Accreditation Scheme for Conformity Assessment (ASCA) and the Use of Chemical Analysis to Support Biocompatibility of Medical Devices

November 6, 2024

Disclaimers

Information in these slides is intended to support discussion about pathways for expanding the ASCA program to include chemical analysis for supporting biocompatibility of medical devices. Information in these slides does not represent FDA policy and should not be construed as such. Not on today's agenda: FDA's draft guidance "Chemical Analysis for Biocompatibility Assessment of Medical Devices" (comments due December 19, 2024)

WELCOME & INTRODUCTION

Terry Woods, Ph.D.

Director, Division of Standards and Conformity Assessment (DSCA)

Morning Agenda

Time	Subject	Speaker(s)
8:30 - 8:45 am	**Welcome and Introduction**	**Terry Woods, Ph.D.**
8:45 - 9:00 am	**Opening Remarks/Background**	**Ed Margerrison, Ph.D.**
9:00 - 10:00 am	**Session 1: Current methods and challenges** • *Interlaboratory study for extraction testing of medical devices* • *Proficiency testing proposal* • *Panel discussion*	**David Saylor, Ph.D.** **Shuliang Li, Ph.D.** **FDA panelists**
10:00 - 10:15 am	**Break**	
10:15 am - 12:00 pm	**Session 2: Presentations from FDA and invited stakeholders** • *Example coverage map: chemical analysis of medical devices* • *Framework for developing a coverage map for chemical analysis of medical devices* • *Panel discussion*	**Jennifer Goode, B.S.** **Industry and test lab speakers** **FDA panelists and industry and test lab speakers**
12:00 - 12:45 pm	**Lunch**	

Afternoon Agenda

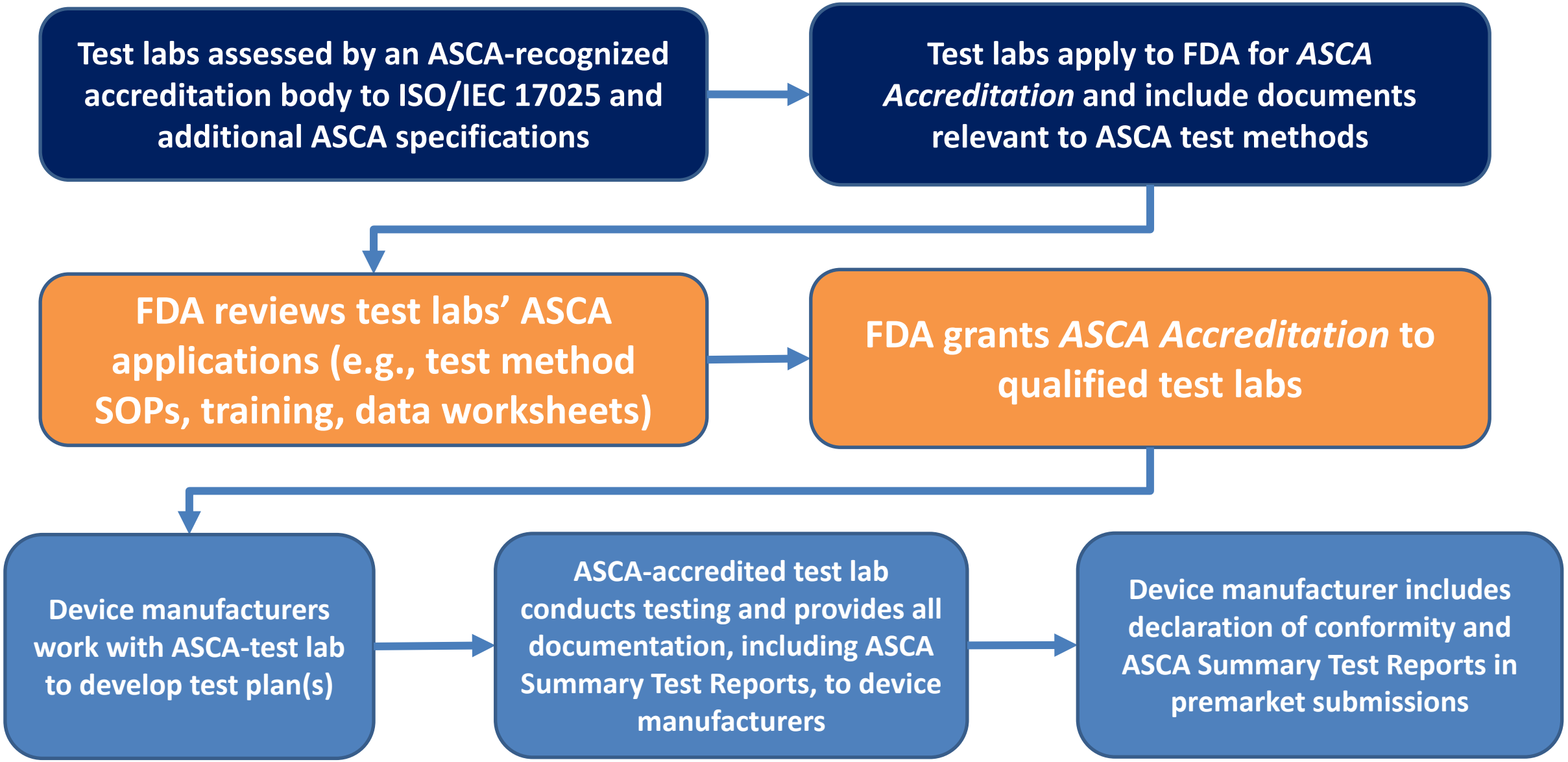
Time	Subject	Speaker(s)
12:45 – 3:00 pm	**Session 3: FDA-led panel discussions** *What should be considered when developing a general approach to chemical analysis of medical devices?* • *Test article preparation* • *Test article extraction* • *Extract processing* • *Reporting threshold*	**FDA-led panel**
3:00 – 3:15 pm	**Break**	
3:15 - 4:30 pm	**Session 4: FDA-led panel discussions** *What should be considered when developing a general approach to chemical analysis of medical devices?* • *Extract analysis* • *Identification and quantification* • *Personnel competency evaluation* • *ASCA Summary Test Report*	**FDA-led panel**
4:30– 4:45 pm	**Wrap up**	**Ed Margerrison, Ph.D.**

THE ACCREDITATION SCHEME FOR CONFORMITY ASSESSMENT (ASCA)

ASCA Goal: Streamline conformity assessment in premarket review

- Reduces time needed for the conformity assessment element of device review
  - Tests approved under ASCA need only an ASCA Summary Test Report during FDA review
- Less need for Additional Information questions, lengthy internal consults and complete test report review
- Allows FDA to communicate common issues to ASCA test labs so they can be addressed systematically before future testing
- Improves the quality of testing and reporting
  - Addresses testing issues for which FDA commonly identifies concerns during review [after testing]

How ASCA Biocompatibility Works



ASCA Standards: Biocompatibility

- Currently ASCA includes the nine most common biocompatibility test methods
- Nine ASCA Summary Test Report templates are available

FDA Recognized Consensus Standard	Test Method(s)
ISO 10993-4	Complement Activation using a U.S. marketed ELISA kit
ISO 10993-4 and ASTM F756	Direct and Indirect Hemolysis
ISO 10993-5	MEM Elution Cytotoxicity
ISO 10993-23*	In Vivo Dermal Irritation, Intracutaneous Reactivity Irritation
ISO 10993-10*	Closed Patch Sensitization
ISO 10993-10* and ASTM F720	Guinea Pig Maximization Sensitization
ISO 10993-11	Acute Systemic Toxicity
ISO 10993-11 and USP 151	Material-Mediated Pyrogenicity
ISO 10993-12	Sample preparation for all test types

