Biological evaluation of medical devices:
PART 18– Chemical Characterization of Materials

PDA WORKSHOP
EXTRACTABLES – LEACHABLES
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What is a ”Safe” Medical Device?

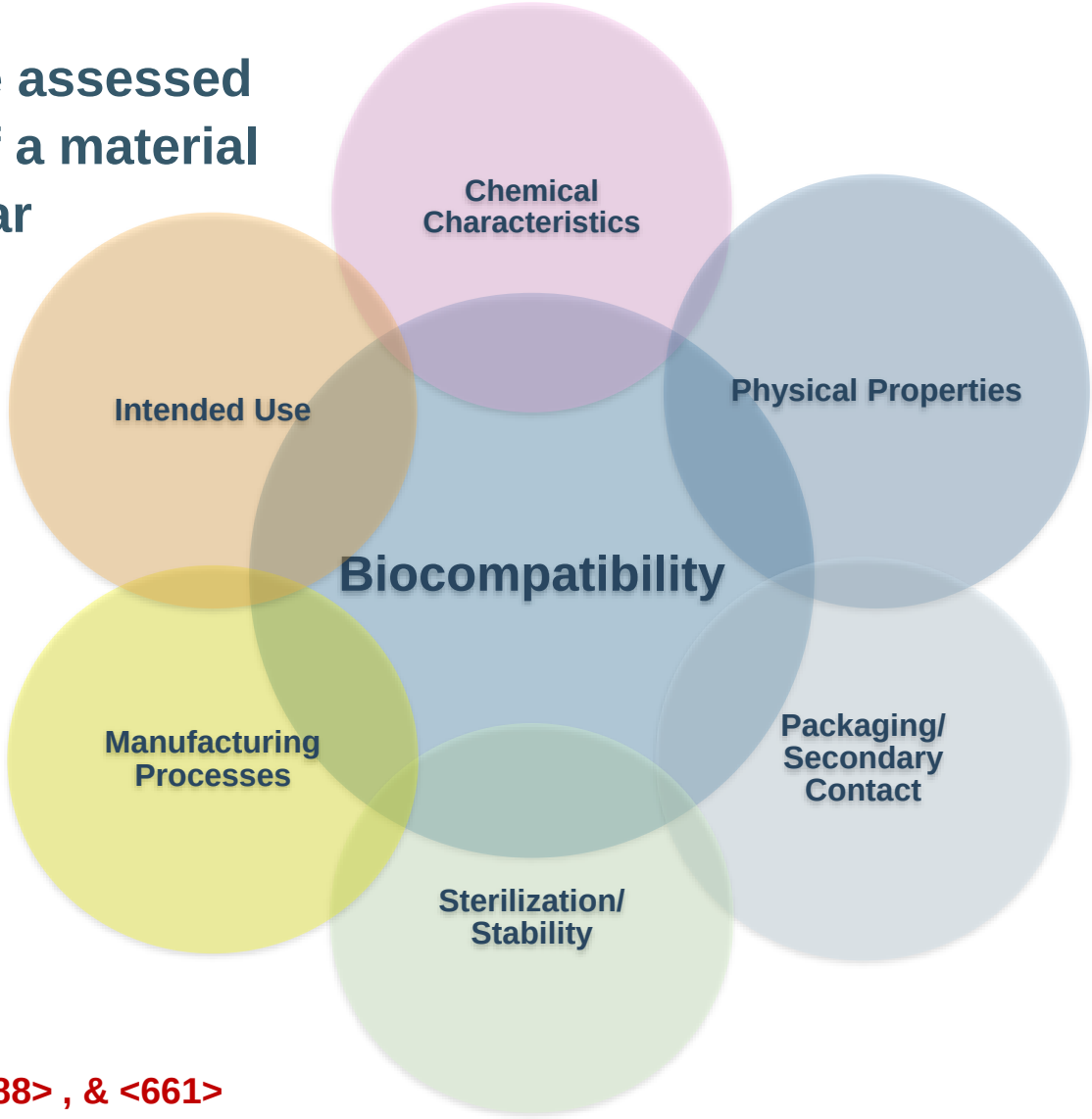
“Essential principles of safety and performance of medical devices”

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

From the Introduction

… this document [provides] a **framework to plan a biological evaluation**… **utilize[ing] scientific advances** in understanding of basic mechanisms, to *minimize* animal [testing] by giving **preference to in-vitro** models and to **chemical… characterization** testing, in situations where these methods yield equally relevant information to that obtained from in vivo models.

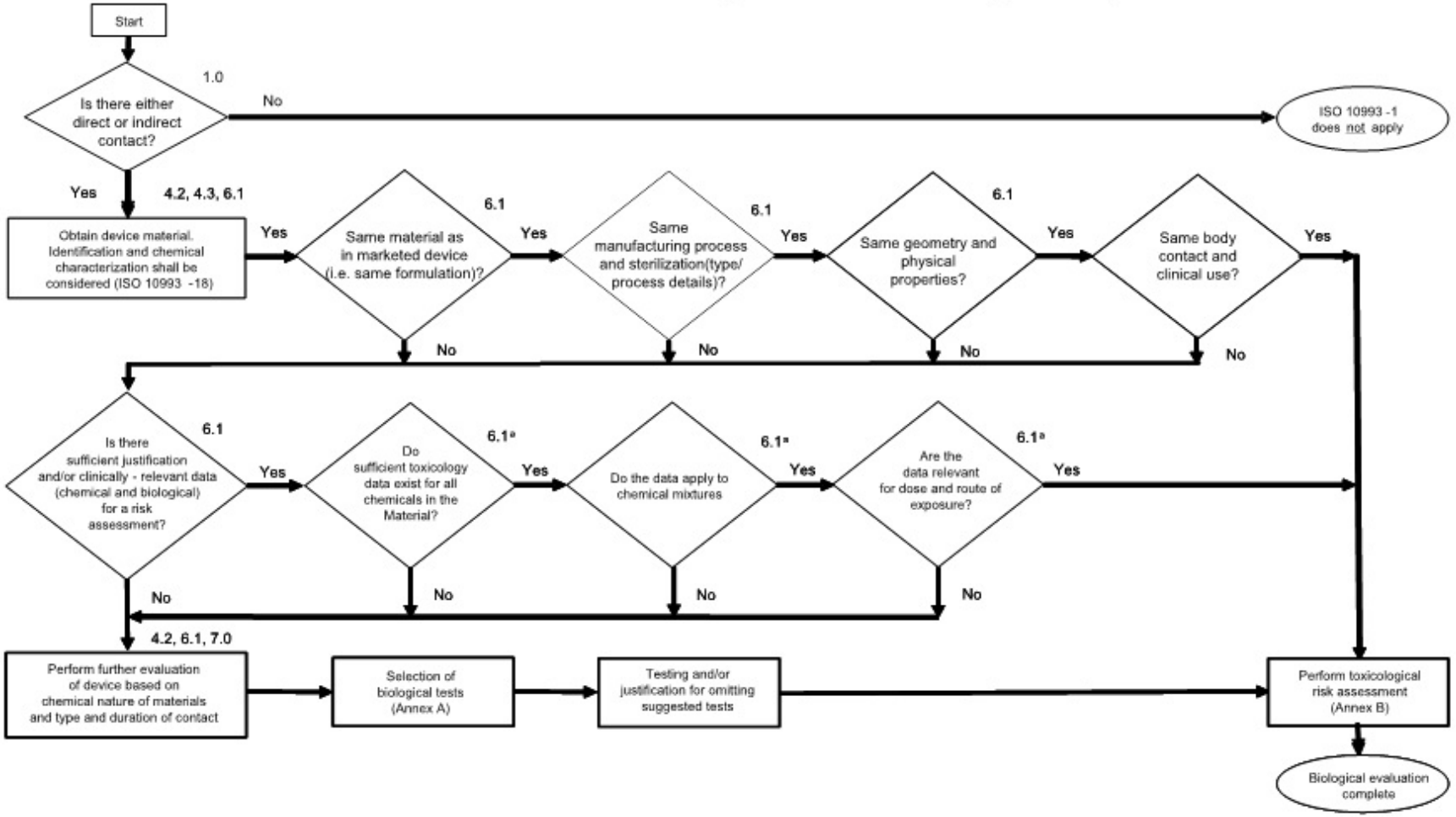
From Section 4.3

Description of medical device **chemical constituents** and **consideration** of material characterization **including chemical characterization** (see ***ISO 10993-18***) ***shall precede*** any **biological testing** (see Figure 1). **Chemical characterization** with an **appropriate toxicological threshold** can be **used** to **determine** if **further testing** is needed (see Annex B, ***ISO 10993-17*** and ***ISO 10993-18***).

Source: ISO 10993-1:2018. Biological evaluation of medical devices. Part 1: **Evaluation** and **testing** within a **risk management** process.

