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?

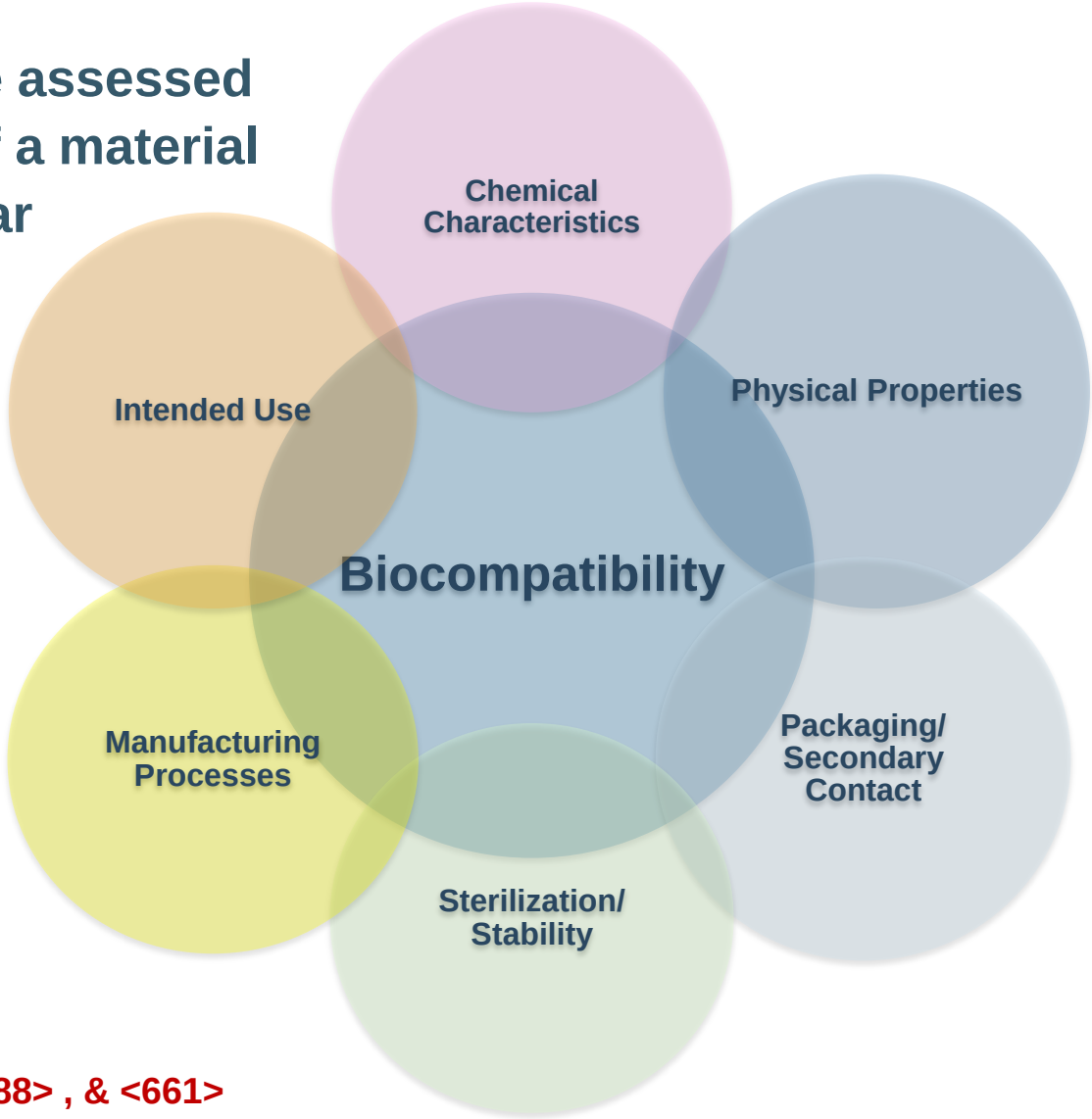
“Essential principles of safety and performance of medical devices”

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 “Safe” and “Biocompatible” mean?

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



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

What are the Standards for a Safe Medical Device?

