Chemical Analysis for Medical Devices: Strategies for Reducing Scientific Questions

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Outline

1. ISO 10993-18:2020; partial recognition.
2. Common questions about chemical analysis approaches when screening for extractables.
    a) General questions.
    b) Questions on extraction.
    c) Questions on AET, Methods and related issues.
3. Concluding remarks.

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Background: Chemical Analysis and Toxicological Risk Assessment

FDA Biocompatibility Guidance (updated September 4th 2020).

- "Potential risks from a biocompatibility perspective should be identified"(pg 9).
- "Address the knowledge gaps either by biocompatibility testing or other evaluations that appropriately address the risks" (pg 9).
- "Chemical analyses can be used to assess the toxicological risk of the chemicals that elute from devices. For example, chemical analysis using exhaustive extraction techniques (per ISO 10993-12) can also be helpful to evaluate long-term toxicity endpoints such as potential carcinogens…In addition, the outcomes of chemical analyses are often sensitive to the parameters of the test. Extraction solvents should be selected to optimize compatibility with the device materials." (pg 11).

https://www.fda.gov/media/85865/download

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FDA Partial Recognition of ISO 10993-18:2020

ISO 10993-18:2020 is partially recognized.

(FR Recognition Number 2-276 Date 07/06/2020)

The following parts of the standard are not recognized:

1. Clause 5.5 second and third sentences.
2. Clause 7, second paragraph, phrase “to assist in any toxicological risk assessment”.
3. Table D.3 in Clause D.5 of Annex D.
4. Formula E2 AND paragraph preceding Formula E2 AND two paragraphs following Formula E2 in Clause E.2 of Annex E.
5. Example C2 in Clause E.4 of Annex E.

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FDA Partial Recognition of ISO 10993-18:2020

1. Clause 5.5 second and third sentences not recognized.
   - ISSUE: AET>LOQ to support toxicological risk assessment (TRA).

     AET: Analytical Evaluation Threshold

     LOQ: Limit of Quantification

2. Clause 7, second paragraph, phrase “to assist in any toxicological risk assessment” not recognized.
   - ISSUE: Grouping of compounds with uncertain identity (based on structural or functional groups) can result in incorrect TRA outcomes.

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FDA Partial Recognition of ISO 10993-18:2020

3. Table D.3 in Clause D.5 of Annex D not recognized.
   - ISSUE: Table identifies "Potential surrogate extraction vehicles for correlating chemical to biological testing" (e.g., ethanol/water mixtures).
     - Example solvents specific for determining reasons for biological test failures.
     - Only relevant to specific analytes/matrix materials included in referenced literature.
     - Not relevant to general analytical chemistry screening studies.

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4. Formula E2 AND paragraph preceding Formula E2 AND two paragraphs following Formula E2 in Clause E.2 of Annex E not recognized.

ISSUE: Uncertainty Factor calculation within AET.

– Technical errors to be corrected by ISO in a future revision to the standard.

– UF = mean/[1-(t x std)]

- "mean" and "t" not used in some literature:

  Jenke 2020, PDA J Pharm Sci and Tech 2020, 74 348-358 "Correcting the Analytical Evaluation Threshold (AET) and Reported Extractable's Concentrations for Analytical Response Factor Uncertainty Associated with Chromatographic Screening for Extractables/Leachables".

  Jordi et al. 2020, Journal of Pharmaceutical and Biomedical Analysis 186 (2020) 113334 "Reducing relative response factor variation using a multidetector approach for extractables and leachables (E&L) analysis to mitigate the need for uncertainty factors".

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5. Example C2 in Clause E.4 of Annex E not recognized.

- ISSUE: Total amount extracted divided by number of days could underestimate toxicological risk for some chemicals, especially when supporting kinetic release data is unavailable (burst vs. zero-order release).
- See ISO TS 21726:2019, clause 5.2 and Table 1 for recommended Dose Based Thresholds (DBTs) based on duration of device use.

