The New ISO 10993-18 Standard:

Impact on Chemical Characterization of Medical Devices

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Impact of the New ISO 10993-18

Session Agenda

- Overview of ISO 10993-18:2020
- Multiple approaches
- Considerations in implementation
  - Sample extractions
  - Replicates (extractions and injections)
  - Reference Standards
  - Unknowns/AET
- Picking a dose based threshold (for AET)

Status of ISO 10993-18

After a 7-year revision process, the revised 10993-18 was published in January 2020

INTERNATIONAL STANDARD

ISO 10993-18

Second edition
2020-01

Biological evaluation of medical devices —

Part 18:
Chemical characterization of medical device materials within a risk management process

Évaluation biologique des dispositifs médicaux —

Partie 18: Caractérisation chimique des matériaux des dispositifs médicaux au sein d'un processus de gestion du risque

Reference number
ISO 10993-18:2020(E)

General Overview of ISO 10993-18:2020

- ISO 10993-1 describes chemical information as an essential first step in assessing biocompatibility – before biological testing
  - As of 2018, “chemical information” is required for all devices
- Part 18 describes a process for characterizing a device (or material):
  - Identification of its materials of construction
  - Characterization of the material composition (i.e., chemical constituents)
  - Reporting constituent information to support assessment of the potential for patient risk in clinical use
- Generally used with ISO 10993-17 Establishing allowable limits for leachable substances (being revised to cover toxicological risk assessment)
- Chemical information should also be an input to the broader biological evaluation process described in ISO 10993-1

10993-18 – Multiple Approach Options

- The chemical characterization process has three possible approaches:
  - Compositional evaluation
  - Extractables evaluation
  - Leachables evaluation
- Not all approaches are required:
  - Compositional evaluation may be sufficient
  - Leachables study may be most efficient (e.g., for indirect contact devices)

