Lessons Learned: Chemical Characterization and Regulatory Submissions

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Experiences with Chemical Characterization

- A Manufacturer's Perspective on Chemistry and Toxicology
  - Essential vs Nice to Have
- Strategies Across CROs vs Strategic Priorities
  - CRO Strategies Vary Widely, All Claim Reg. Acceptance
- Consolidated Review of Regulator Feedback on Chemistry
  - Common Themes in E&L Feedback

Manufacturer Priority No 1

"First, do no harm"

Purpose

We strive to improve the health and quality of people's lives.

People

Teleflex employees are trusted partners of medical clinicians and the patients they serve.

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Manufacturer Priority No 2

Get innovative and legally cleared devices to market in timely and cost-efficient manner

Completely Essential	Necessary Additional Req	"Nice to Have"
Data that objectively supports conservative and skeptical internal stakeholders of patient safety	Data or arguments for compliance to non-scientific regulatory requirements	Additional tests, replicates, or methods that expand dataset without improving safety or odds of regulatory acceptance
Example: extractables data of sufficient quality to convince internal biocompatibility and toxicology groups that device risks are acceptable	Example: exhaustive extraction endpoint data by NVR; or extractables in gas-pathway when condensate can't reach patient	Example: n = 9 replicate testing when n = 3 or 1 is acceptable; or sensitivity lower than required

Translation into Strategies Proposed by CROs

	CRO A	CRO B	CRO C
Exhaustive Extraction Endpoint	72-hr initial followed by 24-hr iterations, measured by GC/MS and LC/MS	72-hr iterations measured by NVR	24-hr iterations for minimum of 3 iterations and maximum of 5 iterations, measured by NVR
Replicates	Single replicate with single device	Triplicate with single device	Single replicate with a minimum of 3 devices pooled
VOCs	Water extract only	Separate 37C water extract only	Water and mid-polar
Semi-Quant	Targeted surrogate and RRF corrected	Targeted surrogate	Single standard and partial RRF correction
Identification	Pay per ID, expert review, extensive time spent	*Everything* ID by machine with cursory review	Confident ID up to certain number of IDs

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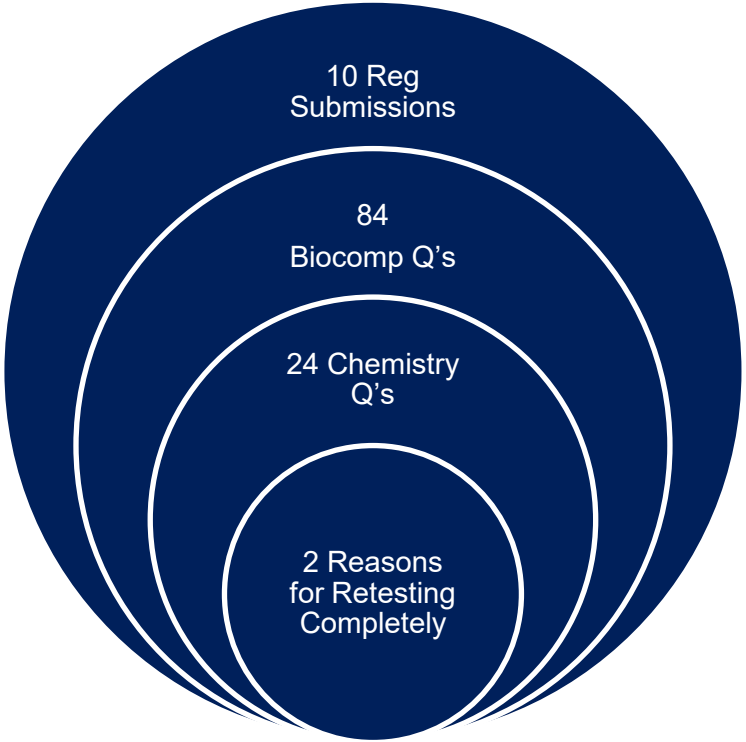
Summary of Regulatory Feedback: A Review of 10 Regulatory Responses