General Questions

FAQ: What biocompatibility endpoints can be addressed by chemical characterization information?

- Systemic Toxicity, Genotoxicity, Carcinogenicity can be addressed by chemical characterization (FDA Biocompatibility Guidance, pg 48).
- Chemical equivalency involves different considerations: see ISO 10993-18:2020, Annex C "Principles for Establishing Biological Equivalence".

Follow up: Could you clarify the level to which chemical characterization and toxicological risk assessment can be used to address acute systemic toxicity? Is this for most chemicals or only for chemicals with specific datasets available?

- The challenge is to identify an appropriate DBT for acute toxicity. If one is using a chronic DBT, it also would be protective for acute, subacute and subchronic endpoints.

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General Questions

FAQ: If there is not a clear standard or FDA guidance on what is expected for chemical characterization, that makes it difficult for the medical device industry to deliver data packages that will be accepted. Does FDA have any plans to fill this gap?

- FDA Biocompatibility Guidance 2020 (Section VII; Attachment E).
- ISO 10993-18:2020 Annex G.

Questions on Extraction

FAQ: Are alcohol/water mixtures (e.g., 50/50 Ethanol/Water) appropriate semi-polar solvents?

- Extractions using alcohol/water mixtures can result in fewer number and/or lower amounts of extractables compared to undiluted alcohol.
- Presence of water may introduce complications in terms of instrument compatibility such as in GC.
- Polymers may selectively absorb one component of the mixture, resulting in:
  - A change in the composition of extraction solvent mixture.
  - Altered polarity.

Questions on Extraction

FAQ: What happens if the material is degraded by the solvent?

"Choice of solvents will depend on device materials and should be justified… extraction conditions (i.e., solvent, temperature, and duration) should not compromise device integrity" (2020 FDA Biocompatibility Guidance Page 48).

- A reasonable effort made to find compatible solvents (e.g. using pilot extraction studies).
- For materials that are not novel, some solubility/compatibility data should already exist. (e.g., silicones: Lee et al. 2003 *Anal. Chem* 75, 6544).
- Polar, semi-polar, and non-polar: can be selected based on Polarity Index. (Snyder LR. *J Chromatography* 1974:92;223-230. and Snyder LR. *J Chromatogr Sci* 1978:16;223-234).

Follow up: If a permanent implant is not compatible with semi-polar solvents, can a sponsor just use polar and non-polar solvents (i.e., no semi-polar solvent studies)?

- Generally, all three are recommended.

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Questions on Extraction

FAQ: What happens if the material is degraded by the solvent?

"Follow up-2: If a nonpolar solvent degrades the polymer, is it appropriate to use a solvent with mixed polarity for the extraction? If visible polymer degradation occurs, does FDA expect the toxicological risk assessment to be done on extractables from the degraded polymer?

- Degraded polymers are not recommended for chemical analysis.
- Consider:
  - How has degradation been determined?
  - If a compatible solvent cannot be identified for analytical chemistry testing, consider biological testing.

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Questions on Extraction

FAQ: Are the extractions different for the chemical characterization than for the biological testing regarding the parameters such as solvents and extraction ratios? Does ISO 10993-12 cover both analytical chemistry and biological testing?

- ISO 10993-18:2020 includes specific instructions on how one can use recommendations in ISO 10993-12 as a starting point for analytical chemistry testing (see ISO 10993-18:2020 Clause D.1 for additional information about selection of solvents).
- Extraction ratios can be changed to facilitate achievement of AET.

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Questions on Analytical Evaluation Threshold

FAQ: For Uncertainty Factor (UF), would the test lab need to justify a selected UF based on their methods and data?

- Yes, providing a justification or supporting evidence for the selected UF is always recommended.

Follow up: What are valid justifications to support an Uncertainty Factor?

- Literature data that includes the RF database components.
- Laboratory data with determination by the formula UF = 1/[1-(RSD)].