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



Surrogate Extraction Vehicles for Biological Testing

Table D.3 — Potential surrogate extraction vehicles for correlating chemical to biological testing

Inclusion of vehicles here does not fully justify their use in chemical-biological comparisons.

Extraction vehicle for biological testing	Potential surrogate extraction vehicle for chemical testing
Water[f]	Water
Physiological saline[f]	Physiological saline
Ethanol/water[f]	Ethanol/water
Ethanol/saline[f]	Ethanol/saline
Dimethylsulfoxide[f]	Dimethylsulphoxide
Culture medium without serum	1/9 (v/v) ethanol/saline[a]
Vegetable oil	1/1 (v/v) ethanol/water[b] (Reference [26])
Polyethylene glycol 400[e]	1/3 (v/v) ethanol/water[c] (Reference [38])
Culture medium with serum	2/3 (v/v) ethanol/saline[d] (Reference [38])

Role of Chemical Characterization in Biological Evaluation of Medical Devices

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

Medical device categorization by			Endpoints of 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	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]
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	g[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		
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		

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.

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 – 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**

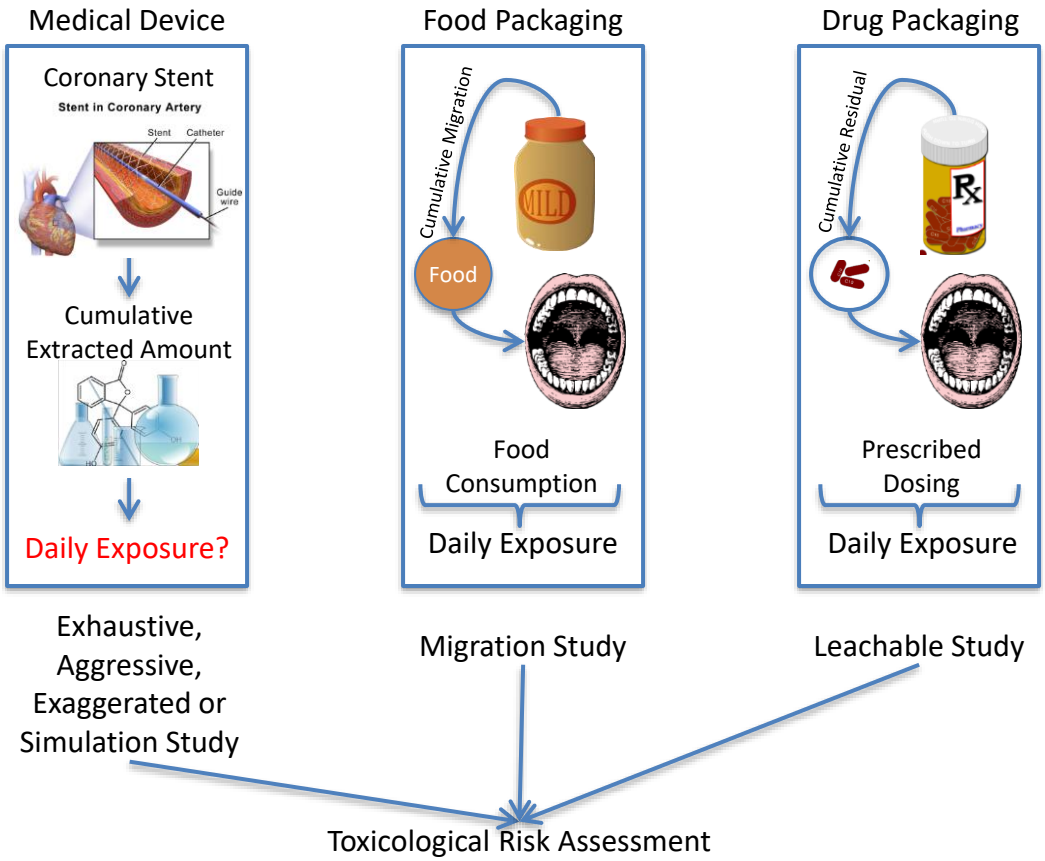
Exhaustive (3.15): extraction, accomplished using **multiple extraction steps**, that solubilizes the **total amount** of **extractable substances** present in a test article, as evidenced when the amount of extractables released in a subsequent extraction step is less than 10% of the amount of extractables released in the first extraction step

Exaggerated (3.14): 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 (3.1): 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 (3.30): 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

Exposure Assessment Issue for Medical Devices



Discussed at Technical Committee Meeting of Experts for ISO 10993-17

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**).

General Principles – Characterization

Chemical Characterization is based on the following:

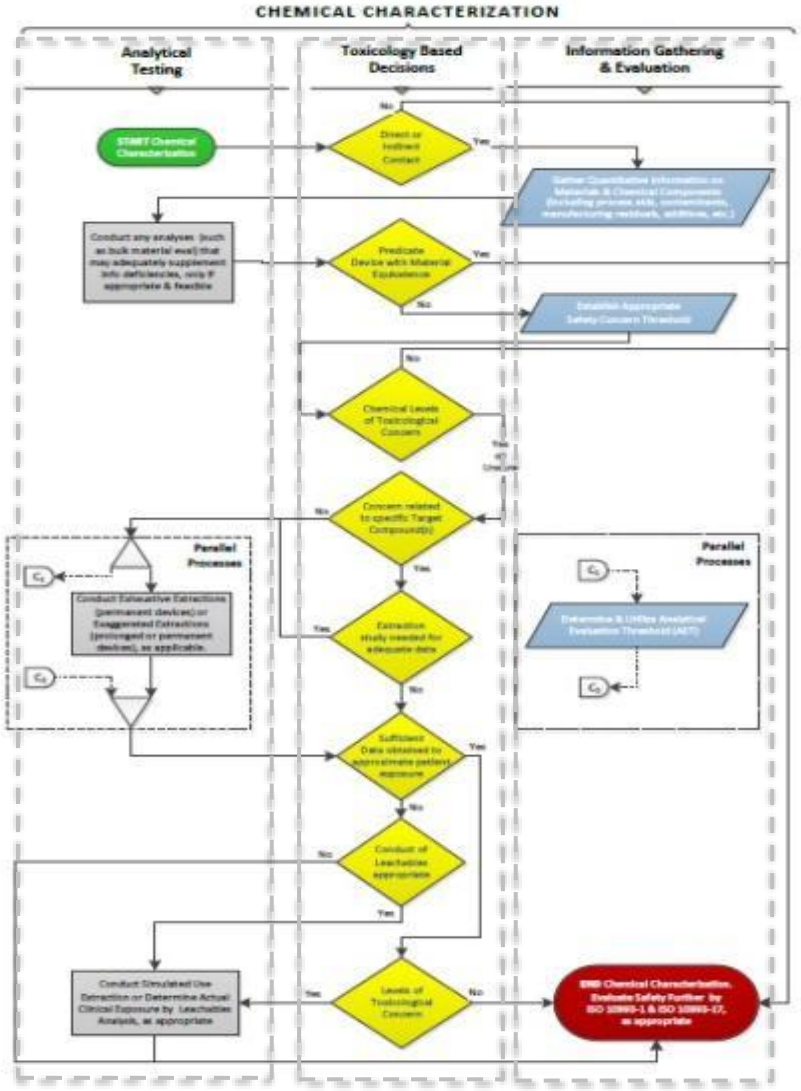
Determining the device's **potential to release chemical substances** under **clinical use** conditions can **provide the basis** for understanding and assessing the device's **potential patient safety impact**.