**ISO 10993-10:2010 split into ISO 10993-10:2021 and ISO 10993-23:2021.*
**ISO 10993-10:2010, ISO 10993-10:2021, and ISO 10993-23:2021 are all included in ASCA.*

Example ASCA Summary Test Report: Cytotoxicity

ASCA Test Method: Cytotoxicity – MEM Elution (ISO 10993-5)
Administrative Information

1. Testing Laboratory Name: Test Lab ABC
2. ASCA Testing Laboratory Identification Number: TL-999
3. Testing Location(s): 123 Main St, XXX, Virginia
4. Testing Date(s): February 1st, 2022—February 28, 2022
5. *ASCA Accreditation* Status on the Date(s) of Testing:
   - ☒ Standard (and particular test method) was in testing laboratory's scope of *ASCA Accreditation*
   - ☒ *ASCA Accreditation* was not suspended

ASCA Test Article Prep SOP#: ***SOP-SamplePrep-123-Rev2.0, SOP-SampleExtr-456-Rev3.0***

☒ Test Article was prepared per the above protocol (no deviations/amendments); or
☐ Test Article was prepared per the above protocol, with the following deviations/amendments[1] (e.g., filtering, extract manipulation, pH adjustment):

Description of deviations/amendments

Test Article:
☒ Entire final finished device
☐ Representative sample selection per SOP
☐ Other:[2] *[DESCRIBE]*

Extraction Solvent:
☒ MEM with 5-10% animal serum
☐ Other:[3] *[DESCRIBE]*

Extraction Ratio:
☒ 6cm²/ml (<0.5mm thick)
☐ 3cm²/ml (0.5-1.0mm thick or molded items > 1.0mm)
☐ 1.25cm²/ml (elastomers > 1.0mm thick)
☐ Other:[4] *[DESCRIBE]*

Extraction Conditions:
☐ 37°C, 24 h
☒ 37°C, 72 h
☐ 50°C, 72 h
☐ 70°C, 24 h
☐ 121°C, 1 h
☐ Other:[5] *[DESCRIBE]*

☒ The test article and extract DID NOT change color, and the extract DID NOT appear turbid or have particles.
☐ There were changes in color/turbidity or particles in the test article and/or extract OR there was swelling/degradation of the test article.[5]

ASCA Test Method SOP #: *SOP-ASCA-MEM-789-Rev2.0*
☒ Test was conducted per the above protocol (no deviations/amendments) and 21 CFR 58; or
☐ Test was conducted per the above protocol and 21 CFR 58, with the following deviations/amendments:[6]

Description of deviations/amendments

Results:[7]

	48 hr Results	72 hr Results	Conclusion
Vehicle Control	Grade 0/0/0	Grade 0/0/0	Performed as expected
Negative Control HDPE	Grade 0/0/0	Grade 0/0/0	Performed as expected
Positive Control Latex	Grade 4/4/4	Grade 4/4/4	Performed as expected
Test Article Extract (100% neat)	Grade 0/0/0	Grade 0/0/0	Non-cytotoxic

I confirm that:
☒ The above summary information includes all original and any retest data; and
☒ I have checked that there are no differences between the complete test report and this ASCA summary test report.

John Standards — 3/15/2022
Name: [TYPED NAME POSITION] — Date

ASCA Revised Draft Guidances

- Draft updates to 3 ASCA guidances released on September 20, 2024
  - Accreditation Scheme for Conformity Assessment (ASCA) Program
  - Biocompatibility Testing of Medical Devices
  - Basic Safety and Essential Performance of Medical Electrical Equipment, Medical Electrical Systems, and Laboratory Medical Equipment
- Commenting period ends December 23, 2024
  - Link: https://www.regulations.gov/docket/FDA-2019-D-3805/document

Proposed New ASCA Biocompatibility Standards

- Mouse Lymphoma Assay (MLA) (ISO 10993-3 and OECD 490)
- Bacterial Reverse Mutation Assay (i.e., Ames Assay) (ISO 10993-3 and OECD 471)
- MTT Cytotoxicity (ISO 10993-5)
- Neutral Red Uptake (NRU) Cytotoxicity (ISO 10993-5)
- XTT Cytotoxicity (ISO 10993-5)

Possible ASCA Expansion: Chemical Analysis

- To add chemical analysis to the ASCA program:
  - Build upon the framework of ISO/IEC 17025 and develop ASCA scheme requirements for conformity assessment of chemical analysis and ISO 10993-18
  - What should be considered when developing a general approach (not on a case-by-case basis) for chemical analysis
    - Procedures (e.g., SOP, worksheets)
    - Personnel training and competency evaluation
    - ASCA Summary Test Report

OPENING REMARKS

Ed Margerrison, Ph.D.

Director, Office of Science and Engineering Laboratories

Some Thoughts on Today's Meeting

- Today is the first FDA public meeting on this topic for a long time
  - Incorporation of totality of evidence remains key
  - Many material changes and substitutions are happening in real time
  - Strategically, the community needs a way to scale our approaches to ensure simplicity and abide by LB needs

  - Many initiatives are underway, ASCA remains a key part of our overall vision
    - How do we define quality of chemistry?
    - How can we know that a material change is acceptable?

Challenges in Chemical Analysis Review

- ISO 10993-18 standard does not have specific methods and acceptance criteria
- Test reports do not include all of the key information needed for premarket submission review which leads to Additional Information requests
- Inconsistency in procedures from lab to lab on sample extraction, extract processing, instrument analysis
- Identification and quantification of extractables from medical devices need higher level of expertise

Result: challenges for FDA review of test methods and results

How ASCA Can Help

- Under the ASCA program, FDA uses ISO/IEC 17025 as a framework to develop ASCA program specifications that can be specific for chemical analysis with input across various stakeholders
- ASCA program specifications can define:
  - Personnel competency evaluation, e.g., training, proficiency test
  - Different testing methods and steps that test lab's procedures (e.g., SOP) need to address
  - Equipment calibration, qualification, and maintenance
  - Data recording and reporting
  - Example ASCA Summary Test Report
- Through an assessment by ASCA-recognized accreditation bodies as well as FDA review of test lab procedures and methods, only a qualified test lab can receive *ASCA Accreditation* and be listed as an ASCA-accredited test lab.

How ASCA Could Improve Chemical Analysis Review

- ASCA standardizes reporting
  - Provides ASCA Summary Test Report template
  - Ensures that key information is included in the reports
- Front-end investment leads to downstream time savings
  - FDA reviews labs' test methods once during their *ASCA Accreditation* evaluation, not as part of each individual device submission review
- Streamlines the review of chemical analysis, leading to fewer questions/deficiencies
- ASCA-accredited test labs are publicly listed

Interlaboratory Study for Extraction Testing of Medical Devices

David M. Saylor, Ph.D.

ASCA Workshop

November 6, 2024

Overview

- Motivation
- Materials and methods
  - 9 intentional additives in 2 matrices
- Reporting: chemical identification and quantitation
- Statistical analyses and implications
- Non-targeted (non-intentionally added) analytes

Motivation

Chemical analysis of medical devices can exhibit significant variability:

- Many parameters can affect the results of chemical analysis of medical devices: extraction, extract processing, analytical instrumentation, reporting threshold, identification and quantification methods, data processing, etc.
- Each lab has their own methodology and analytical instrument capability to detect and quantify chemicals.
- There are no acceptance criteria to judge whether test labs methods are sufficient to detect and quantify chemicals from medical devices for toxicological risk assessment.