Evaluation Strategy

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

Reference Materials

Part 12: Sample preparation and reference materials

Risk Assessment

Part 17: Establishment of allowable limits for leachables

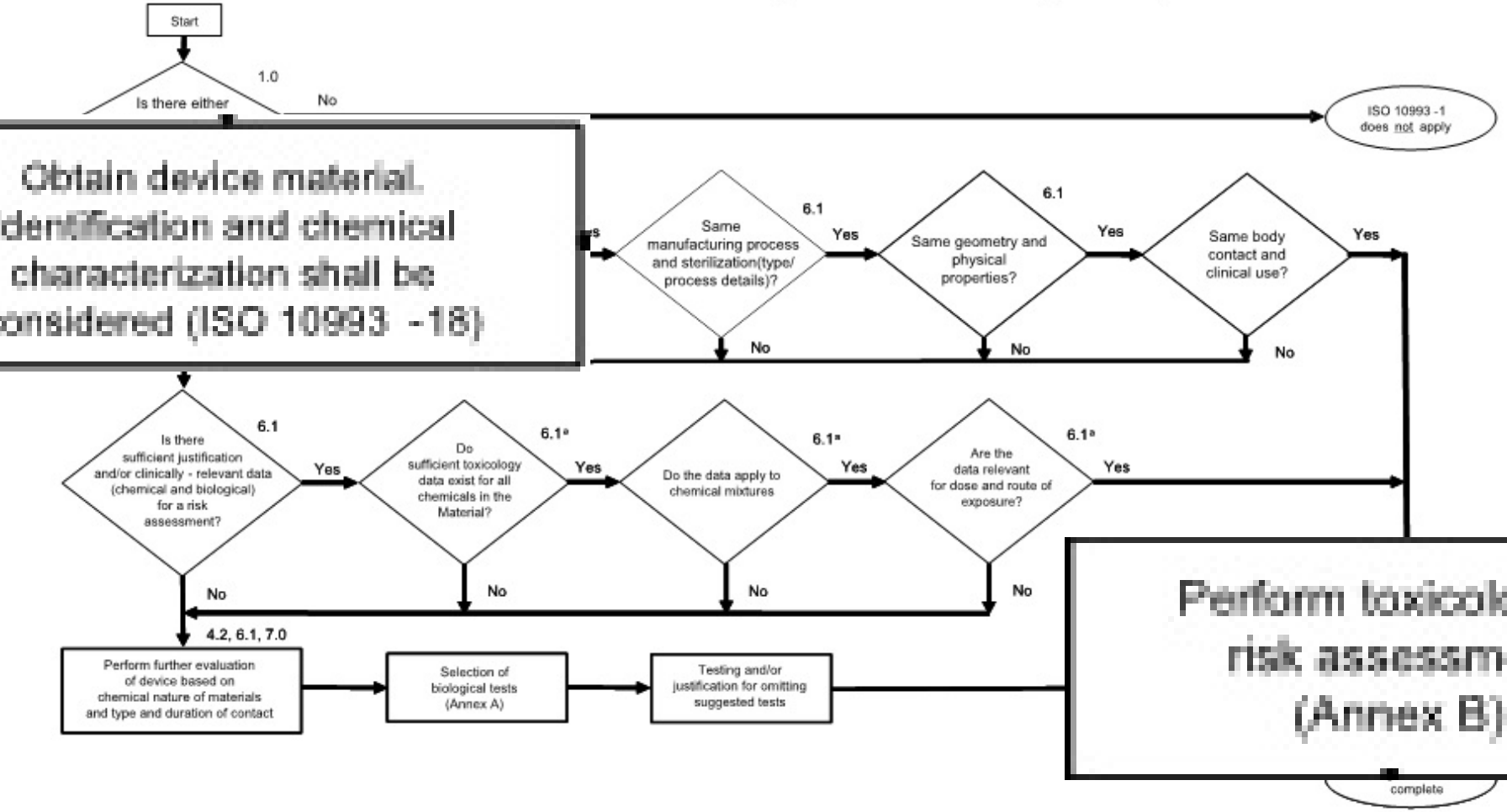
Materials Characterization

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**.

Applicability of 10993-18

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 should be considered*.**

Part 18 specifically: 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.
- 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): Equivalence

- 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.