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**,

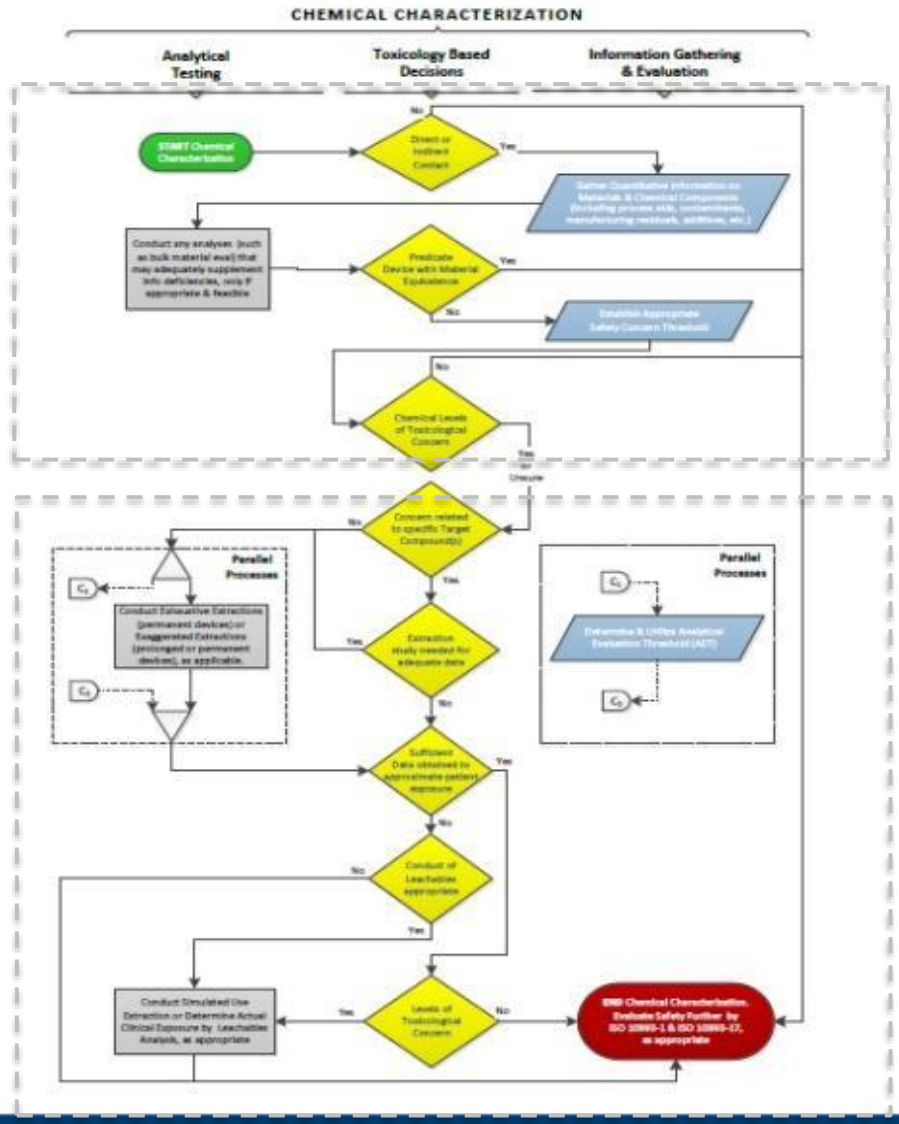
> it could **potentially be necessary to** obtain information **demonstrat**ing the **extent** to which the **substances** will be **leach**ed under the **clinical use** conditions of the finished product to **estimate** the **risk** arising from them.

<u>This can be estimated by conducting extraction studies of the device</u>

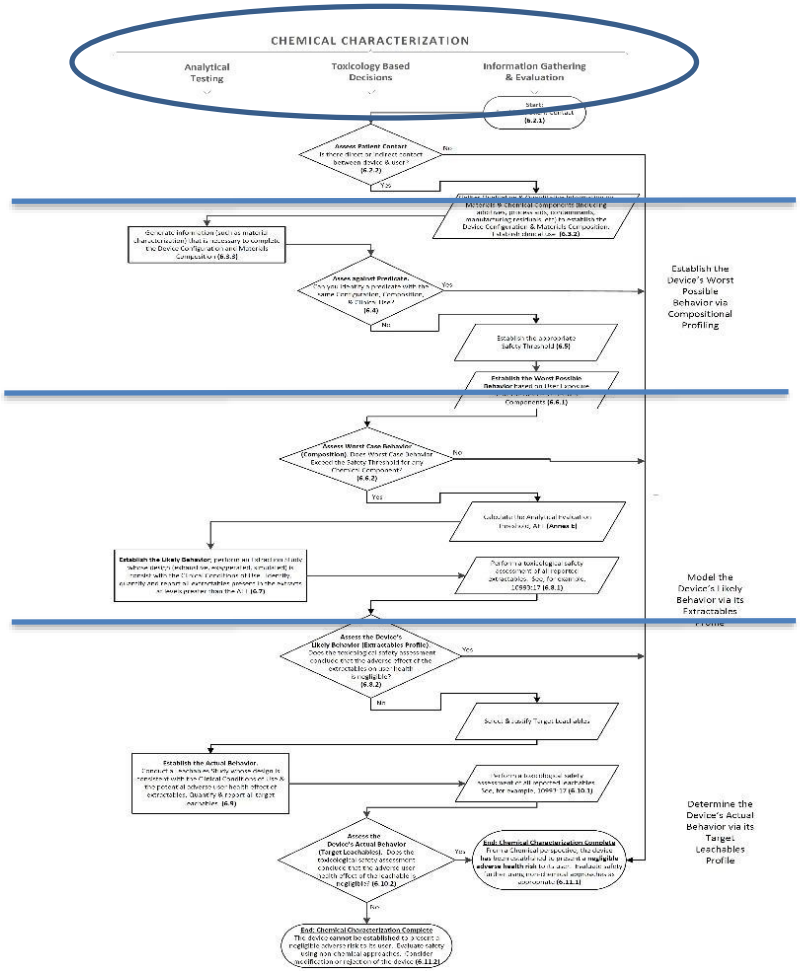
Characterization Procedure - PREVIOUS



Characterization Procedure - PREVIOUS



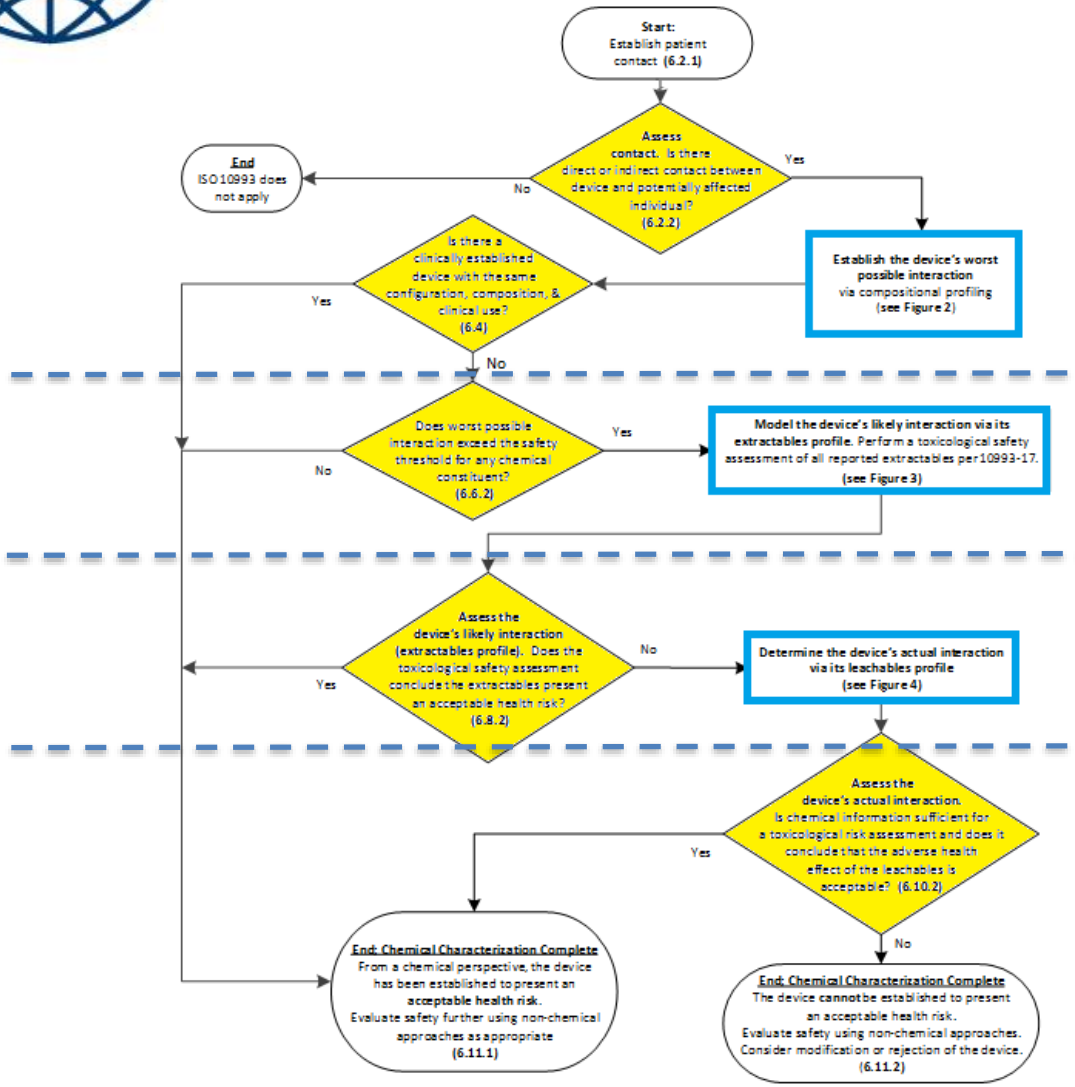
Future of ISO 10993:Part 18 – Version 10