How can we more effectively reduce variability to improve reproducibility between laboratories?

Previous ILS studies

Product Quality Research Institute (PQRI) initiative [1]:

- Reported concentrations for most extractables found spanned an order of magnitude.

ISO 10993-12 study on impact of extraction parameters [2]:

- Significant disparity between the reported results (both observed extractables and reported quantity)

-> Neither study was designed to quantify variance of the results

[1] D. Jenke, et al., PDA Journal of Pharmaceutical Science and Technology 67 (5) (2013) 448–511.
[2] T. Heise, et al., Regulatory Toxicology and Pharmacology 131 (2022) 105164.

Inter-laboratory study objective

- Determine the repeatability (variation within laboratories) and reproducibility (variation among laboratories) in quantitation.

- Initial focus: high concentration analytes, e.g. intentional additives.

Approach – alternate version

- 2 materials: HDPE and PP; doped with (the same) 9 additives
- 2 solvents: IPA and Hexane
- Fixed: time, temperature, extraction ratio, extract reduction, extract processing, analytical instrumentation, reporting threshold
- Variable: agitation parameters, vessel type, vessel size, method conditions, system suit./QC, data processing, identification method, quantification method

Material	Controlled
Extraction Solvent	Controlled
Extraction Temp	Controlled
Extraction Time	Controlled
Extraction Ratio	Controlled
Extraction Agitation Parameters	Uncontrolled
Extract Vessel Type	Uncontrolled
Extract Vessel Size	Uncontrolled
Extraction Vessel Cleaning/Conditioning	Uncontrolled
Extract Reduction	Controlled
Extract Processing	Controlled
Analytical Instrumentation	Controlled
Method Conditions	Uncontrolled
System Suitability/QC Conditions	Uncontrolled
Data Processing (peak picking, integration, etc.)	Uncontrolled
Identification Method	Uncontrolled
Quantification Method	Uncontrolled
Reporting Threshold	Controlled

Participating labs

- 7 laboratories agreed to participate
- One lab excluded due to significant deviations from the protocol.
- To supplement, included results from 2 additional labs with complete knowledge of additives (targeted analysis on a subset of additives)
- 8 labs in total included in the analysis

Additive tiers

- Tier 1: disclosed / targeted
  - BHT
  - Irganox 1076
  - Irganox 1010
  - Erucamide
- Tier 2: within list / suspect screening
  - Octobenzone
  - Tinuvin 326
  - BBOT
- Tier 3: undisclosed / NTA
  - Irganox 3114
  - EBS

All compounds nominally loaded at 0.1%, with one exception:

- Irganox 1010 at 0.2%

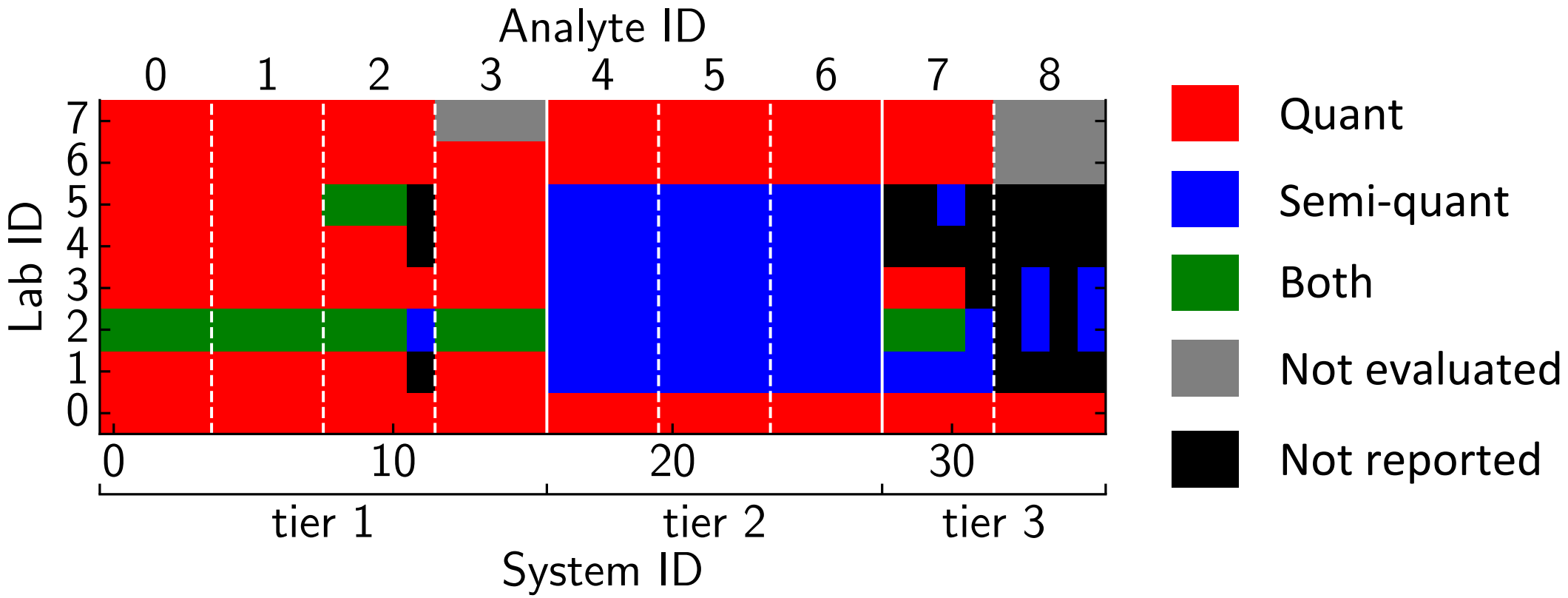
Data Analysis

- Based on ASTM E691-21 "Standard Practice for Conducting an Interlaboratory Study to Determine the Precision of a Test Method"
- Two primary metrics:
  - Repeatability: precision of the results with the same method on identical test items in a single laboratory; quantified by σ_r (square root of the variance within laboratories)
  - Reproducibility: precision of the results with the same method on identical test items in different laboratories; quantified by σ_R (square root of the variance among laboratories)
- Note: $\sigma_R \geq \sigma_r$

Inclusion criteria

- Data from different methods (LC-MS, GC-MS) were aggregated to increase N for each material system (analyte, matrix, solvent)
- Quant and Semi-quant assessments considered separately
- For each condition (combination of polymer, analyte, solvent and quantitation method), a lab was included if data from at least two replicates were reported
- If the number of included labs (N) >=5 for a specific condition, the condition was included in the statistical assessment