  NOTE: RSD is relative standard deviation of Relative Response Factors of an appropriately curated response factor database.

These criteria are generally considered to justify UF either by literature or laboratory data:

- Diversity of chemical classes.
- Representative compounds of the extract.
- # of compounds.

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Questions on Analytical Evaluation Threshold

FAQ: Can you comment on the DBT that is appropriate for absorbable devices that persist less than 30 days before total absorption?

- The DBT is selected based on the worst case duration of contact within the body (i.e. toxicokinetics). While the absorbable compound(s) may be nondetectable after 30 days, the material components or degradation products may have been taken up into the tissues where they may persist for a much longer time.

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Questions on Analytical Evaluation Threshold

FAQ: If an extractable after exhaustive extraction from a long-term implant is assumed to be delivered to the patient in the first day, it seems the DBT should be 120 µg rather than 1.5 µg. Can you comment?

- Selection of TTC/DBT can be based on either…
  - the number of days the medical device is in contact with the body OR
  - the number of days a user could be exposed to the chemical (i.e., release kinetics).
- ISO TS 21726:2019, Clause 5.2, describes the selection of TTC for comparison to a maximum concentration of an identified or unidentified constituent in an extract.
- The proposed approach would not protect against a lower toxic dose being released over more days.
  - For example, 100 µg released in a single day, may not be toxic (< TTC of 120ug for < 24h exposure).
  - However, if the total amount of 100 µg is slowly released at a dose of 2.5 µg/day for 40 days, this might be toxic (> TTC of 1.5ug/day for > 30d exposure).

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Questions on Analytical Evaluation Threshold

FAQ: IF AET is less than LOQ, what are preferred strategies for sample concentration?

- There are no preferred strategies: Possible approaches include:
  - Solvent volume reduction
  - Solvent exchange
  - Choice of extraction ratio
- If any method is proposed for concentration, spike and recovery experiments can qualify that composition of extract is maintained.
- For SVOC analysis, additional care is needed since semi-volatile compounds can be lost more easily.

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Questions on Analytical Evaluation Threshold

FAQ: Is the Uncertainty Factor used in AET a correction factor? i.e. is it used to multiply the calculated semi-quantified amounts to obtain a better estimate?

- According to ISO 10993-18:2020 (Clause 5.5): The AET is the reporting threshold above which identification and quantification are reported. The Uncertainty Factor is used to calculate the AET.
- To obtain better estimated amounts in semi-quantified extractables, more reference standards with more chemical similarity (hence response factor) are recommended.

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Questions on Methods

FAQ: What is the advantage of coupling an UV detector to LC-MS analysis?

- It is generally recommended to use UV and ELSD/CAD detectors for LC in addition to MS:
  a) They are complementary.
  b) If an extractable can be semi-quantified by a method other than MS, it may be confirmatory.
  c) They can fill in identification/detection gaps for MS detection.

  Disadvantages (of UV and ELSD/CAD):
  a) Not everything is UV absorbent.
  b) UV is generally less sensitive .
  c) ELSD/CAD is not sensitive to compounds with modest volatility (due to high flow in the detector).

Follow up: Can detectors be "combined", to reduce Uncertainty Factor?

- As many device extracts are unique, and commonly used detectors or analytical methods detect a subset of extractables, such generalizations may be not applicable.

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Questions on Methods

FAQ: Can you comment on the likelihood of the NVR matching the mass determined after chemical analysis?

- If there is a significant difference in the NVR amount in identified and quantified non-volatile extractables this indicates there are unidentified extractables.
- Explanation of any discrepancies between the two quantification approaches can be helpful.

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Final Thought

Not sure what is the best approach for chemistry testing?

Contact CDRH:

a) Pre-submission
   https://www.fda.gov/media/114034/download
b) Technical Contacts on Guidance Documents
c) Technical Contacts listed in Recognized Consensus Standards
   https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm
d) Division of Industry and Consumer Education (DICE)
   https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice

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Thank you!

Questions?

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