Key Definitions (1)

toxicological risk assessment

act of determining the potential of a chemical to elicit an adverse effect based on a specified level of exposure

chemical characterization

process of obtaining chemical information, accomplished either by information gathering or by information generation, for example, by literature review or chemical testing

Key Definitions (2)

Extractables

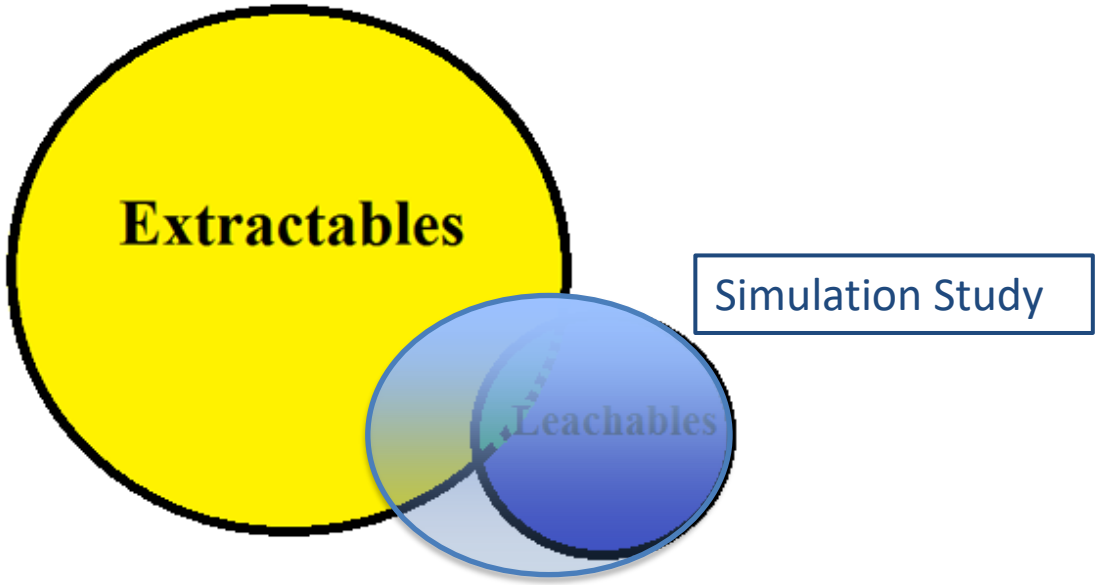
substances that are **released** from a medical device or material of construction when the device or material is extracted using **laboratory extraction conditions** and **vehicles**

Leachables

substance that is **released from a medical device** or material **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)

Medical Device Configuration

listing of a medical device's **components** (qualitative), including 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** (definition not actually found in 10993-18)

Exhaustive: multi-step extraction conducted until **the amount of material extracted in a subsequent extraction step is less than 10%** by gravimetric analysis (or achieved by other means) **of that determined in the initial 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**

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 using a method **that simulates clinical use**

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!

In general, there can be four objectives of a chemical characterization:

1) To correlate chemical data to the results of biological testing performed as described elsewhere in ISO 10993 (**"standard" extraction as described in 10993-12**),

2) To establish the compositional aspects of the configuration of a medical device or the composition of a material of construction (**digestion, dissolution or exhaustive extraction**),

3) To establish the **worst case extractables profile** of a medical device or material as either

   a. the **total pool of extractables** in the device (**exhaustive extraction**) or

   b. the **maximum amount** that can be extracted under defined experimental conditions that **exaggerate a device's typical conditions** of use (**exaggerated or accelerated extraction**), and

4) To establish the extractables profile of a medical device or material under its typical conditions of use (**simulated extraction**).

The Right Extraction for the Right Circumstance

Contact Category	Recommended Extraction Conditions	Credible Alternatives
Limited contact devices	Simulated use conditions[a]	Exaggerated conditions
Prolonged contact devices	Exhaustive conditions	Exaggerated conditions[b,c]
Long-term contact devices	Exhaustive conditions	Exaggerated conditions[b,c,d]

a With suitable justification.

b Examples of instances where exhaustive extraction would not typically be required include:

- Single use devices used for less than 24 hours, where repeat use of a new device each day would result in categorization as prolonged or long-term contact:
- Single use devices used for several days, where repeat use of new devices would result in categorization as prolonged or long-term contact; and
- Reusable devices, where a patient may be exposed to repeated use of the same device, resulting in categorization as prolonged or long-term contact. When an exaggerated extraction is used for a reusable device, the extraction should properly account for the duration of each individual use.