Chemical Characterization

- Toxicology based decisions
- Information Gathering
- Information Generating

Characterization Procedure (Flow Chart v12)



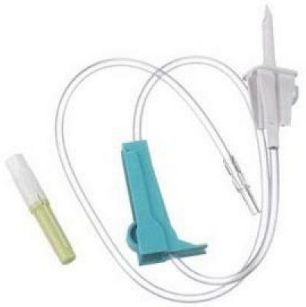
Establish **worst possible** behavior via Compositional Profile

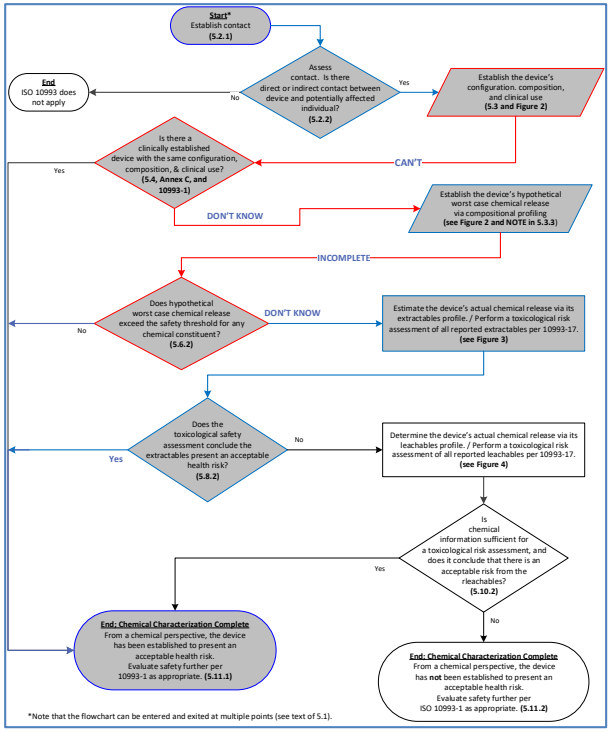
Model **LIKELY** behavior via **Extractables** Profile

Determine **ACTUAL** behavior via Leachables Profile

Controlled Extraction Study ONLY

***NEW ECD* comprised of materials with safe history of USE (IV Xfer Set)**

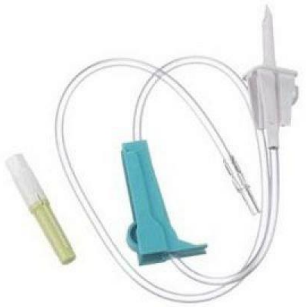


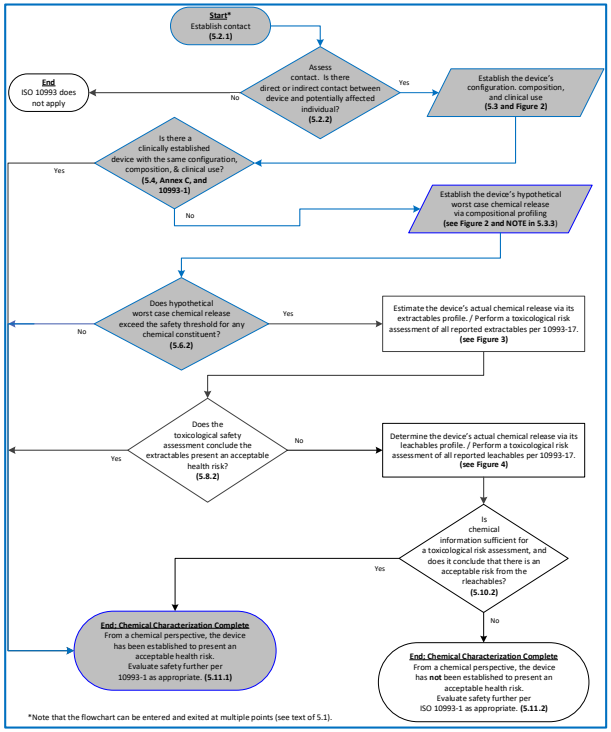


- **CANNOT** establish device's configuration, composition, and clinical use
  - **CANNOT** make a comparison to another device
- **CANNOT** completely establish device's "worst case" chemical release via compositional profiling
  - **CANNOT** evaluate worse case release against safety threshold
- **Estimate** device's actual chemical release via its extractables profile
- **Perform** a toxicological risk assessment of all reported extractables per 10993-17

Controlled Extraction Study ONLY

Modified ECD **comprised of material change (IV Xfer Set)**

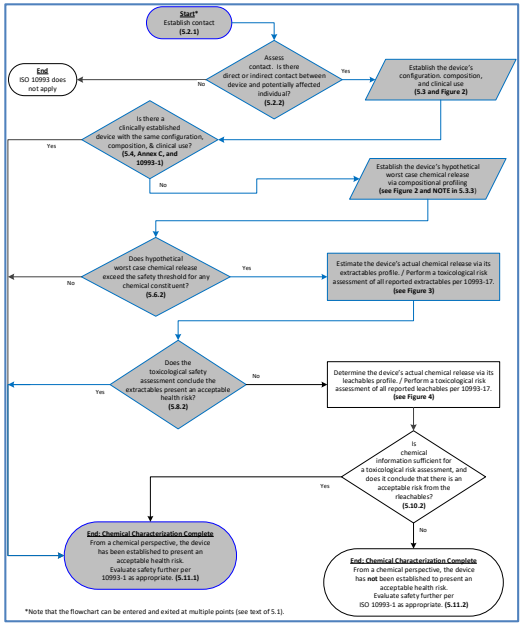




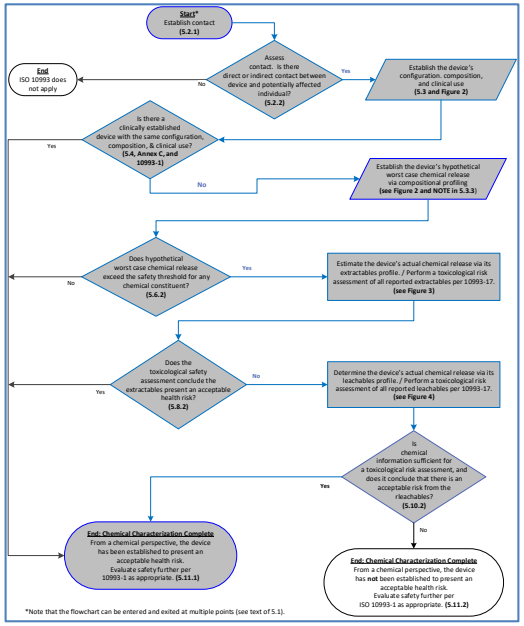
- **Establish** device's configuration, composition, and clinical use
  - Compare to another (safe) device
- **Completely establish** device's "worst case" chemical release via compositional profiling
- **Evaluate** worse case release against safety threshold
- **Estimate** device's actual chemical release via its extractables profile
- **Perform** a toxicological risk assessment of all reported extractables per 10993-17

ISO 10993-Part 18: Navigating Flow Charts

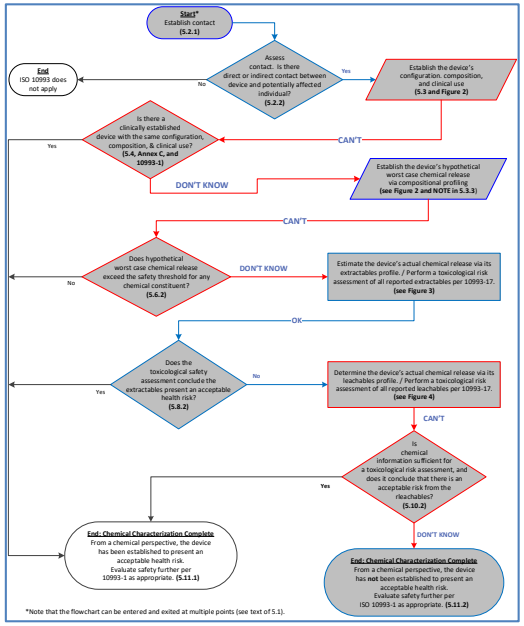
Safety by Material Info & CES



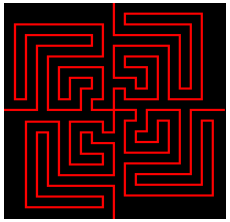
Safety by Mat. Info, CES & Targeted Release Kinetics



Safety not determined by Chemical Means

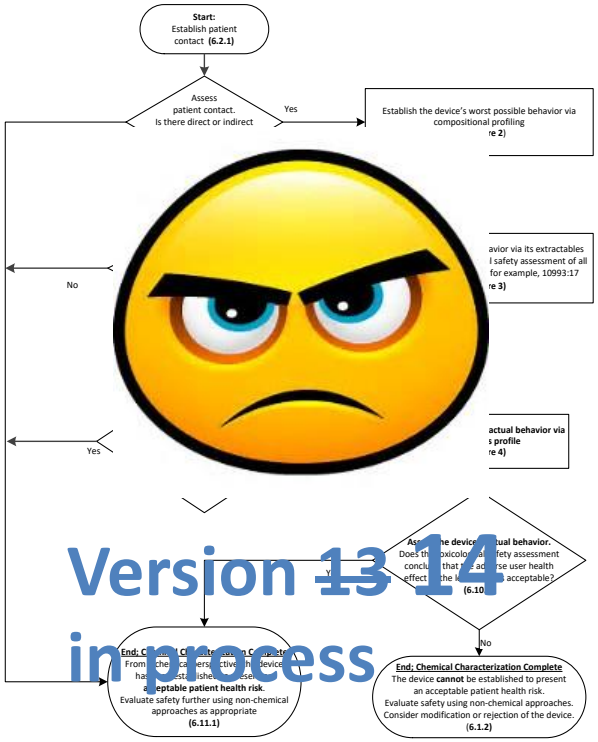


Think about Part 18 as a maze



- Has multiple points of entry
- Has multiple points to exit
- Has multiple paths

Future of ISO 10993:Part 18 – ~~Version 12~~



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.

