be available** as **leachables** from a device during the **routine clinical use** of the device

Relationship of Extractables & Leachables

Controlled Extraction relevance to clinical application



Overlap **is based on** ***how well*** **Controlled Extraction study** ***models*** **Clinically Relevant condition**

Key Definitions – Types of Extractions (5)

Why are there so many different types of extractions?

Because the extraction should match the objective of the chemical characterization!

MEDICAL DEVICE CATEGORIZATION			EXAMPLES		SAMPLE PREPARATION FOR MATERIAL CHARACTERIZATION													
					Typical Model Solvents							Typical Extraction Conditions						
					Consider Extraction Solvent as related to Clinical Use:							Consider Extraction Condition as related to Clincal Use						
					Commonly Utilized (but not limited) Solvents Include:	3. Simulated Use	1. Exaggerated 2. Accelerated 4. Exhaustive				Other Solvents for consideration Include:	Commonly Utilized (but not limited) Conditions Include:	3. Simulated use	1. Exaggerated 2. Accelerated		4.Exhaustive Extraction		Other Conditions for consideration Include:
NATURE OF BODY CONTACT		Contact Duration: A – Limited (<24h) B – prolonged (>24h – 30 days) C – permanent (> 30days)	Device Example	Material of Construction		Model Solvents of Intended Use Demonstate -Extractable Solubility & -Material Effects	Purified Water (polar)	1/9 (v/v) ethanol/saline	2/3 (v/v) ethanol/saline	1/1 (v/v) ethanol/water			Clinical Use Conditions (Relative to Storage and/or In Use Conditions)		50°C for 72h	70°C for 24h	Extraction Temperature: 50°C ± 2°C Transition/Degradation Temp Extraction Duration: Determined by		As appropriately determined through clincal considerations
SURFACE DEVICE	Skin	A			As appropriately determined through clincal considerations		X				As appropriately determined through clincal considerations					X		
		B					X	X							X			
		C	Insulin Delivery Pump - Part A	Multi				X	X	X					X		(X)	
	Mucosal Membrane	A					X									X		
		B						X		X					X			
		C						X	X	X					X		(X)	
	Breached / Compromised Surface	A					X									X		
		B						X		X					X			
		C	Wound Healing Adhesive	CA				X	X	X					X		(X)	
EXTERNAL COMMUNICATING DEVICE	Blood Path (indirect)	A				X		X		X			X			X		
		B	IV Administration Set	PVC, PE,& Silicone		X		X		X			X		X			
		C				X		X	X	X			X		X		(X)	
	Tissue/Bone/Dentin	A						X		X						X		
		B						X		X					X			
		C	Insulin Delivery Pump - Part B	Multi				X	X	X					X		(X)	
	Circulating Blood	A	Vascular Delivery Device	Polyeurathane				X		X						X		
		B	PICC Catheter (<30 days)	Polyeurathane				X		X					X			
		C						X	X	X					X		(X)	
IMPLANT DEVICE	Tissue/Bone	A						X		X						X		
		B						X		X					X			
		C	Orthopedic Spinal fusion device	Composite of PEEK & titanium				X	X	X					X		(X)	
	Blood	A						X		X						X		
		B						X		X					X			
		C						X	X	X					X		(X)	

General Principles (1)

Chemical characterization can facilitate the biological safety assessment process in three ways:

1. By providing the *chemical information* that is a **necessary input** into **comparing** the medical device in question with potential predicate devices (**establish equivalence**),
2. By providing the *chemical basis* for ***comparing*** the medical device in question to a *relevant standard* (**establish conformance**),
3. By providing the chemical information that serves as the basis for a toxicological risk assessment (enable assessment).

General Principles – Characterization Procedures (2)

Chemical Characterization is based on the following:

1. The issue of **biocompatibility** is **only relevant** for devices that have **direct** or **indirect** patient contact.

2. The extent of **chemical characterization** should **reflect** the nature and duration of the **clinical exposure**

   AND

   the physical **form** of the **materials used** and shall be determined **with the toxicological risk assessor** based on the data necessary to **evaluate** the **biological safety** of the device.