C Exaggerated conditions can be appropriate for external communicating or non-absorbable surface contact devices, with justification.

d An example is a device comprised entirely of non-absorbable metal (e.g., a vascular stent), because migration of constituents from within the material is not possible, and the constituents of interest are related to the surface only and exaggerated extraction can be adequate to generate a complete extractables profile.

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 (5)

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**.

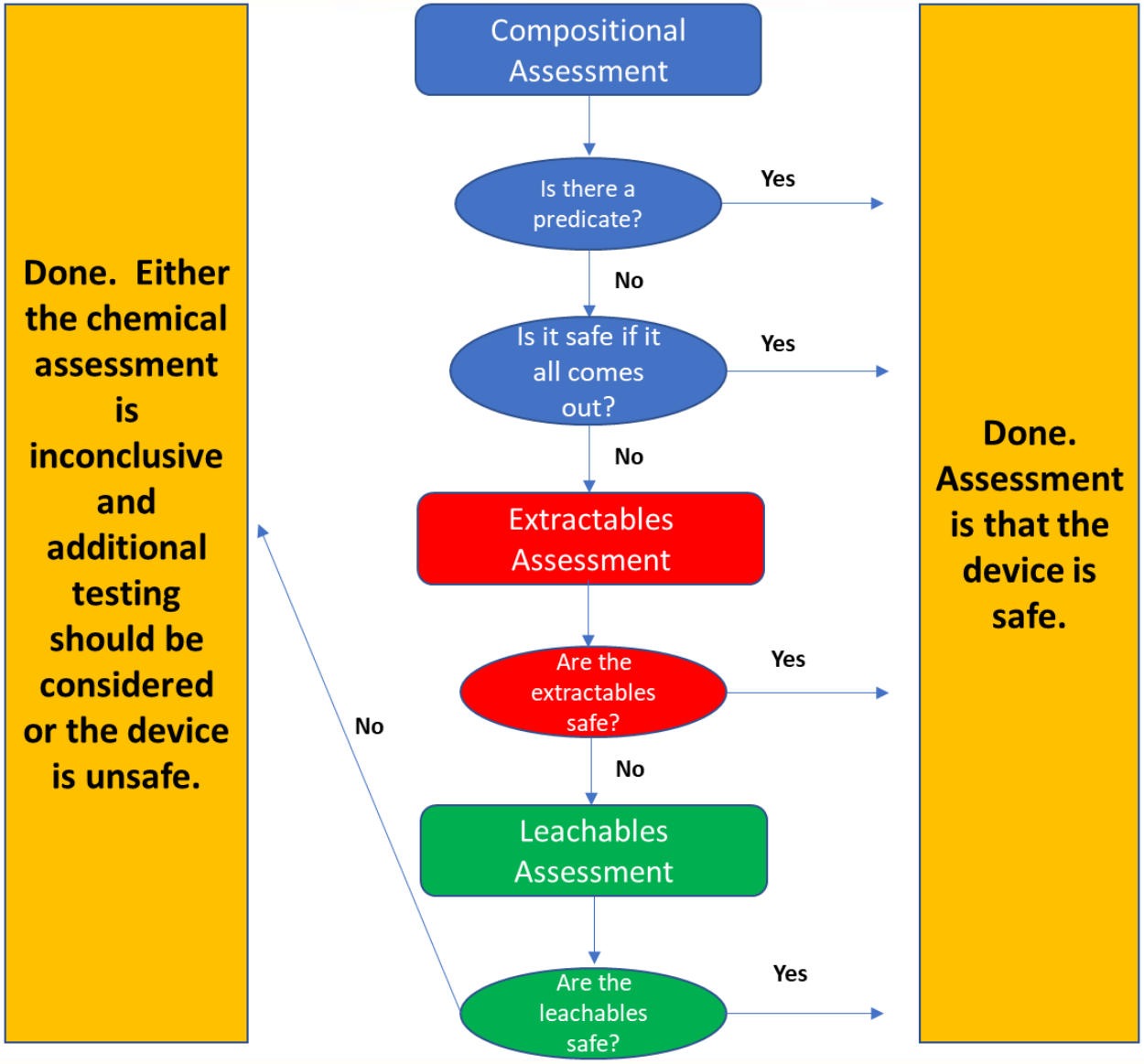
General Principles – Change Control (6)

… 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*.