Analytical Methods for E&L Screening

Material Type	Characteristic	Example methods [a]	Qualitative (Identity)	Quantitative
All	Organic extractables, VOC	HS–GC with FID and/or MS	X	X
		Total organic carbon (TOC)	—	X
	Organic extractables, SVOC	GC, with FID and/or MS	X	X
		Total organic carbon (TOC)	—	X
		NMR	X	—
	Organic extractables, NVOC	LC, with UV and/or MS	X	X
		NMR	X	—
		Total organic carbon (TOC)	—	X
		Non-volatile residue	—	X
	Elemental extractables	X-ray fluorescence	X	X
		ICP-AES, ICP-MS	X	X
	Anions	Ion chromatography	X	X

[a] Not comprehensive or exclusive.

More than 1 way to get to your destination in E&L!

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 & Rigorous

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

Understaning Part 18; Normative Structure

1. Scope
2. Normative references
3. Terms and definitions
4. Symbols and abbreviations
5. Characterization procedure
   - 5.1 General
   - 5.2 Address contact with a potentially affected individual
   - 5.3 Establish medical device configuration and material composition
   - 5.4 Assess versus a clinically established material or medical device
   - 5.5 Establish appropriate safety threshold
   - 5.6 Assess the hypothetical worst-case chemical release based on total exposure to the medical device's chemical constituents
   - 5.7 Estimate the medical device's actual chemical release; perform extraction study
   - 5.8 Assess the medical device's estimated chemical release (extractables profile)
   - 5.9 Determine the medical device's actual chemical release; perform leachables study
   - 5.10 Assess the medical device's actual chemical release (leachables profile)
   - 5.11 Exiting the chemical characterization process

Understaning Part 18; Normative Structure

6 Chemical characterization parameters and methods
- 6.1 General
- 6.2 Chemical composition
- 6.3 Extractables and leachables
- 6.4 Structural composition or configuration
- 6.5 Analytical methods

7 Reporting of the chemical and/or compositional data

References

Understaning Part 18; Informative Structure

Annex A: General principles of chemical characterization

- A.1 Reporting of the chemical and/or compositional data
- A.2 The uses of chemical characterization
- A.3 The analytical evaluation threshold (AET)
- A.4 The role of chemical characterization in biological analysis

Annex B: Information sources for chemical characterization

- B.1 General
- B.2 Information from the material supplier
- B.3 Chemical analyses
- B.4 National and international material and/or product standards
- B.5 Reporting chemical descriptions of materials
- B.6 Reporting general information concerning chemical nature of materials
- B.7 Material master file

Annex C: Principles for establishing biological equivalence

Annex D: Principles of sample extraction

- D.1 General
- D.2 Approaches to establishing the compositional aspects of the configuration of a medical device or the composition of a material of construction
- D.3 Exaggerated extraction to establish the worst-case extractables profile of a medical device or material

Understaning Part 18; Informative Structure

D.4 Simulated or accelerated extractions to establish clinical use extractables profiles

D.5 Extractions performed for correlating chemical characterization with biological testing

Annex E: Calculation and application of the analytical evaluation threshold (AET)

E.1 Discussion

E.2 Calculation of the AET

E.3 Determination of the uncertainty factor, UF

E.4 Use of the AET

E.5 Exclusions to the AET; cohorts of concern

Annex F: Reporting details for analytical methods and chemical data

F.1 General

F.2 Reporting of analytical data to facilitate toxicological safety assessment

F.3 Details of test article preparation (extraction)

F.4 Extract preparation for analysis

F.5 Description of the analytical methods for testing prepared extracts

F.6 Performance metrics for the analytical methods

Contact the presenter at:
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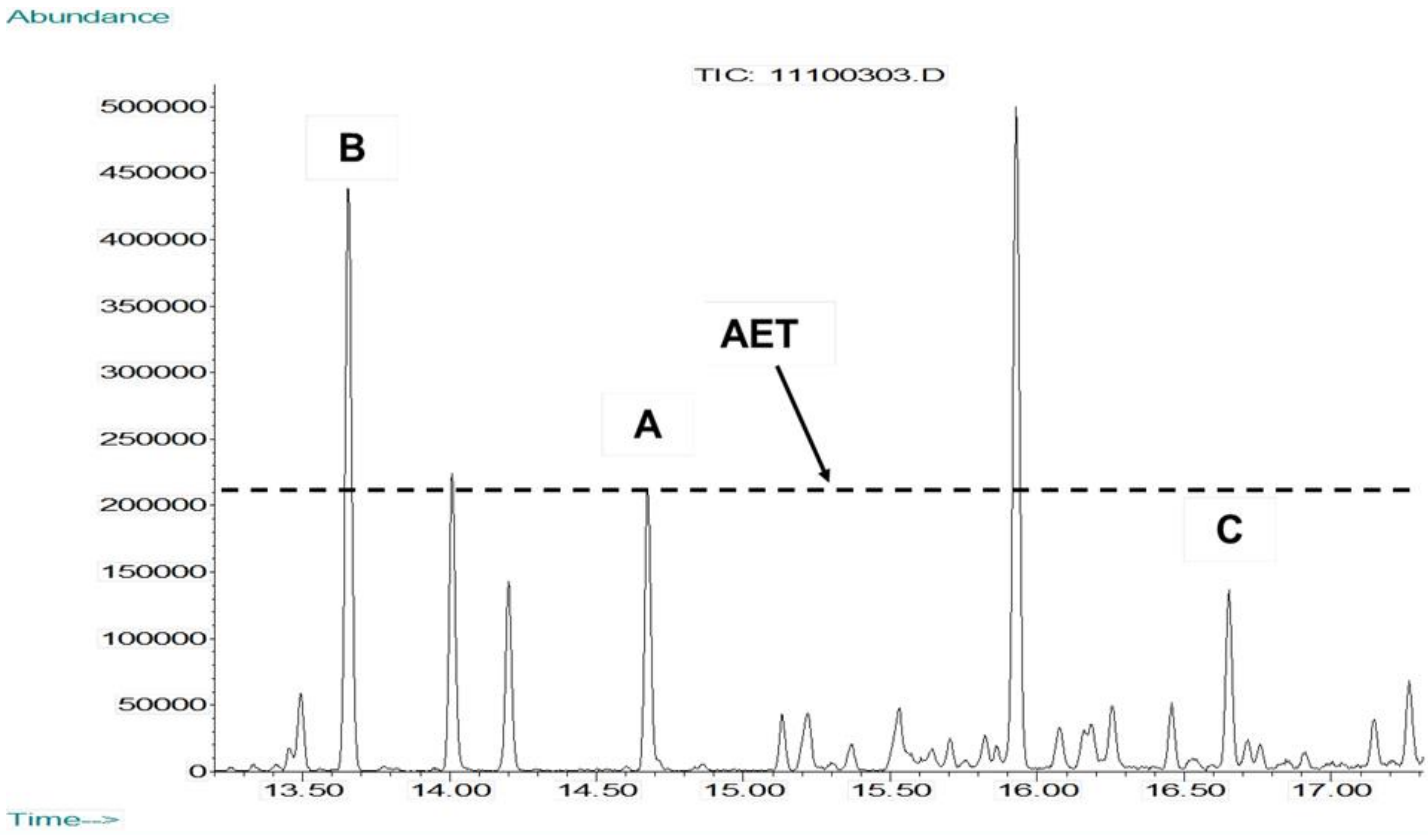
Thank you!