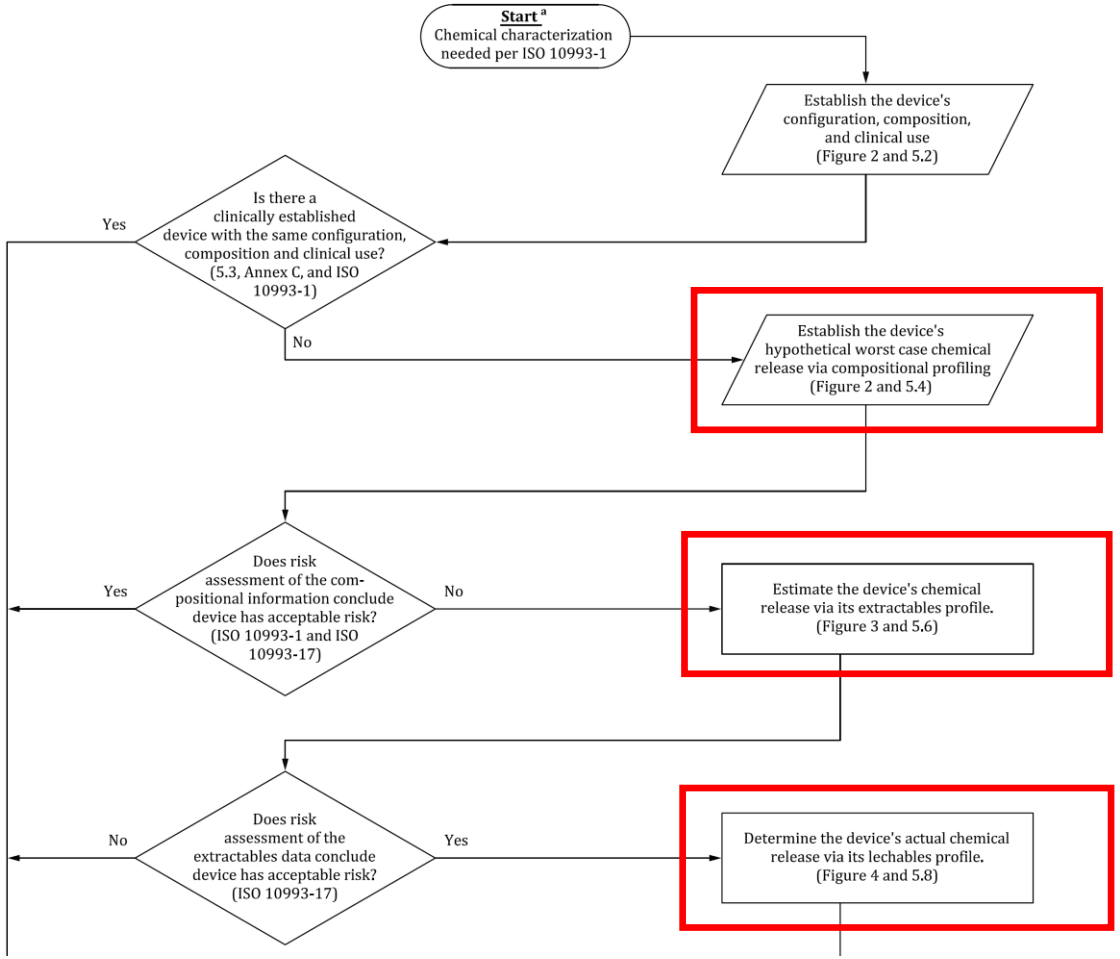


Figure 1 — General chemical characterization process

10993-18 – Compositional Approach

- Describe device configuration (i.e., list components)
- Determine the material composition
  - Information from suppliers
  - Other sources (literature or relevant standard)
  - Include processing (e.g., aids, residues)
- Consider other factors, such as:
  - Duration and nature of patient exposure
  - History of material use
- Assess risk from the compiled information
  - Tox assessment of composition (per 10993-17)
  - Broader biological evaluation (per ISO 10993-1)