Reporting summary

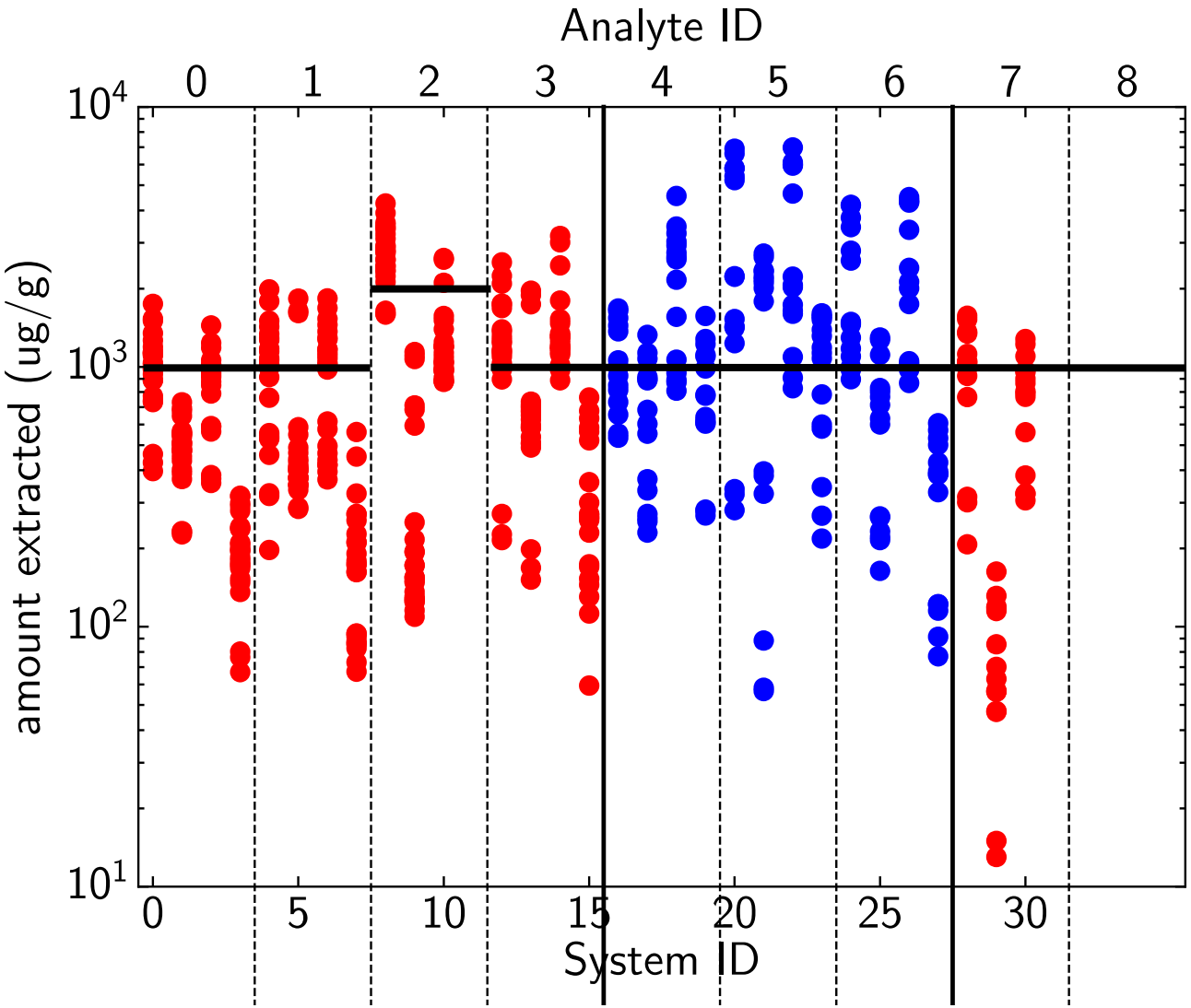


Included systems (n ≥ 5):

quantitative = 18

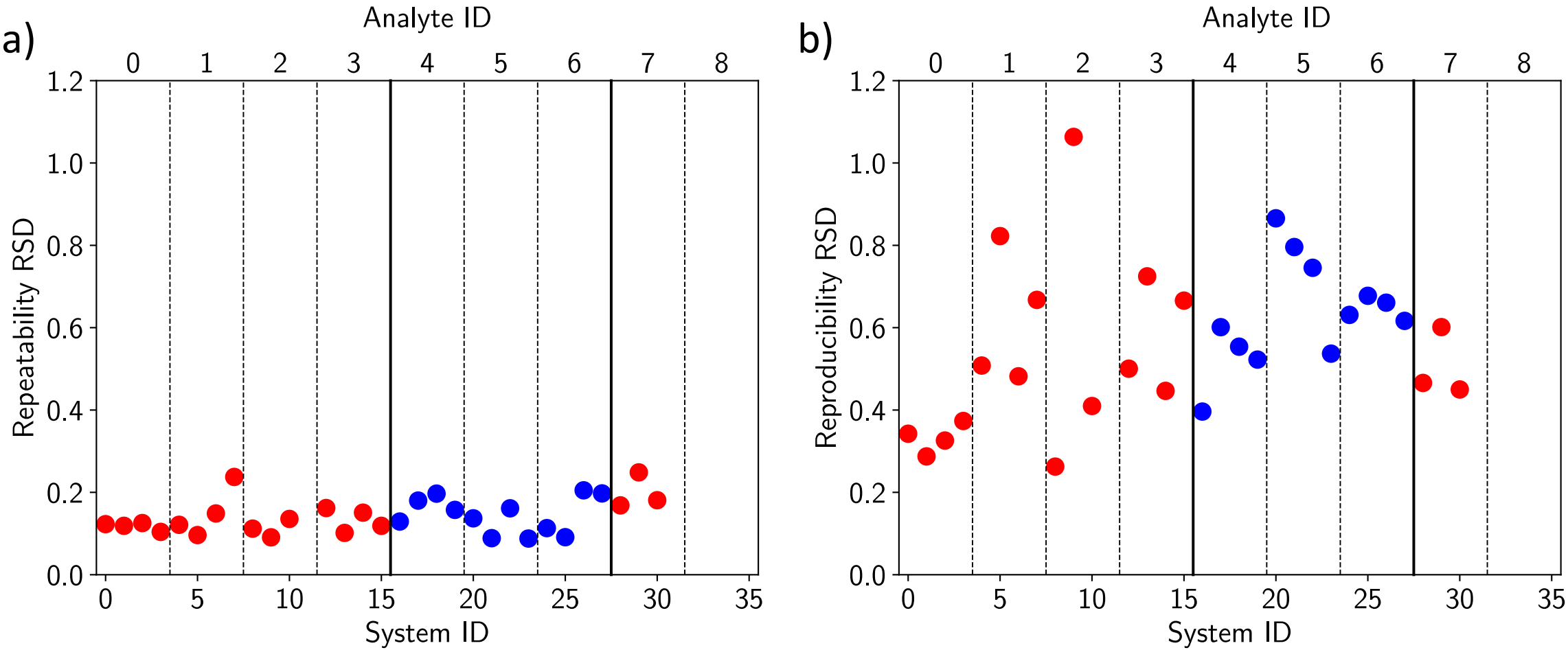
semi-quantitative = 12

Raw data



- ≈ 0.5-1 orders of magnitude total variation within each system
- Appears independent of tier, analyte or quantitation method

Overall results



Implications

- Following ASTM E691-21, we can specify repeatability (r) and reproducibility (R) limits
- Limits defined as “the value below which the absolute difference between two individual test results obtained under the respective conditions may be expected to occur with a probability of approximately 0.95”

	Mean	Range	Central 90 % Range
r	0.40	(0.25, 0.69)	(0.25, 0.62)
R	1.6	(0.74, 3.0)	(0.85, 2.4)

- Implies, e.g., results of the same testing from two laboratories could exhibit differences up to 240% with 95 % confidence for 95 % of all systems.