General Principles – Characterization Procedures (3)

Chemical Characterization is based on the following:

3. Establishing the ***configuration*** of a device is the **necessary first step** in establishing the device's **biocompatibility** as
   a. use of ***appropriate materials*** of construction predisposes a device to biocompatible
   b. ***knowledge of the materials*** of construction could provide the *starting point* for establishing *chemical equivalence*.

4. Establishing the **chemical composition** of the materials of construction is a **necessary step** in establishing a device's **biocompatibility**, as
   a. the *composition* of the individual materials can serve as the basis for establishing chemical equivalence to a clinically established device, and
   b. **chemical entities** contained in a material are logical **sources** of **extractables & leachables**

General Principles – Characterization Procedures (4)

Chemical Characterization is based on the following:

5. Determining the device's **potential** to **release chemical substances** under **clinical use** conditions can provide the **basis** for understanding and assessing the device's **potential patient safety impact**.

   Although any of the **substances** in a material or additives used in the process of manufacturing a medical device **could be leached** from the device and thereby become bio-available,

   it could potentially be **necessary** to obtain information **demonstrating** the **extent** to which the **substances** will be **leached** under the **clinical use conditions** of the finished product to **estimate the risk arising from them**.

   This can be estimated by conducting extraction studies of the device.

General Principles – Close Collaboration (4)

The successful completion of the **chemical characterization** outlined in this document ***requires*** expertise in **material science** and **analytical chemistry** to ***provide*** the **necessary** qualitative and quantitative **data** that a risk assessor can use to **assess device safety**.

Toxicology expertise is ***required*** in understanding the types of compounds that might be of toxicological concern so that the **materials** and **chemistry experts** can **design appropriate experiments**.

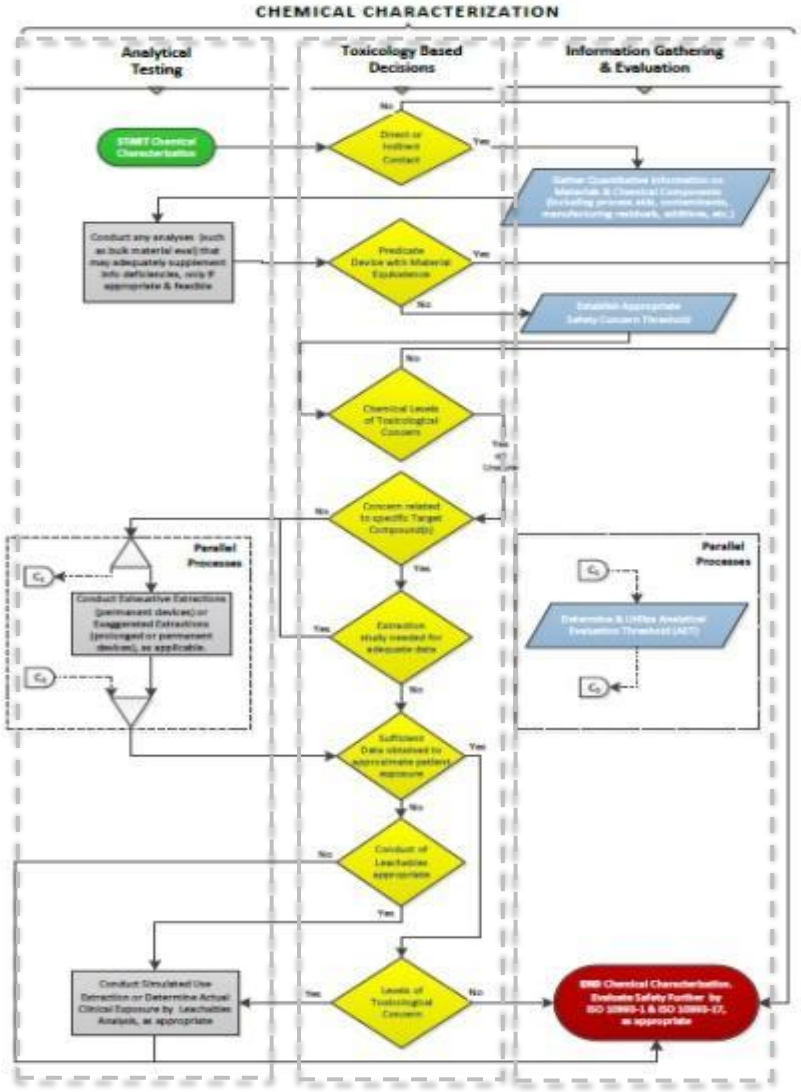
General Principles – Change Control (5)