Special Topics; The Analytical Evaluation Threshold (AET)

3.2 analytical evaluation threshold, AET

threshold below which the analyst need not identify or quantify leachables or extractables or report them for potential toxicological assessment (see Annex E)



Special Topics; The Analytical Evaluation Threshold (AET)

$$AET\ (\mu g/mL) = DBT\ (\mu g/day) \times (A/BC) \times UF$$

where:

A is the number of devices that were extracted to generate the extract,

B is the volume of the extract (measured in mL),

C is the clinical exposure to the device (# of devices a user would be exposed to in a day under normal clinical practice).

DBT is a Dose Based Threshold (e.g., TTC or SCT)

UF is an uncertainty factor that could be applied to account for the analytical uncertainty of the screening methods used to estimate extractables' concentrations in an extract.

Calculation Example:

Circumstances:

- The device is used in an acute therapy which is completed in 7 d.
- On each day of therapy, 2 devices are required.
- In the extraction study, 4 devices were extracted in 100 ml of extracting solvent.
- The extraction study was performed in such a manner (e.g. with the appropriate device surface area to extraction solution volume ratio) to produce an appropriate and analytically expedient extract.
- The analytical method used to screen the extracts for extractables was supported by a response factor database which established that the extractables' response factors were acceptably consistent between extractables.

Special Topics; The Analytical Evaluation Threshold (AET)

In this case,

DBT = TTC = 120 µg/d (duration of treatment ≤ 1 month from ICH M7),
A = 4 devices,
B =100 mL,
C = 2 devices/day,
UF = 1.

$$\text{AET (µg/mL)} = \text{DBT (µg/day)} \times (\text{A/BC}) \times \text{UF}$$

$$\text{AET (µg/mL)} = \{120 \text{ µg/day} \times [4 \text{ devices}/(2 \text{ devices/day} \times 100 \text{ mL})]\} \times 1$$

$$\text{AET (µg/mL)} = 2.4 \text{ µg/mL}$$

Special Topics; The Analytical Evaluation Threshold (AET)

An uncertainty factor (UF) is added to the calculation of the AET to account for the analytical uncertainty that arises due to the variable accuracy.

- When the analytical uncertainty is known and acceptable, a UF value of 1 can be justified.
- Otherwise, the uncertainty factor is based on an assessment of the analytical method.
  - An UF value of 2 has been proposed as being appropriate in certain situations.
  - In all cases, the value of the uncertainty factor must be justified.
  - A UF can be established and justified via statistical analysis of a response factor database.
  - A UF should never be assigned to a method like LC/UV/MS, where the response factors vary so much.
- In cases where the variation in response factors is either unknown or large, an appropriate value of UF may be so large (e.g., UF values of 10 or greater) that the AET cannot be applied.

Special Topics; The Analytical Evaluation Threshold (AET)

Exemptions to the AET Concept:

"Cohorts of concern" are compounds that possess structural groups of such high potency that intakes even below the threshold of toxicological concern (TTC) would be associated with a potential for significant carcinogenic risk.

Thus, "cohorts of concern" can be unsafe even if their levels are below the AET.

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.

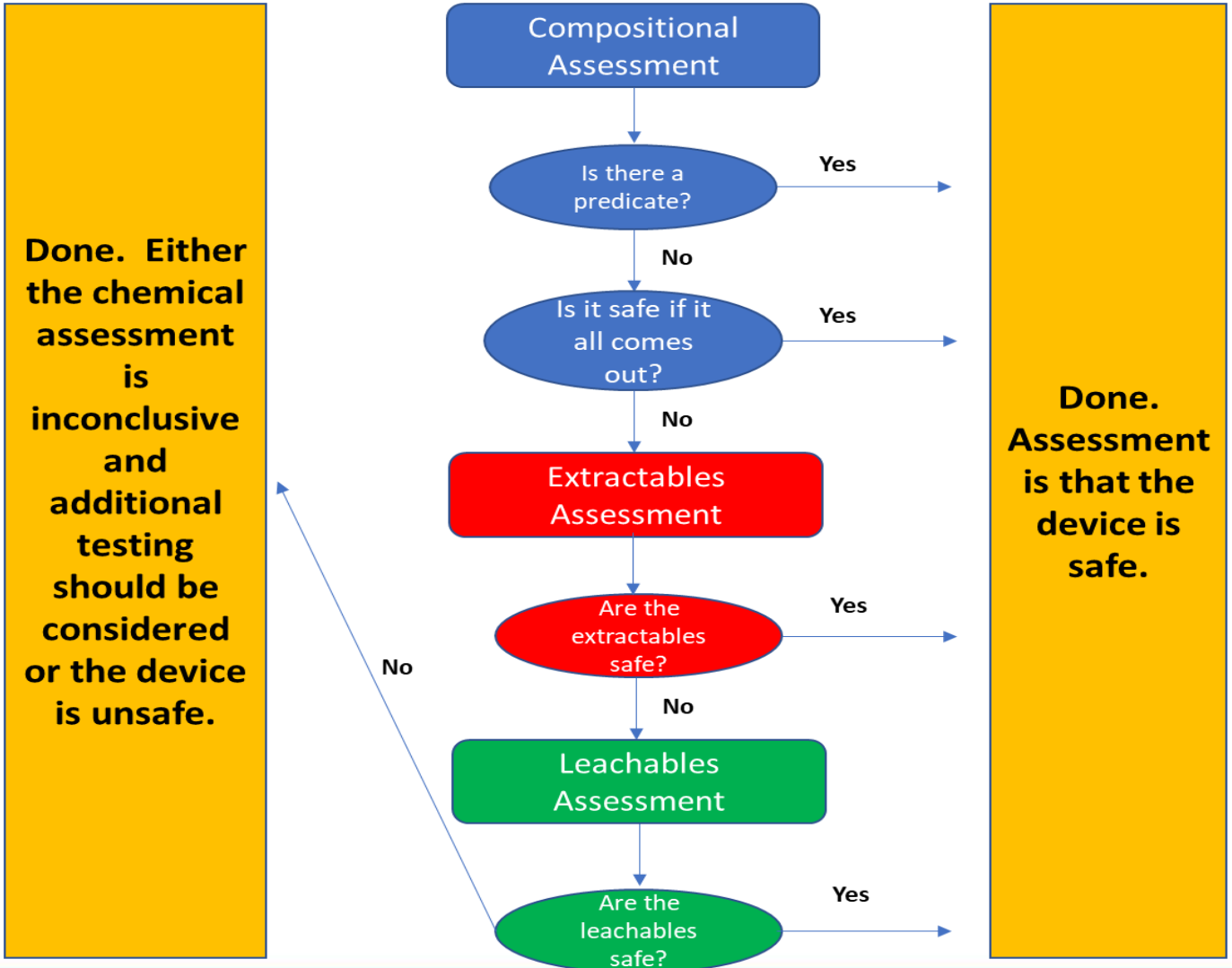
Reporting of Data (2)

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.