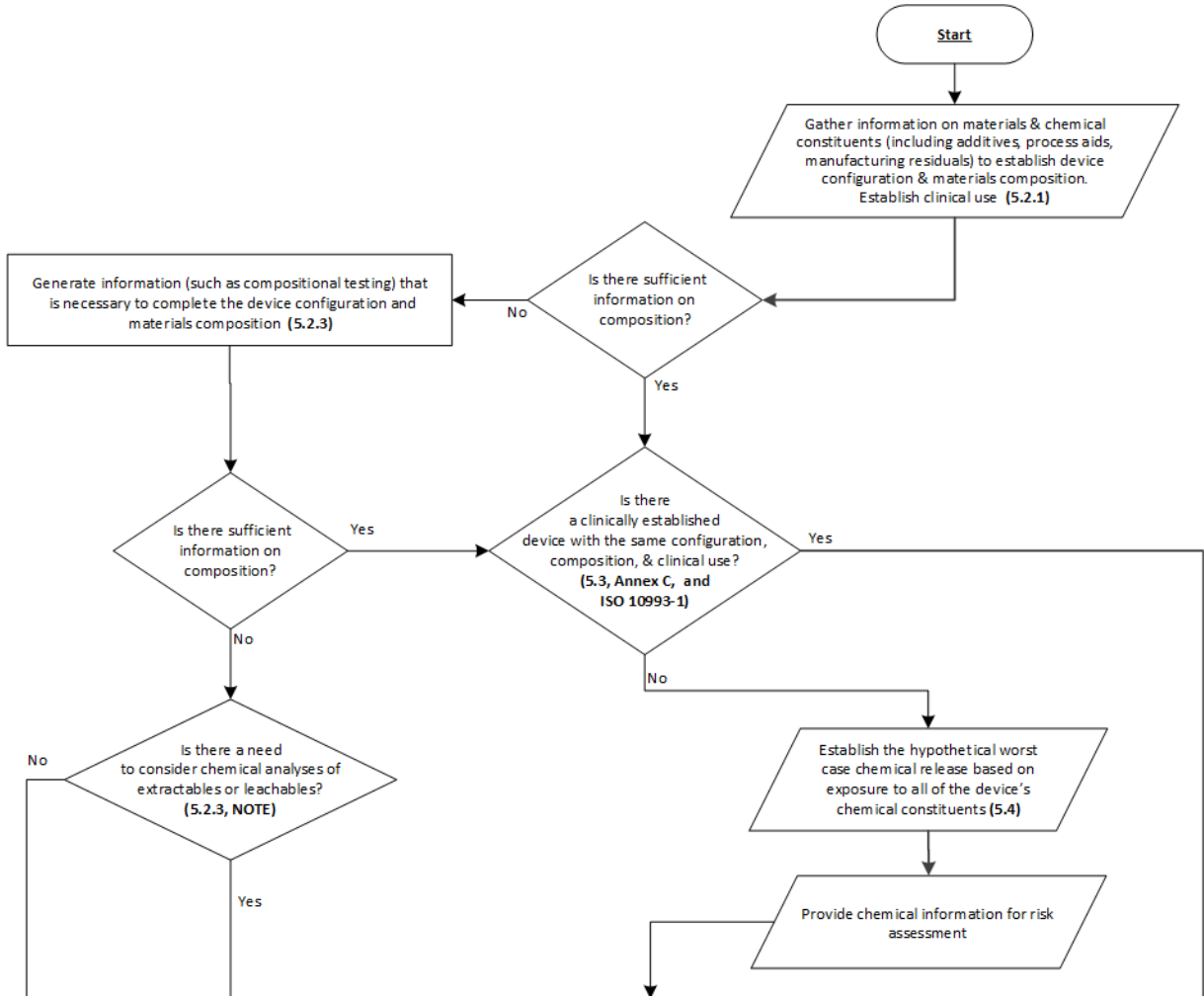


Figure 2 — Compositional profiling process

Considerations for Compositional Approach

- Composition information always needed, and may be sufficient
  - Materials with extensive clinical use history
  - Well understood materials (e.g., ASTM Nitinol vascular stents)
  - Devices/materials with short or non-invasive contact (e.g., ureteral dilator, bandages)

- In particular, ISO 10993-1:2018; Section 6.1 states:

  The extent of physical and/or chemical characterization required depends on what is known about the material formulation, what nonclinical and clinical safety and toxicological data exist, and on the nature and duration of body contact with the medical device. At a minimum, the characterization shall address the constituent chemicals of the medical device and possible residual process aids or additives used in its manufacture.

Beyond Composition – Chemical Analysis

- Although compositional information may be sufficient, chemical analysis is needed in some circumstances:
  - A constituent of potential concern is identified (e.g., the total quantity in the composition exceeds an acceptable threshold)
  - If formulation and processing information is insufficiently complete
  - If there is a safety signal from biological testing
  - As a substitute for some biological testing

NB: Extractables testing is likely needed for any implant

Extractables and Leachables in 10993-18

Leachable – a chemical substance that is released from a device during its clinical use

Extractable – substance that is released from a medical device or material of construction when the medical device or material is extracted using laboratory extraction conditions and vehicles

- These align with long established definitions in E&L community
- Leachables are most relevant, but often pose challenges
  - Difficult to acquire sample (e.g., leachables in patient tissue/fluid)
  - Difficult to analyze sample (e.g., interference of biological matrix)