… the **biological safety** of the **medical device** is inferred over the device's time in market only so long as the device's **materials of construction** and **manufacturing process** *remain unchanged*.

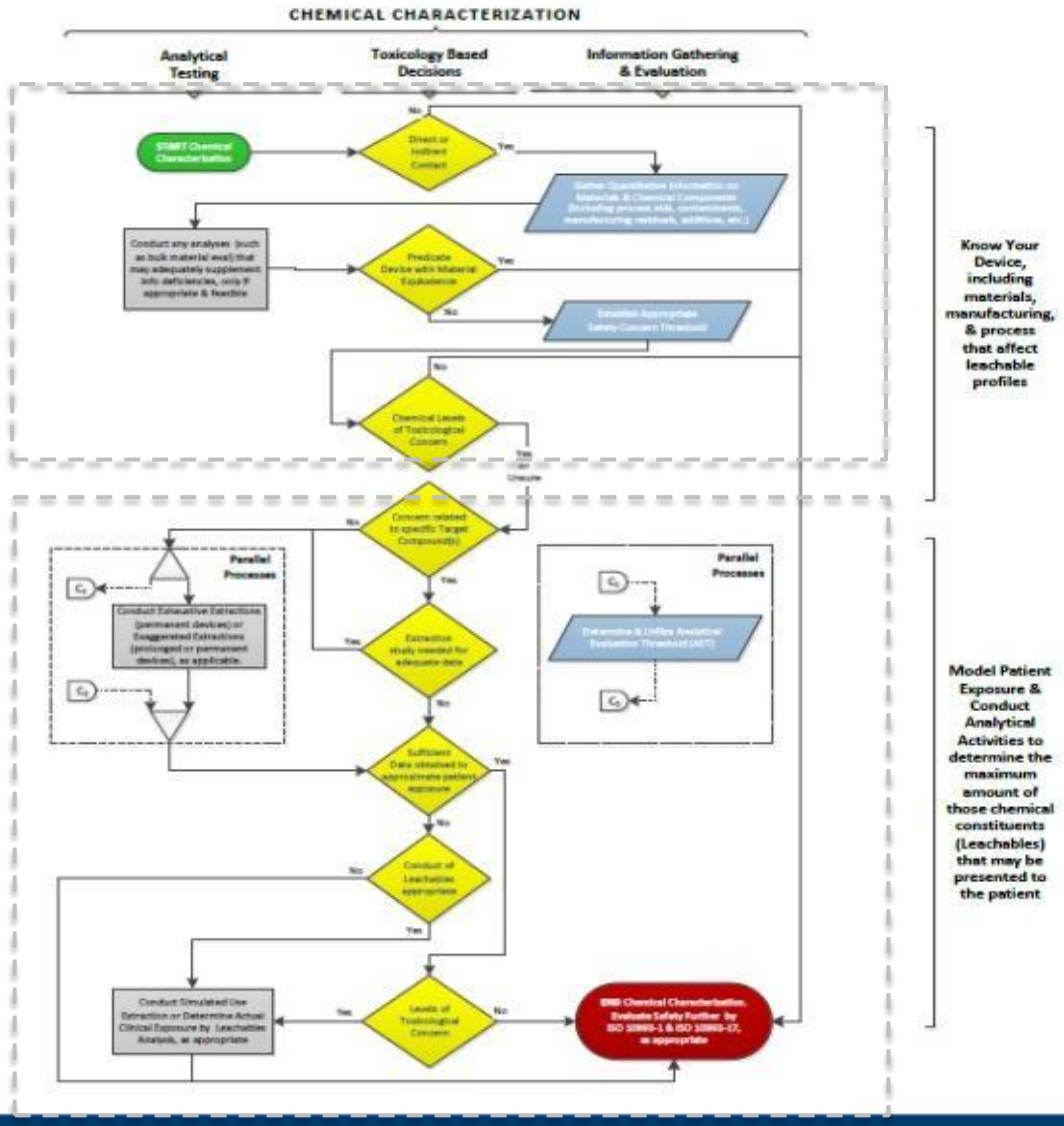
It is important that **controls** be introduced to **prevent** a *material supplier* from **changing** the **composition** of a material supplied without prior notification to the *medical device manufacturer*.