Navigating the Part 18 Process, Flow Charts

High Level General Flow Chart

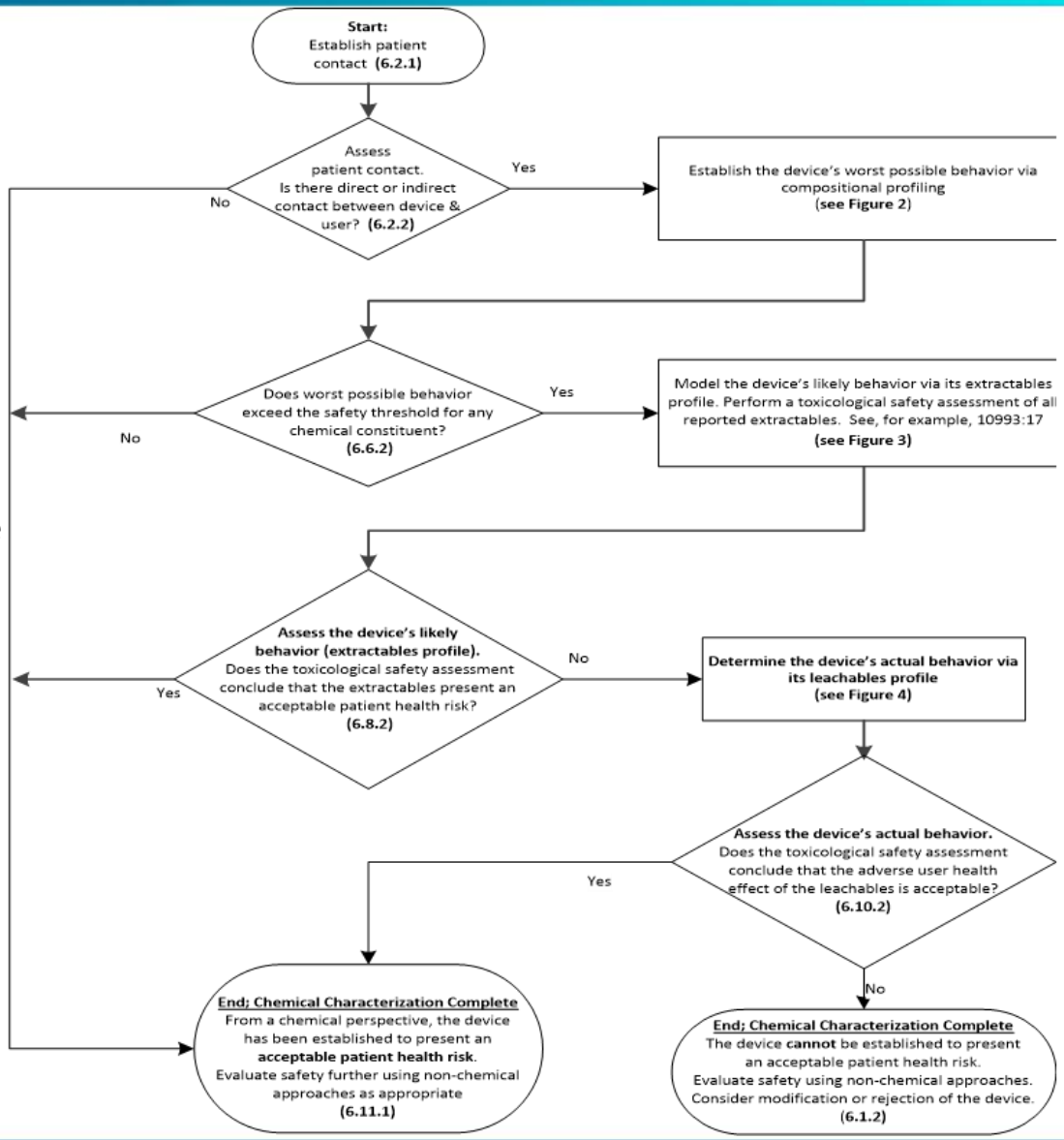


Navigating Part 18; The Overall Flow Chart

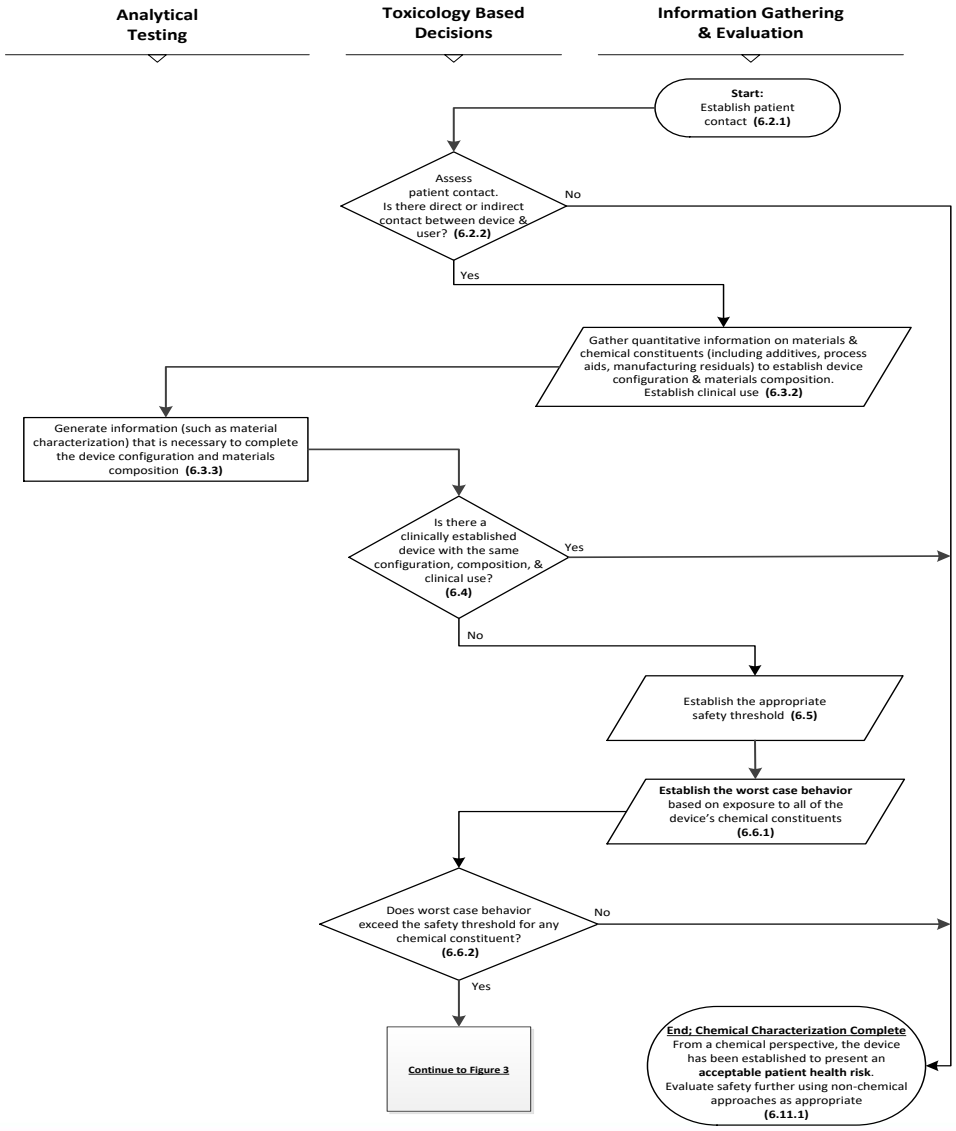
Three Step Process:

1. Establish Composition
2. Establish Extractables Profile
3. Establish Leachables Profile

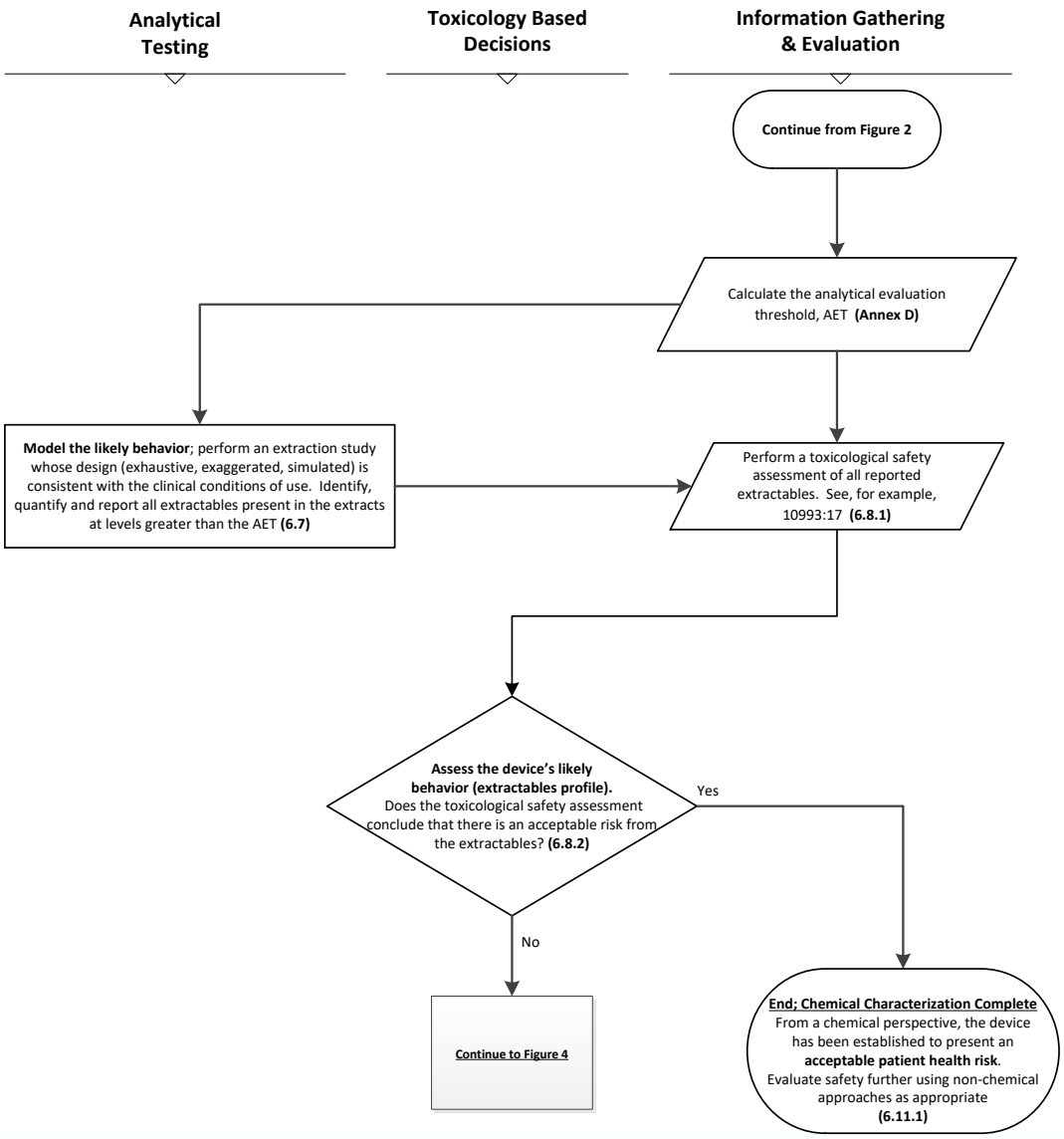
Between each step one asks “is the device safe? As soon as one can say “yes, it is safe”, then one exits the process.