  \+ May be most practical for indirect contact devices (similar to drug container)
- NB: Simulated use extractions often incorrectly called leachables studies

10993-18 – Extraction Considerations

- Consider ISO 10993-12, but don't be constrained by it
  - For example, samples may need to be diluted or concentrated
- Regulators generally expect both polar and non-polar extraction vehicles, where possible
- In addition to polar and non-polar extraction vehicles, use of a 3rd, semi-polar vehicle expected for long term contact (e.g., implants)
- If non-polar solvent degrades material(s), use a less non-polar solvent (see Table D.1)
  - Be prepared to show evidence of solvent incompatibility
    - Cracking, crazing, swelling, particulates, turbidity, dissolution
  - The test lab should be able to help with this aspect

Solvent Polarities

Table D.1 — Parameters of solvents commonly used for extraction of polymeric medical devices/materials

	Solvent[a]	Polarity index[50]	Boiling point (°C)[b]
Polar	Water[c]	10,2	100
Semi Polar	Dimethyl sulfoxide	7,2	189
	Acetonitrile	5,8	82
	Methanol	5,1	65
	Acetone	5,1	56
	Ethanol[d]	4,3	78
	Tetrahydrofuran	4,0	65
	n-Propyl alcohol	4,0	97
	i-Propyl alcohol	3,9	82
	Dichloromethane	3,1	41
Non-Polar	Toluene	2,4	111
	Cyclohexane	0,2	81
	Heptane	0,1[e]	98
	n-Hexane	0,1	69

This table is informative only (i.e., not normative)

10993-18 – Replicates

- Increased expectations in the minimum number of extraction replicates: generally triplicate, unless otherwise justified
  - Evidence of low variability in materials of construction
  - Evidence of low variability in extraction process (likely will require data)
- Triplicate injections expected, but what to report?
  - Values from representative chromatograms?
  - Mean values?
  - Upper 95% confidence limit
  - Maximum values? (some evidence FDA may want to see this)
  - How to select (e.g., maxima from across multiple chromatograms)?
- Potential for up to 27 runs/method! (3 solvents x 3 extractions x 3 injections)