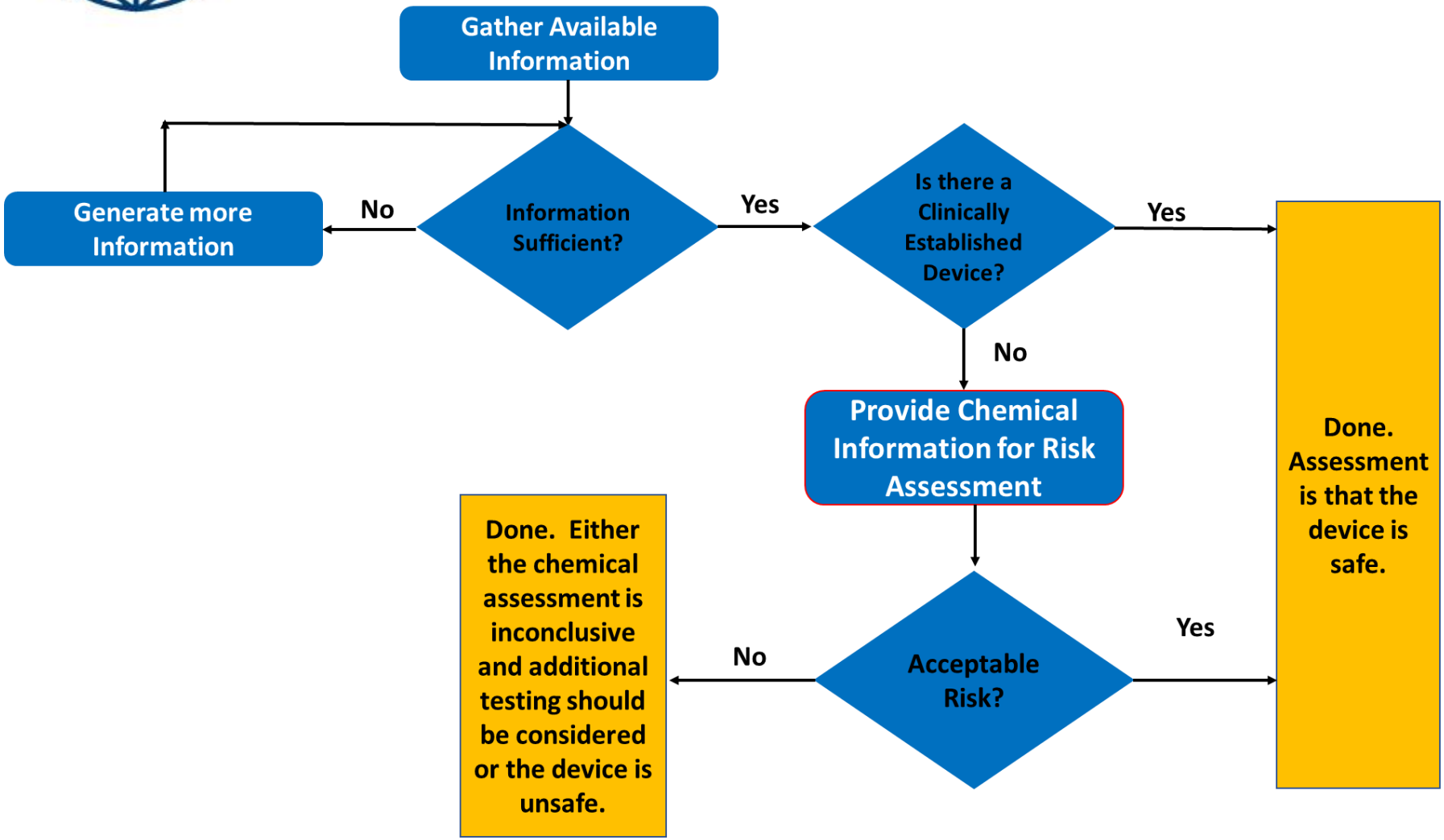
It is important that **controls** be introduced to **prevent** a *material supplier* from **changing** the **composition** of a material supplied without prior notification to the *medical device manufacturer*.