R variability - factor comparison

- Differences between quantitative (RSD_{mean} = 0.52) and semi-quantitative (RSD_{mean} = 0.63) were **not significant** (p=0.11)
- Differences between HDPE (RSD_{mean} = 0.53) and PP (RSD_{mean} = 0.60) were **not significant** (p=0.35)
- Differences between Hexane (RSD_{mean} = 0.50) and IPA (RSD_{mean} = 0.64) were **significant** (p=0.04) – more so for quantitative methods

Supplemental analyses

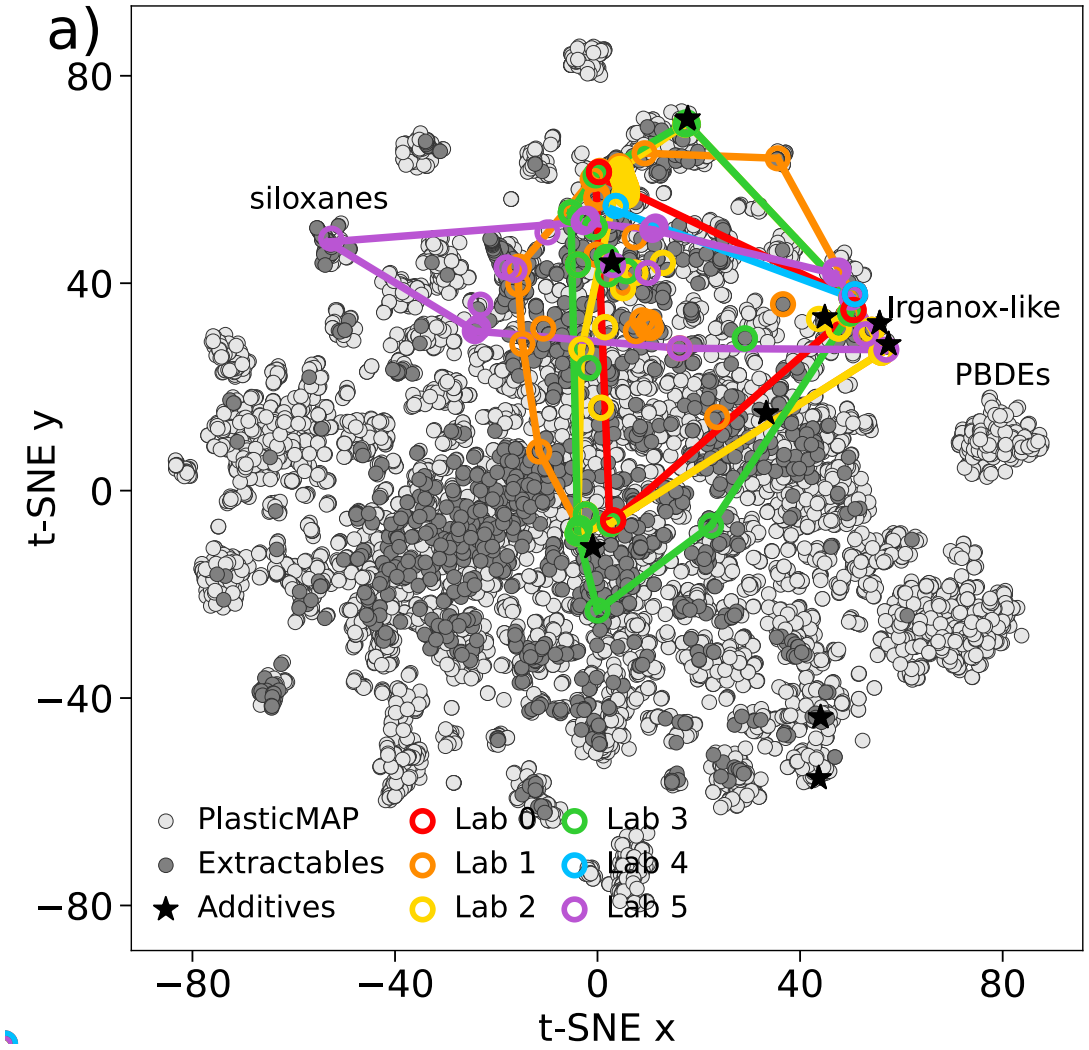
- Sources of variability were examined using the targeted compounds and calibration data submitted :
  - Extent of extraction at 50°C for 72 hours (1% to exhaustive)
  - Calibration range (and if reported concentrations were in range)
  - Dilution factors used
  - Analytical method used
  - Regression method used
  - Variation from analytical method vs. extraction

Supplemental findings

- No clear trend based on calibration practices or concentration range
- Better agreement for analytes within calibration range relative to those outside of calibration range
- Intra-lab injection variability ~2%
- Intra-lab extraction variability ~10%
- Substantial variability observed between 2 different analytical methods reported by the same lab for the same extracts (difference as high as 75%)

Non-targeted analysis (NTA) chemicals

- Chemical space defined using ~200 descriptors
- t-SNE method for 2D visualization
- NTA chemicals located within larger chemical spaces
- Space of NTA chemicals for each lab defined by convex hull in 2D
- 5/6 labs exhibited significant overlap



Summary

- Laboratories consistently reported analytes that were explicitly disclosed (targeted) or disclosed within a list (suspect screening), but not those that were undisclosed.
- Raw data suggest 0.5-1 orders of magnitude difference in quantitation for a typical system.
- This translated to a reproducibility (inter-laboratory) RSD of between 40-80%, which was ~4x the repeatability (intra-laboratory) RSD.
- Supplemental assessment suggests that variability in quantitation associated with analytical method may be a substantial contribution to the overall variability.
- Chemical space analysis suggests the majority of labs (5/6) reported a chemically similar range of NTA.

Proficiency Testing Proposal

Shuliang Li, Ph.D.

November 6, 2024

How ASCA Can Help

- Under the ASCA program, FDA uses ISO/IEC 17025 as a framework to develop ASCA program specifications that can be specific for chemical analysis with input across various stakeholders.
- ASCA program specifications can define, for example:
  - Personnel competency evaluation, e.g., training, proficiency test
  - Testing methods and steps that test lab's procedures (e.g., SOP) need to address
  - Equipment calibration, qualification, and maintenance
  - Data recording and reporting
- Only a qualified test lab can receive *ASCA Accreditation* and be listed as an ASCA-accredited test lab on FDA's website. Qualification is obtained through an assessment by ASCA-recognized accreditation bodies, as well as FDA review of test lab documentation (e.g., procedures, trainings, reports).
- Under ASCA, FDA can develop examples of ASCA Summary Test Reports so that key information needed for premarket review can be presented in a streamlined format.
- To be confident in the results provided in chemical analysis reports, some of the variabilities and uncertainties seen with analytical chemistry testing need to be reduced. To understand interlaboratory variability, proficiency testing can be considered under ISO/IEC 17025 framework.

Proficiency Testing Proposal

- Use of chemical mixtures instead of materials fortified with additives, to remove variability related to the extraction process.
    - —Example: synthetic chemical mixture in an organic solvent (e.g., isopropanol).
- No extract processing except for dilution (if needed for assessment in the analyte-specific linear range).
- Evaluate:
    - —interlaboratory variability in instrument methods and coverage.
    - —analyst competency

Proficiency Test Proposal

- Chemicals
  - —Labs/Analysts blinded: chemical identities unknown, concentration unknown
- Method:
  - —System suitability test conducted with established acceptance criteria
  - —Procedurally defined and qualified analytical methods (e.g., GC-MS, LC-MS)
- Goal:
  - —Identify all chemicals in the mixture (at quantities that would be reasonable to detect in a medical device-relevant non-targeted analysis)
- Potential small scale round robin study to test the feasibility of a standardized approach to proficiency testing

Discussion Questions

- ***Based on the round robin data presented and your experience, what are the key sources of variability?***
- ***What sources of variability can a test lab effectively control? What sources of variability are more difficult for a test lab to control?***

Discussion Questions

- ***Do you conduct proficiency testing to qualify your analysts?***
- ***How often do you conduct proficiency testing?***
- ***How do you design and perform proficiency testing? What are the key aspects to consider when designing proficiency testing? For example, how do you select chemicals and concentrations for proficiency testing?***
- ***If proficiency testing is not used, how do you assess your analysts' competency?***

Discussion Questions

To be confident in the results provided in chemical analysis reports, some of the variabilities and uncertainties need to be reduced. To understand interlaboratory variability, proficiency testing can be considered under ISO/IEC 17025 framework.