Feedback on Chemistry

9 Cases: Method(s) not sensitive enough (AET v LOQ, UFs for AET too low, NVR LOQ too high)

7 Cases: Request for method suitability information (spike and recovery, calibration curves)

4 Cases: Request for exhaustive extraction instead of exaggerated

2 Cases: Nitty-gritty analytical (APCI vs ESI)

1 Case: Improper extraction vehicle

1 Case: Number of peaks on chromatogram disagree with number of compounds reported

Feedback on Chemistry: Sensitivity

"Your report include an AET calculation and the AET is 0.10 µg/device. However, ***the Limit of Quantification (LOQ) is not reported****, nor is a comparison made per Annex E of the ISO 10993-18:2020 for any of your analytical methods for organic compounds.* ***FDA needs these values to ensure that your instruments are able to detect and semi-quantify compounds at levels above the AET****."*

General Response: Over last 2 years, CROs have developed method suitability data proactively supplied in reports-

Feedback on Chemistry: Sensitivity

"You included an AET calculation where an UF of 2 is included. However, you have not included a justification for the UF. The AET is calculated based on the following formula (ISO 10993-18:2020 Formula E.1): AET = DBT × A/(B × C × D) / UF. The UF depends on the analytical method and needs to account for the level of variation of the Response Factors (RFs) of the observed or expected extractables. ***FDA recommends that you use the formula UF = 1/[1-(RSD)].***

In your submission, please describe how you calculated your UF, including a description of the RF database. FDA recommends that you apply the following criteria to support the RF database obtained by literature data or laboratory-generated data: diversity of chemical classes, representative compounds of the extract, and number of compounds.

Feedback on Chemistry: Sensitivity

The area of the report concerning the NVR states that "NVR is only reported when at least 2.0 mg NVR is detected." However, an NVR limit of 2.0 mg makes your ***NVR determination method unsuitable for extractables analysis because it does not adequately determine chemical residue levels needed to support the safety of the materials which are done with analytical balances that measure a factor of 100 better, to 20 µg.*** *It is important to measure the NVR amount with a reasonable level of accuracy as this information is an orthogonal method to other analytical chemistry techniques to obtain the amount of non-volatile extractables.*

General Response: CROs, manufacturers, and regulators remain at an impasse on NVR, especially when subject device is all-metal, all-glass, or small (mass less than 1 g).

Feedback on Chemistry: Method Suitability

Sample processing steps may result in loss of volatile organic compounds (VOCs) and semi-volatile organic compounds (SVOCs). To ensure that your sample processing method is appropriate, ***please provide your verification method (e.g., spike and recovery)*** *demonstrating that the sample processing steps performed are appropriate and do not result in VOC and SVOC loss….*

FDA recommends that ***any extract manipulation steps*** *(such as solvent exchange or concentration)* ***are accompanied with method qualification information****, including a description of the recovery rates for the internal standards*

Feedback on Chemistry: Resulting in Retest

In your chemical characterization, you conducted the analytical extractions at 50°C for 72 hours; however, ***you have not demonstrated the exhaustive endpoint using NVR*** *screening…*

General Response: Expectation is 100% clear. Exhaustive extraction endpoint determination by NVR is required, even when there is sound scientific justification to do otherwise.

Feedback on Chemistry: Resulting in Retest

You detected a compound in a general category without a CAS number… please delineate whether this compound was tentatively identified, confidently identified, or confirmed identification. ***If it was tentatively identified, it should be assessed using the TTC approach…***

The GC-MS chromatogram shows a broad, unresolved peak… ***Please perform further experimentation*** *or analysis to resolve the chromatogram peaks and report the identity and quantity of the individual compounds in the hexane extract.*

General Response: Under current regulatory policy, even a single unknown (or in this case a partially identified compound) above the TTC can lead to retesting.

Note: Treatment of this issue could change when new 10993-17 is published-

Conclusions

Progress in Med Device E&L Has Been Dramatic!

- 8 years ago: No method suitability, often no LC/MS, often machine-only identifications, “unknowns” simply not reported, significant differences across CROs
- Today: Analytical methods have proven accuracy and precision across representative functional groups, consensus on general analytical scope, data better protects patient safety

Outlook: conversations like this need to continue to help CROs, manufactures, and regulators reach consensus on approaching chemistry for toxicology using protective, scientifically valid, and risk-based practices.