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

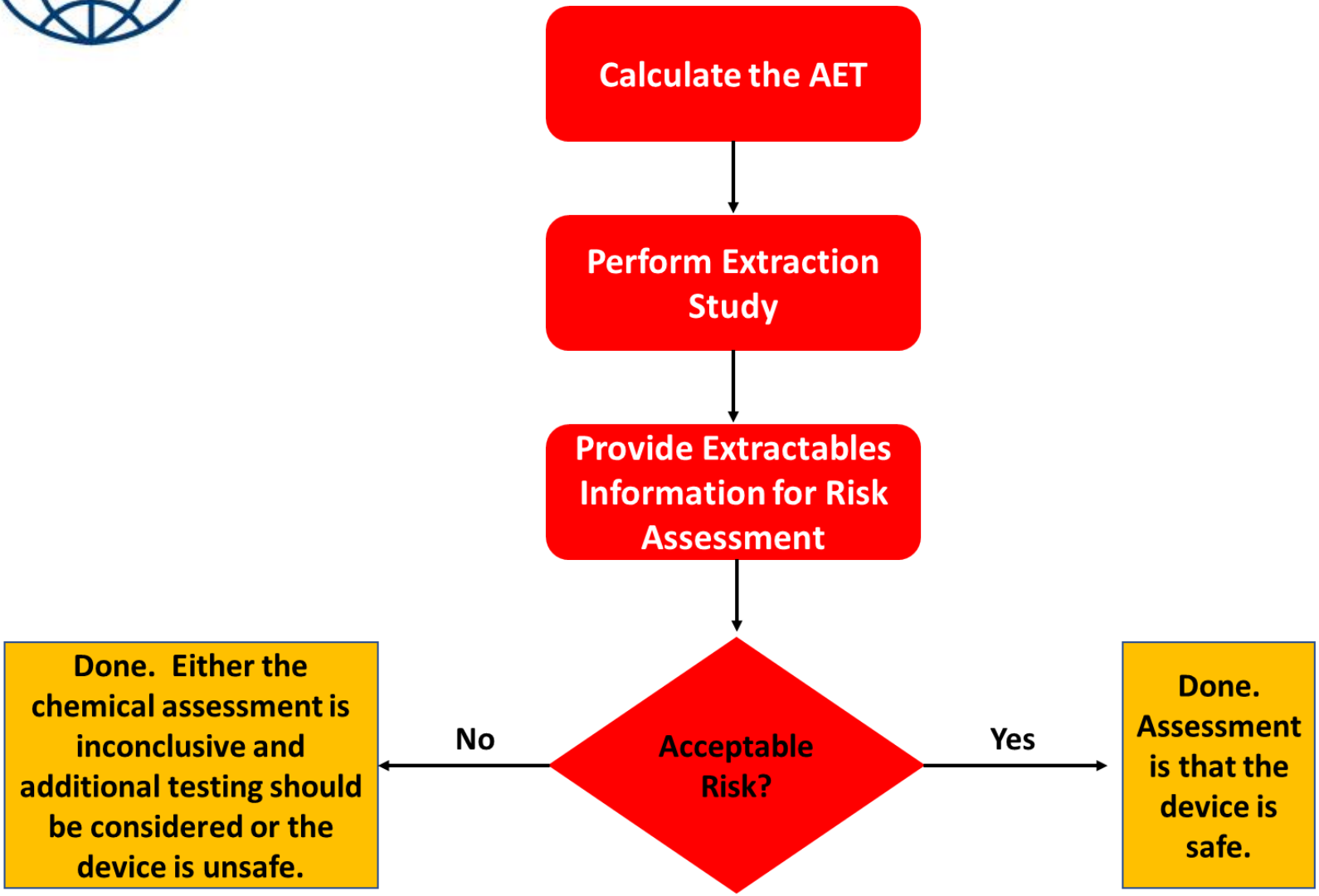
Characterization Procedure - Overall



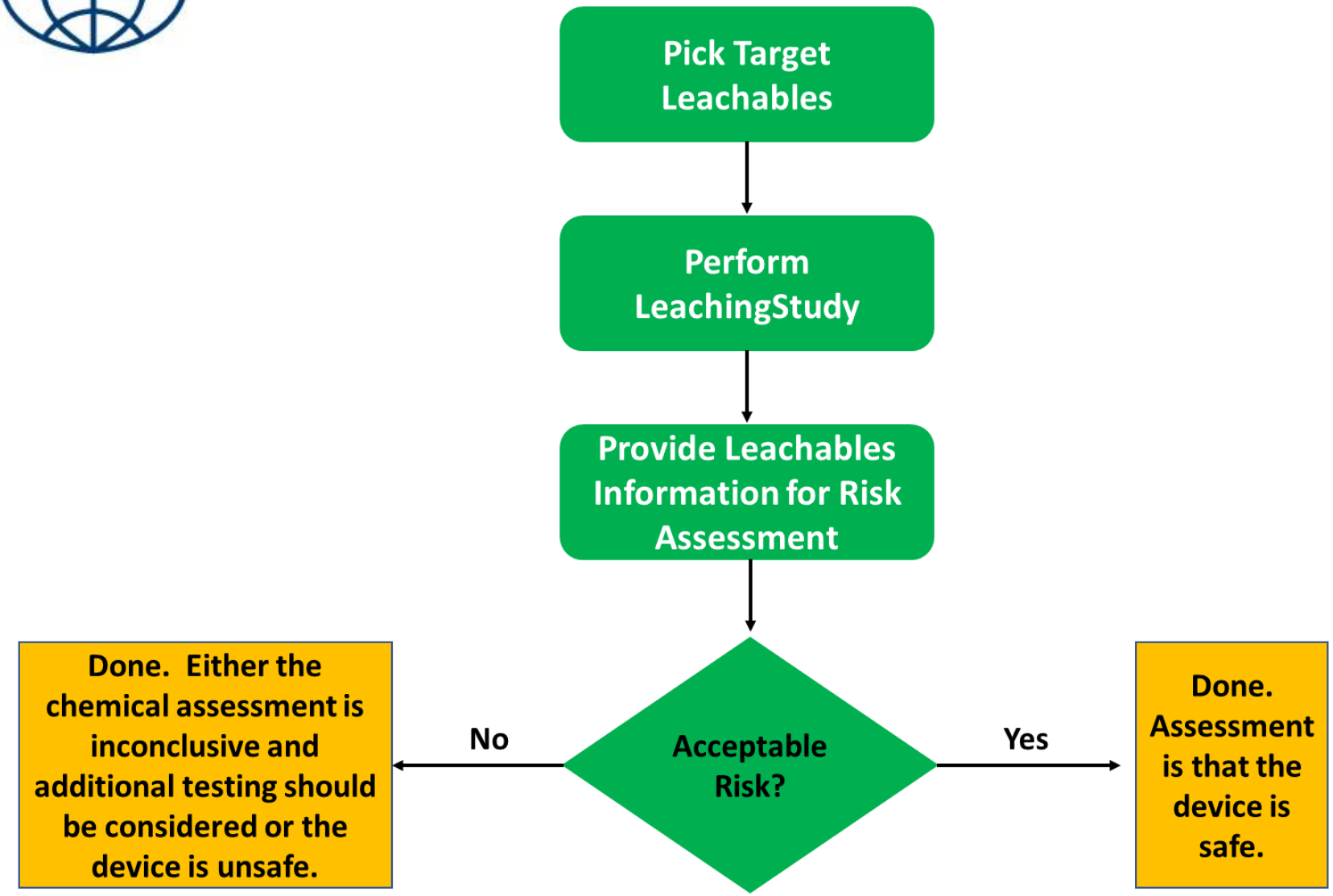
Characterization Procedure – Compositional Assessment



Characterization Procedure – Extractables Assessment



Characterization Procedure – Leachables Assessment



Chemical Assessment in Biological Evaluation

Biocompatibility Endpoints where Chemical Assessment has limitations:

Sensitization – ***Well established thresholds are still under question***

Irritation – ***Limited available Literature***

Implantation – ***Mechanical/ Physical properties must also be assessed***

Haemocompatibility – ***Mechanical/ Physical properties must also be assessed***

Pyrogenicity – ***Source may be chemical or biological***

When Chemical Assessment may provide insight to specific biological tests:

It must be comprehensive and rigorous

When in lieu of traditional biocompatibility testing, rationale must be fully justified

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 G.

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**: General principles of chemical characterization
- **Annex B**: Information sources for chemical characterization
- **Annex C:** Principles for establishing biological equivalence
- **Annex D:** 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 E:** 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 F:** Qualification of analytical methods used for extractables/leachables
- **Annex G:** Reporting details for analytical methods and chemical data

Contact the presenters at:
john.iannone@teleflex.com
dennisjenke@triadscientificsolutions.com (www.triadscientificsolutions.com)

Thank you!