- ***Are there any lessons learned from the presented round robin data that could be helpful in designing proficiency testing, if included under ASCA?***
- ***What are your thoughts on self-administered proficiency testing vs. use of an FDA provided proficiency test sample (e.g., chemical mixture)?***
- ***What concentration (or range) could be used for the chemicals, individually or as part of a chemical mixture?***

Example Coverage Map: Chemical Analysis of Medical Devices

Jennifer Goode, B.S.
Biocompatibility Program Advisor
FDA/CDRH Office of Product Evaluation and Quality

ASCA Workshop
November 6, 2024

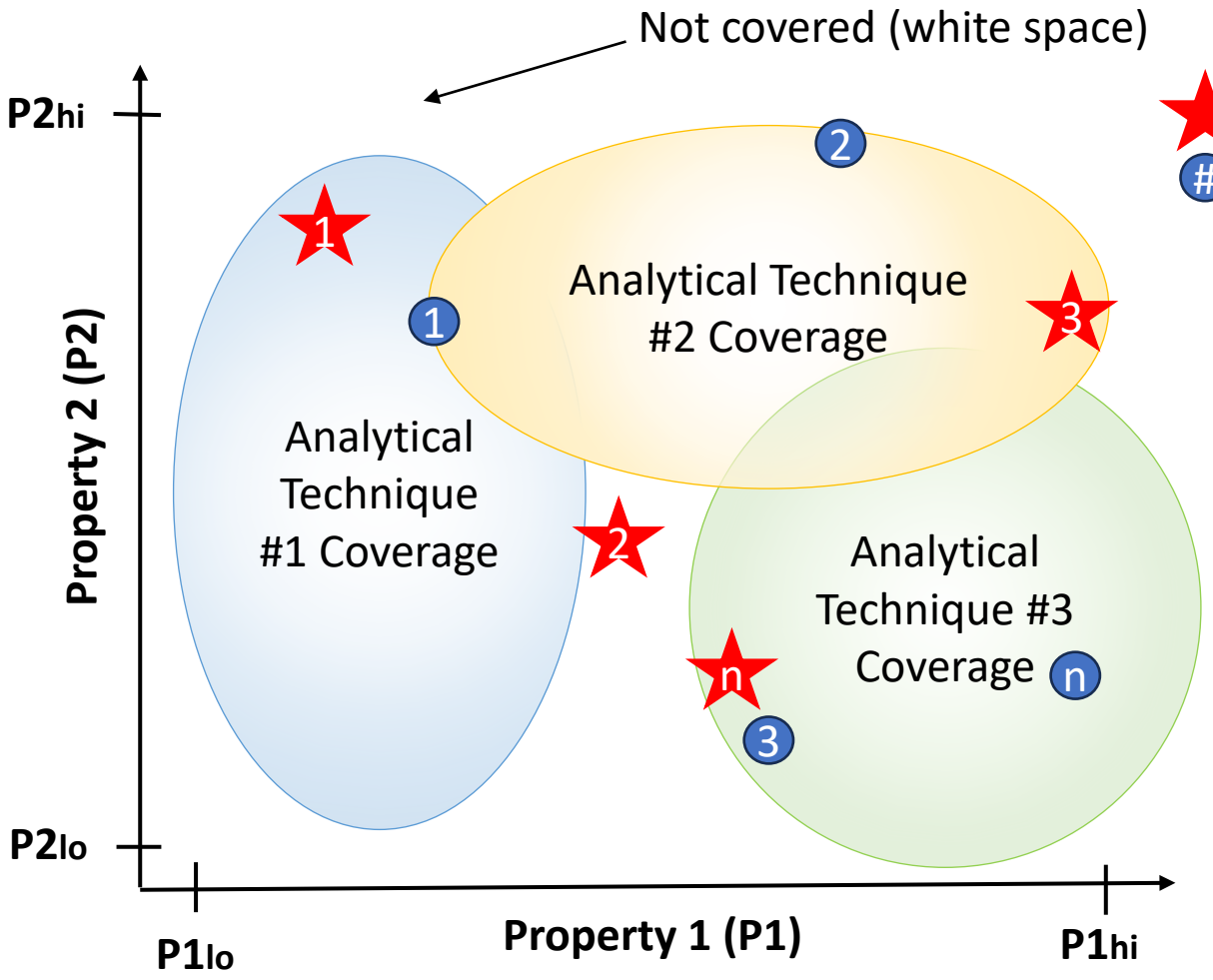
Proposal: Conceptual ASCA Coverage Map

A coverage map could be used as a tool to:

- Demonstrate the ability of a laboratory* to detect a suitably large set of chemicals with a breadth of:
  - physicochemical properties, and
  - response factors.

*using their own protocols and equipment

Proposal: Conceptual ASCA Coverage Map (cont.)



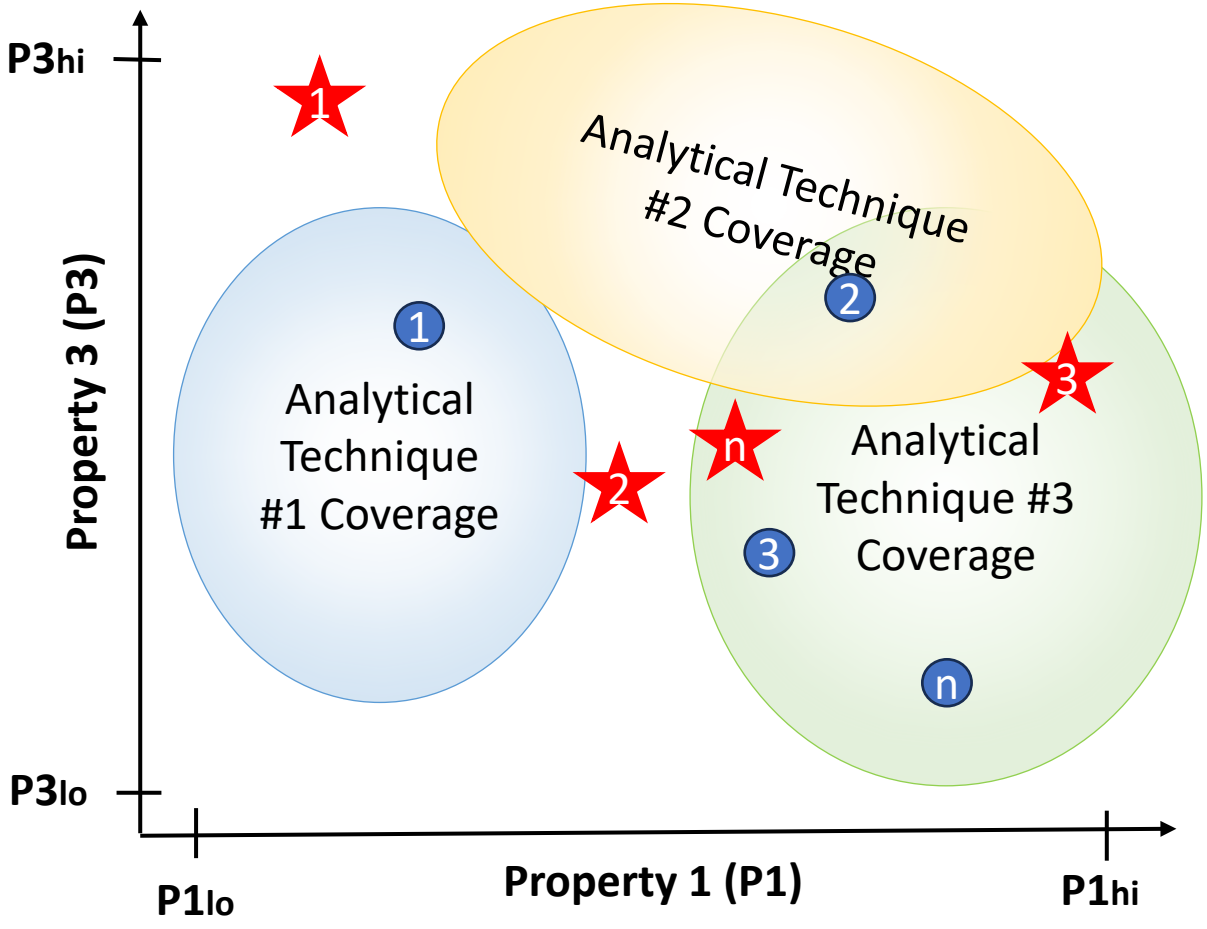
Cohort of concern chemical (medical device relevant)