Analytical Considerations

- Generate chemical profile of extractions using appropriate analytical methodology; typically:
  - Gas Chromatography-Mass Spectrometry (GC-MS) – semi-volatile substances
  - High Performance-Liquid Chromatography-MS – non-volatile substances
  - Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) or OS
  - Others to consider include
    - Head Space GC-MS – volatile substances
    - Ion Chromatography – small cations and anions
- Use library matching from available compound databases as well as analytical expertise to identify analytes
  - Experts are working to develop guidance on state of the art

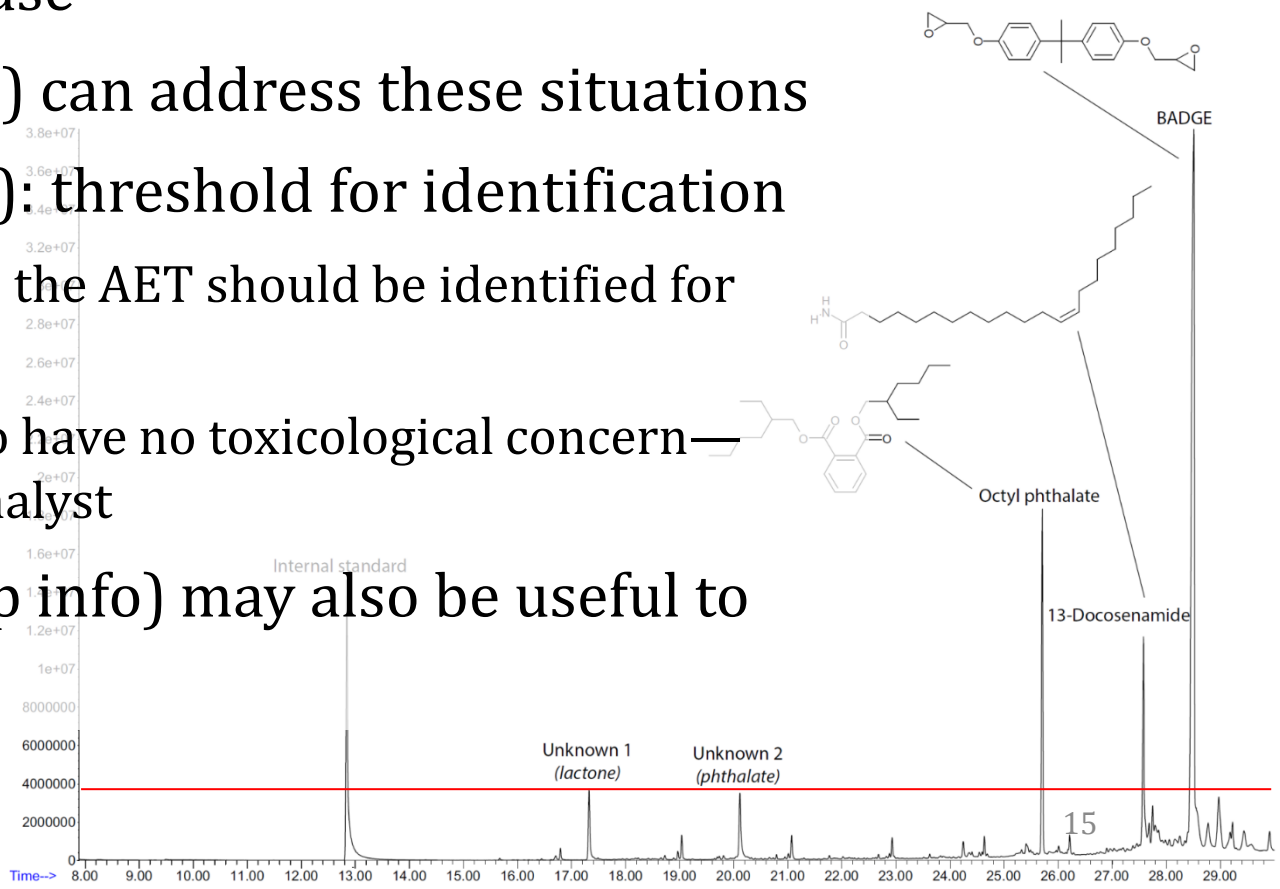
Quantitation / Reference Standards

- Traditional work in extractables studies for medical devices has used single point calibration with a single reference standard
  - New part 18 refers to this as "**estimated quantitative analysis**"
- An updated definition of "**semi-quantitative analysis**" has been added; in this approach, quantitation is based on the relative responses of the analyte and a surrogate reference standard
  - A recent paper from Mark Jordi's lab does a nice job of presenting the topic*
- Regulators are now expecting multiple levels [concentrations] of standards, as well as use of multiple reference standards