The *manufacturer* shall **assess** the **consequences** of any notified **changes** on the **biological safety** of the product.

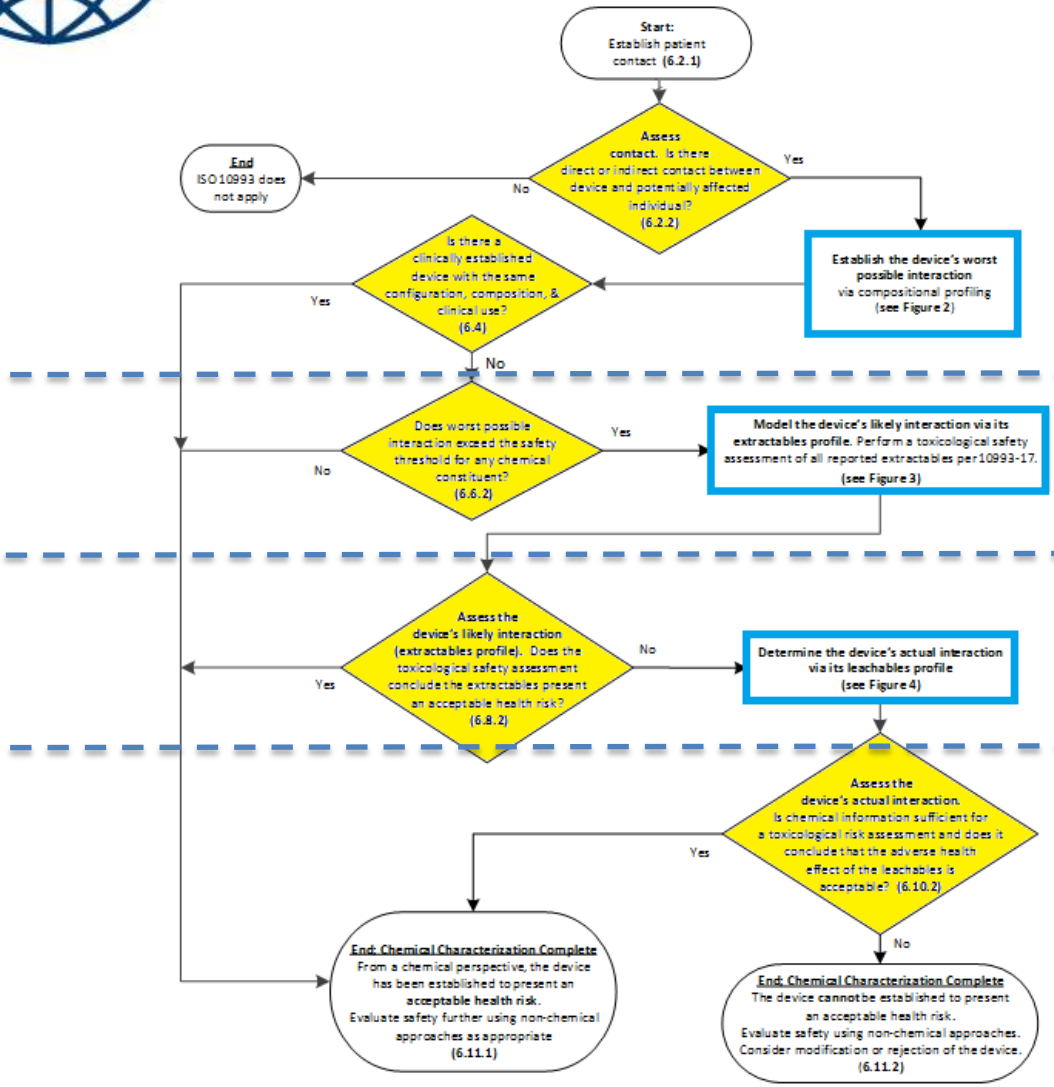
Characterization Procedure - PREVIOUS



Characterization Procedure - PREVIOUS



Characterization Procedure



Establish **worst possible** behavior via Compositional Profile

Model **LIKELY** behavior via **Extractables** Profile

Determine **ACTUAL** behavior via Leachables Profile

Chemical Characterization Parameters and Methods (1)

Chemical characterization data **CAN** be produced by **testing** a test article (device or material) **directly** in its natural state (*for example, IR analysis of a film*)**,**

HOWEVER, it is **more typically** the case that the **generation** of such **chemical characterization data *requires* 2 processes**,

1. the **solubilisation** of all or part of the test article (where solubilisation refers to processes such as **extraction** & **dissolution**),

AND

1. the **analytical testing** of the **resulting solution**.

Chemical Characterization Parameters and Methods – Solubilization (2)

Important Considerations:

1. The nature of the **solubilisation** step shall **match** the **intent** and **purpose** of the testing.
2. The **vehicles/media** used for **solubilisation** should be **considered** in the context of the methods chosen for **testing** those extracts, as the vehicles should be **compatible** with the test methods employed to **analyse** the extracts.
3. If visible **particles** or precipitates occur during extraction, and are **not solubilized**, these should be **analysed** as well, using applicable methods.

Chemical Characterization Parameters and Methods – Analytical Testing (3)

Items Relevant to Analytical Testing:

1. Analytical **test methods** are **provided** *(in name but not in detail)* and discussed for establishing **chemical composition**.

2. Analytical **test methods** are **provided** *(in name but not in detail)* and discussed for **extractables & leachables profiling** *(organic and elemental).*

3. Analytical **test methods** are **provided** *(in name but not in detail)* and discussed for assessing the **structural composition** of device materials.

4. Considerations around the **qualification of analytical methods** are discussed.

Reporting of Data (1)