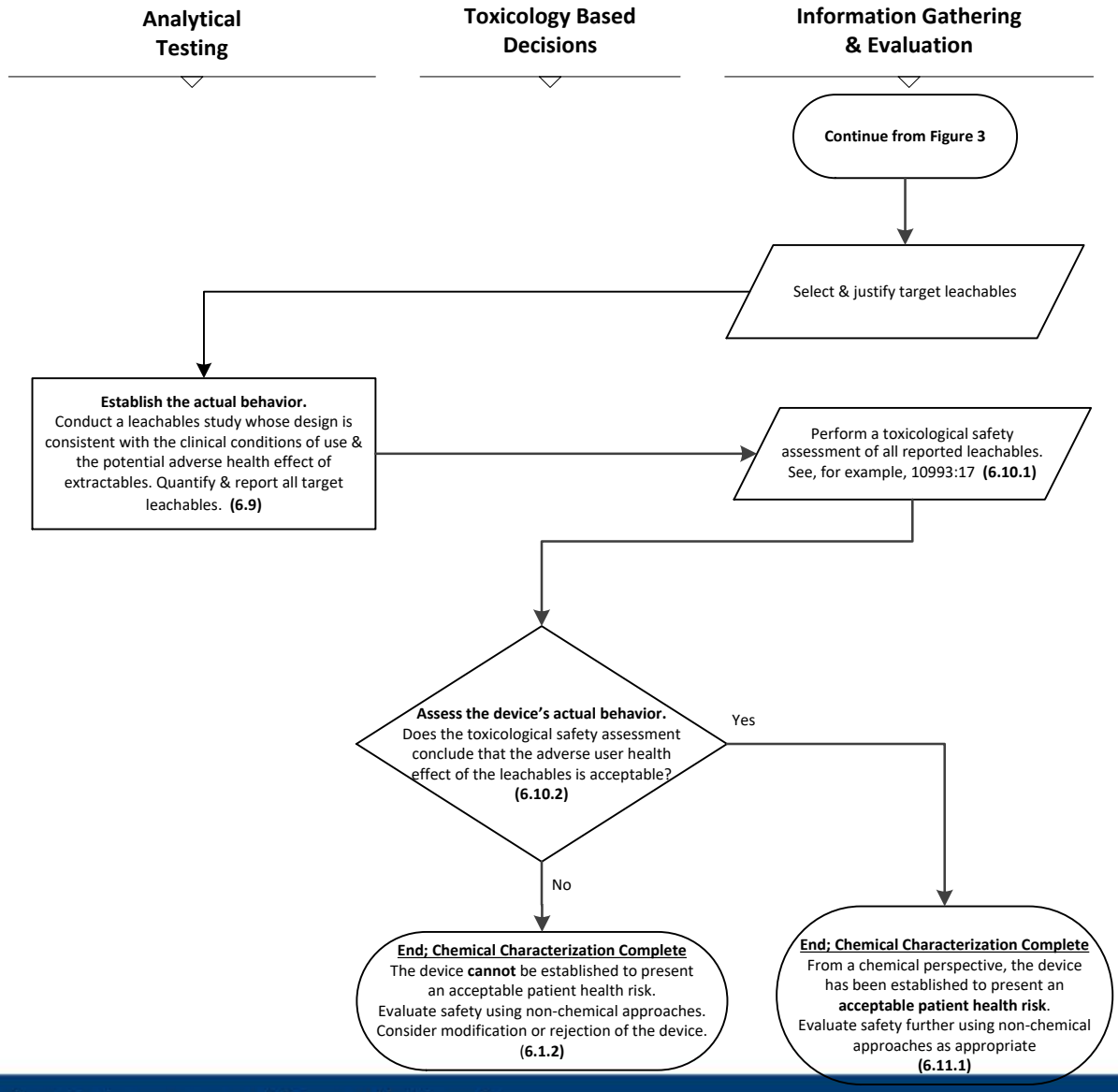
Navigating Part 18; Compositional Testing Flow Chart



Navigating Part 18; Extractables Flow Chart



Navigating Part 18; Leachables Flow Chart



Objective 1: Correlating Chemical Data with Biological Testing

Purpose:

To explain or manage a biological test result

Practice:

When correlating chemical characterization with biological testing, it is clear that the best case is when the chemical testing and the biological testing occurs on the same extract.

Problem:

An extraction solvent that is appropriate for biological testing might not be amenable to chemical testing.

Objective 1: Correlating Chemical Data with Biological Testing

Solution:

Either a surrogate extraction solvent must be found to facilitate the chemical testing or the extract for biological testing must be manipulated to make it analytically viable.

Table D.3 — Potential surrogate extraction vehicles for correlating chemical to biological testing

Inclusion of vehicles here does not fully justify their use in chemical-biological comparisons.

Extraction vehicle for biological testing	Potential surrogate extraction vehicle for chemical testing
Water[f]	Water
Physiological saline[f]	Physiological saline
Ethanol/water[f]	Ethanol/water
Ethanol/saline[f]	Ethanol/saline
Dimethylsulfoxide[f]	Dimethylsulphoxide
Culture medium without serum	1/9 (v/v) ethanol/saline[a]
Vegetable oil	1/1 (v/v) ethanol/water[b] (Reference [26])
Polyethylene glycol 400[e]	1/3 (v/v) ethanol/water[c] (Reference [38])
Culture medium with serum	2/3 (v/v) ethanol/saline[d] (Reference [38])

Objective 2: Establishing the Composition and Configuration of Medical Device

"The greatest potential chemical impact of a medical device is achieved when the device's entire composition is transfered to the potentially affected individual during clinical use. This would be accomplished, for example, if an implantable medical device were to dissolve during clinical use or if an externally communicating device were to be completely leached during clinical use."

Establishing composition and configuration, typically requires test article solubilisation followed by chemical testing of the resulting solution. Solubilisation can be accomplished in several different manners including dissolution or digestion.

An exhaustive extraction establishes the absolute maximum amounts of extractables that can be removed (extracted) from the medical device or material and thus defines the upper bound on the amount of leachables that could potentially be released by the device or material during clinical use/lifetime. In many circumstances, an exhaustive extraction will accomplish the same outcome as digestion or dissolution.

Objective 3: Worst-case Extractables Profile

1. If by worst-case one means “all that is present in the device comes out”, then an exhaustive extraction is required.

2. If by worst-case one means “the maximum amount that can be extracted under the worst possible clinical use conditions”, the an exaggerated or accelerated extraction is appropriate.

Objective 4: Simulated Extractables Profile

The simulated extraction is performed when either

- the clinical conditions of use cannot be achieved in the laboratory
- The use of the clinical conditions produces a solution for testing which cannot be analytically profiled for leached substances.

If the clinical conditions of use can be replicated in the laboratory and if the resulting solution can be analytically profiled for leachables, then the value of performing a simulated extraction is lessened and it is reasonable to suggest that the simulated extraction be replaced with an actual leachables study.

The purpose of a simulated extraction is to produce an extractables profile which closely matches the clinical case leachables profile. A simulated-use extraction establishes the actual amount of extractables that will be released as leachables by the medical device or material during clinical use/lifetime.

Objective 4: Simulated Extractables Profile

- The simulated extraction is accomplished by using extraction conditions (i.e., temperature and duration, contact surface area) that mimic the conditions of clinical use.
- Additionally and as appropriate, the simulated extraction can be performed with a vehicle whose extraction power equals that of the solution that mediates the clinical contact between the medical device and potentially affected individual.

Objective 5: Leachables Profile

3.23
leachable
substance that are released from a medical device and to a potentially affected individual during its clinical use

Note 1 to entry: Leachables studies establish the type and amount of compounds that are released from a device under its actual conditions of clinical use.

For certain devices, (for example, implant), it is either not possible or not practical to perform an actual leachables study and a simulation extractables study is performed instead. However, the substances revealed by a simulated extraction study are simaulted extractables and not actual leachables.

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** shall be examined **with the toxicological risk assessor** to determine 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**.