* Jordi M.A., Khera S., Roland K., et al. Qualitative assessment of extractables from single-use components and the impact of reference standard selection. J. Pharmaceutical and Biomedical Analysis. 2018;150:368-376.

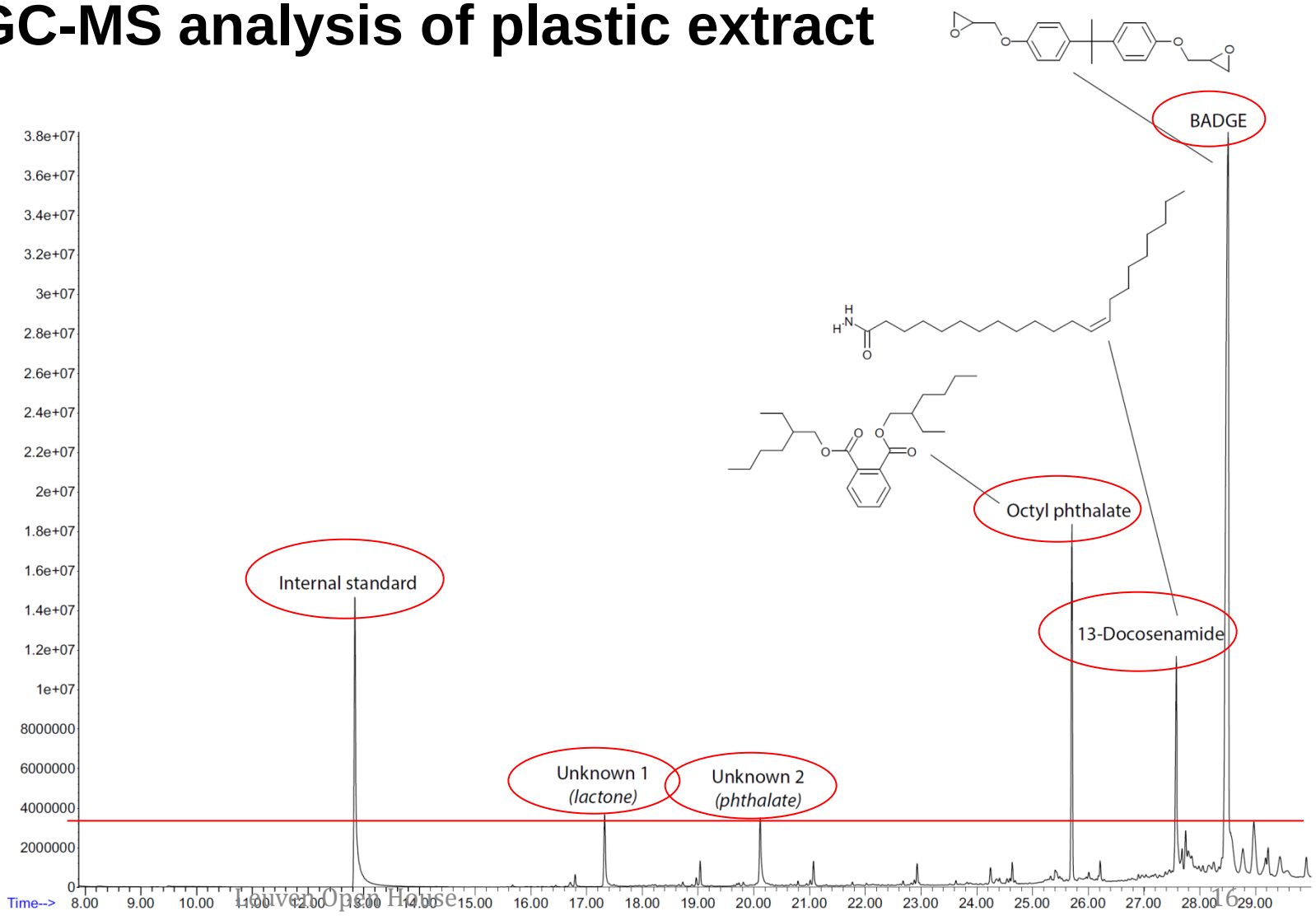
Dealing with Unknown Substances

- The preceding slides have assumed that identities of all analytes have been determined – this is not always possible
- Unknown substances must be considered, because they have potential to affect safety of the material in clinical use
- Toxicological safety thresholds (TTC, SCT) can address these situations
- The AET (analytical evaluation threshold): threshold for identification
  - Extractables whose concentrations are above the AET should be identified for toxicological risk assessment
  - Extractables below the AET are considered to have no toxicological concern—therefore do not need identification by the analyst
- Partial identification (i.e. functional group info) may also be useful to toxicologist



Illustrating the Threshold Concept

GC-MS analysis of plastic extract



*Nerin C, Ubeda J, Alfaro P, et al. Compounds from multilayer plastic bags cause reproductive failures in artificial insemination. Scientific Reports **4**, Article number: 4913 (2014) doi:10.1038/srep04913*
http://www.nature.com/articles/srep04913

10993-18 – Calculation of the AET

The AET in µg/ml can be calculated as given in Formula E.1:

$$AET = \frac{DBT \times \frac{A}{BC}}{UF} \qquad \text{(E.1)}$$

where

A is the number of medical 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 medical device (number of devices a user would be exposed to in a day under normal clinical practice);

DBT is the Dose Based Threshold (e.g., TTC or SCT) in µg/d;

NOTE: A toxicologist should be consulted in selecting a specific threshold that can support risk assessment;

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. See E.3 for a discussion on how to determine the proper value to assign to UF.

The extract processing (e.g., any dilution or concentration steps) should be considered during analytical concentration calculations and the calculation of the AET value adjusted accordingly.

AET and UF Equation

- An error in the UF equation made its way into the published document

A statistical approach to establishing and justifying a particular UF is statistical analysis of a database of response factors specific to the analytical method being considered and the population of extractables for which that method is applicable. In one possible approach, the value of the UF would be linked to the relative standard deviation of the response factors according to Formula (E.2):

$$\text{mean} / \left[1 - (t \times \text{std})\right] \qquad \text{(E.2)}$$

where

mean	is the mean response factor from the reference database;
t	is the desired degree of confidence;
std	is the standard deviation in the response factor database.

- E.2 should be 1/(1-RSD)
  - Consistent with PQRI formulation
  - NB: Approach falls apart when RSD closely approaches or exceeds 1
  - Amendment to the document will be needed

Choice of DBT (dose based threshold)

- Calculating AET requires a DBT be identified (e.g., TTC)
- ISO/TS 21726 and ICH M7 guidance on mutagenic drug impurities:

Table 2: Acceptable Intakes for an Individual Impurity

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

- For a long term implant, one might consider 1.5 µg to be appropriate (given long term exposure to the device)
- **However**, there are problems with this approach…

Choice of DBT (continued)

- Exhaustive extractions are recommended for long term devices to assure that **total** exposure is estimated conservatively
- The ICH M7 limits are for "Daily intake" – establishing **daily** exposure to leachables is challenging, if not impossible