Reports for the Communication of Chemical Data Should Include:

1. Test article (material or device) description and details;
2. Analytical methods and extraction conditions;
3. Surrogate standard information and detection method for the estimation of unknowns observed in the analysis of the test solutions;
4. Qualitative data generated;
5. Quantitative data generated;
6. Estimated clinical exposure to chemicals.

See also Annex E.

Reporting of Data (2)

Requirements for Reporting Data:

1. As necessary and appropriate, **identified substances** in the test solutions could be **grouped into compound classes**, based on structural or functional similarities, to assist in any toxicological risk assessment.
2. Any **quantitative data** shall be presented in a way that permits **estimation** of **human exposure**.
3. Data establishing the **identity of relevant substances** (e.g., extractables and leachables) shall be presented in a way that permits the toxicological safety assessment of the substance.
4. Reports containing vendor data would include a discussion of the **relevance of** the **vendor data** to the toxicological safety assessment.
5. The Report should contain detailed information that establishes the ***appropriateness*** of the **analytical process** employed.

Informative Annexes

- **Annex A**: Information sources for chemical characterization
- **Annex B**: Principles for judging chemical equivalence in support of a toxicological risk assessment
- **Annex C:** Principles of sample extraction
  - Extraction performed for correlating chemical characterization with biological testing (containing a Table of proposed extraction solvents)
  - Approaches to establishing the compositional aspects of the configuration of a medical device or the composition of a material of construction
  - Exaggerated extraction to establish the worst-case extractables profile of a medical device or material
  - Simulated or accelerated extractions to establish clinical use extractables profiles
- **Annex D:** Calculation and application of the analytical evaluation threshold (AET)
  - Calculation of the AET
  - Determination of the uncertainty factor, UF
  - Use of the AET
  - Exclusions to the AET; cohorts of concern
- **Annex E:** Reporting details for analytical methods and chemical data

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Thank you!