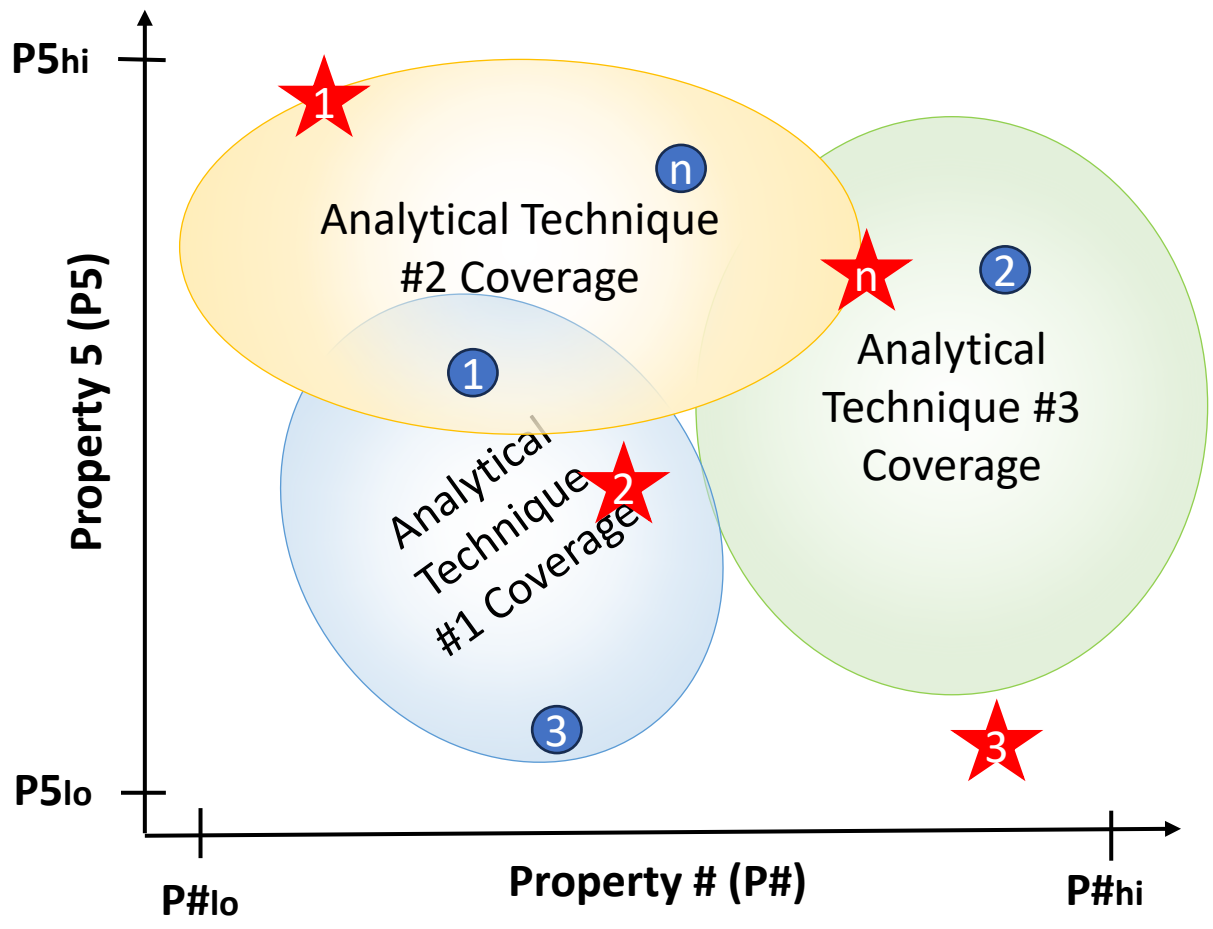
Proficiency test chemical?

Properties?	Ranges?
Property 1	$P1_{lo}$ – $P1_{hi}$
Property 2	$P2_{lo}$ – $P2_{hi}$
Property 3	$P3_{lo}$ – $P3_{hi}$
…	…
Property #	$P\#_{lo}$ – $P\#_{hi}$

Plot each property against the others?

Proposal: Conceptual ASCA Coverage Map (cont.)





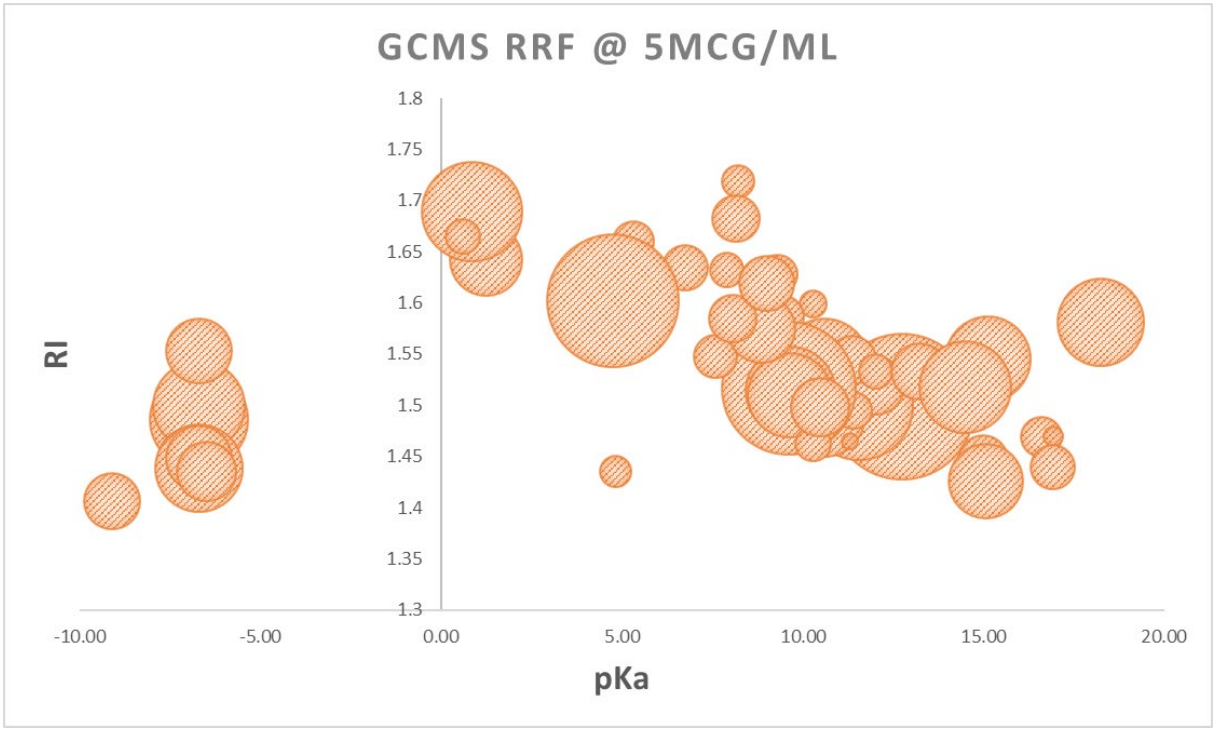
Proposal: Properties and Ranges for Consideration