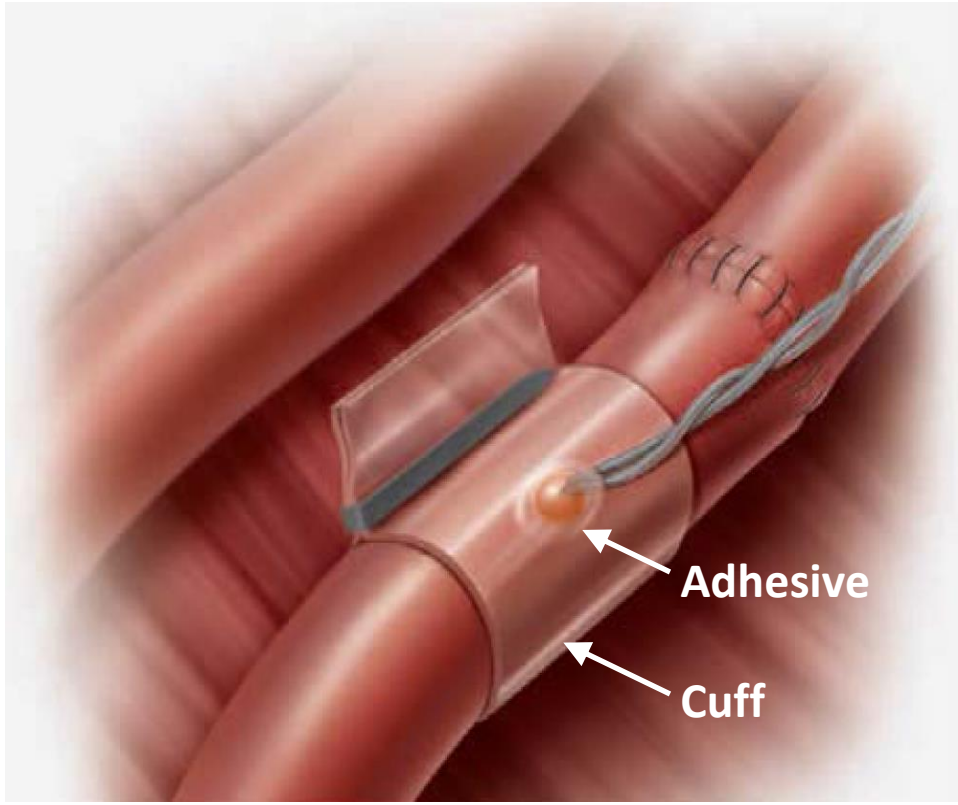
Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

- Exhaustive extractions reveal **<u>total</u>** amounts of leachables, but don't provide good way to understand **<u>daily</u>** release/exposure
- Although there is interest in using 1.5 µg, the resulting DBT is excessively conservative (see next slide)

Impact of Excessively Conservative DBT

- Vascular flow monitor, used after reconstructive micro-vascular procedures (free-flap transfers)
- Silicone cuff and adhesive have long term exposure: implant mass ~18.2 mg
- Device underwent exhaustive extraction

Solvent	Non-Volatile Residue (µg/device)			Total NVR (µg/device)
	Replicate 1	Repl. 2 (% of 1)	Repl. 3 (% of 1)	
Hexane	210	18 (8.4%)	N/A	228
IPA	150	19 (13%)	3.0 (2.1%)	172
Water	0	0 (N/A)	N/A	0



- Excessively conservative 1.5 µg DBT means **daily** exposure to NVR for lifetime (≥ 3,652 days)
- 228 µg/day × 3,652 days = 832,656 µg or 833 mg

833 mg is over 40x the total mass of the device!

Choice of DBT (cont.)

- Using 1.5 µg DBT is clearly bad science, so how should one choose DBT?
- One approach: Calculate the **total** exposure possible for each category

Duration of Treatment	≤ 1 month	> 1 – 12 months	> 1 – 10 years	> 10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5
Conservative exposure duration*	31 days	365 days	3652 days	>3,652 days
Total exposure [µg/device]	31 × 120 = 3,720 µg	365 × 20 = 7,300 µg	3,652 × 10 = 36,520 µg	>3,652 × 1.5 = >36,520 µg

- Remembering that exhaustive extractions give the **total** amount released, an assumption of release in < 1 month gives a conservative exposure
  - Therefore 120 µg is a reasonable threshold
- Alternatively, consider simulated use extraction and/or evaluation of release rates

Chemical Characterization Pros and Cons

+ Minimizing animal use in accordance with ISO 10993-2 (i.e., in place of some *in vivo* toxicity testing, like chronic tox or genotox)
+ Greater sensitivity than biological testing
+ Well suited for assessing equivalence of a proposed device (or material) to a prototype or clinically established device
– Does not usually eliminate the need for all biological testing
  - Other material/device properties may cause adverse biological response (e.g., irritation, thrombogenicity, hemolysis, implantation
  - Toxicology data may not exist for biological endpoints of interest (e.g., sensitization)
– May be difficult to simulate clinical use conditions
– Acceptability of unknown substances may be difficult to establish with certainty (e.g., excluding cohort of concern)

Conclusions/Summary

- ISO 10993-1 now calls for chemical characterization for all device types
- ISO 10993-18:2020 clarifies that:
  - Chemical characterization does not necessarily require analytical testing
  - Various approaches to the process are possible
  - Multiple solvents, extractions, injections, and methods drive a **LOT** of work
- Many uncertainties remain regarding
  - Application of reference standards
  - Identification reliability
  - Selection of dose based thresholds

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