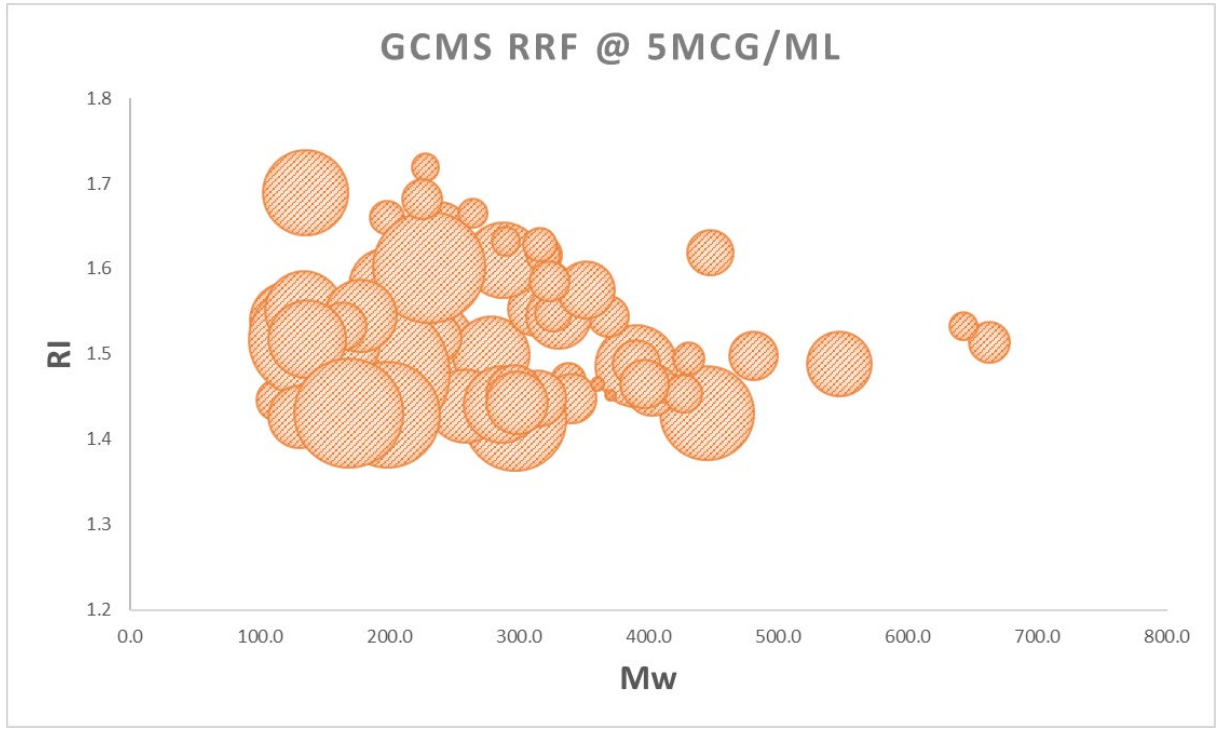
#	Possible Properties*	Possible Ranges*
P1	Double bond equivalent (DBE)	-2 to 25
P2	Molecular Weight (MW)	102 to 1178 (g mol-1)
P3	Boiling point (BP) at 760 mmHg	148 to 922 (°C)
P4	Acidity (pKa)	-9.1 to 18.25
P5	Partition Coefficient (LogP)	-0.7 to 23
P6	Refractive Index (RI)	1.289 to 1.757
Others?	…	…

*NOTES:

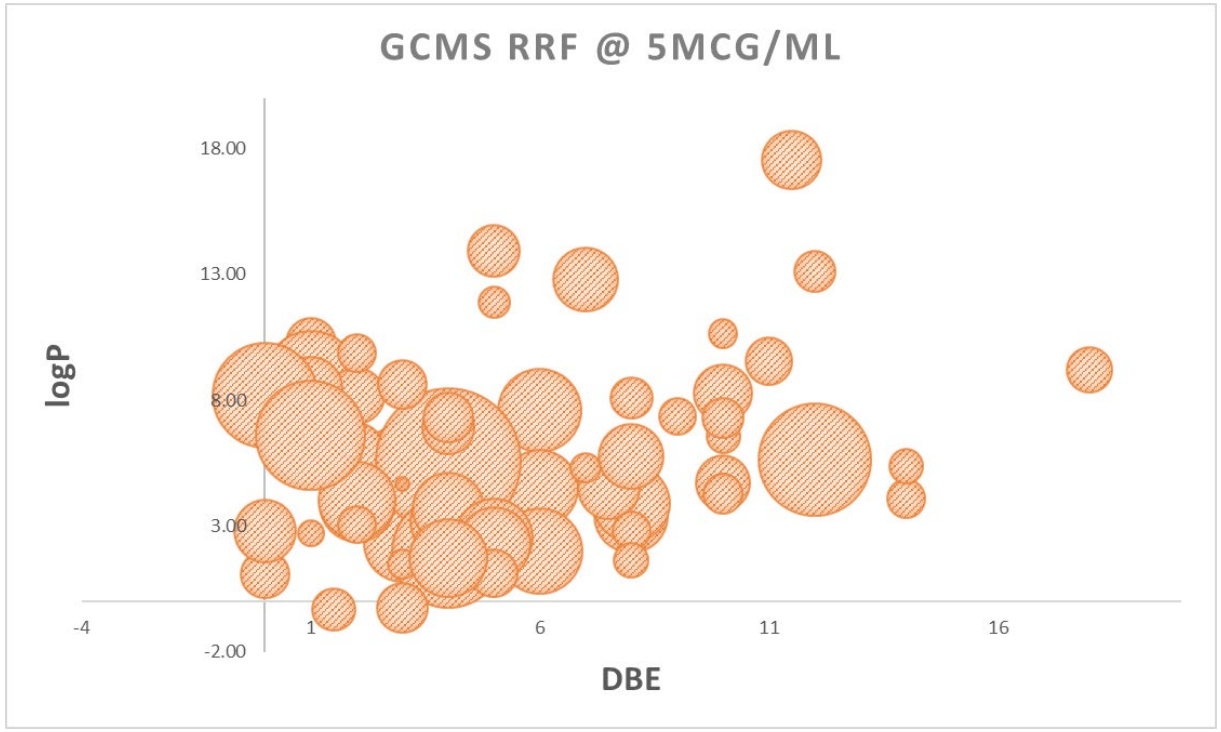
- If the properties and ranges are appropriate, the actual chemicals used to develop a lab-specific database should not matter, as long as sufficient coverage (TBD) can be demonstrated.
- The proposed ranges from the CDRH-published Chemical List for Analytical Performance (CLAP) may change as more medical device chemicals are investigated and added to the published list. https://cdrh-rst.fda.gov/chemicals-list-analytical-performance-clap

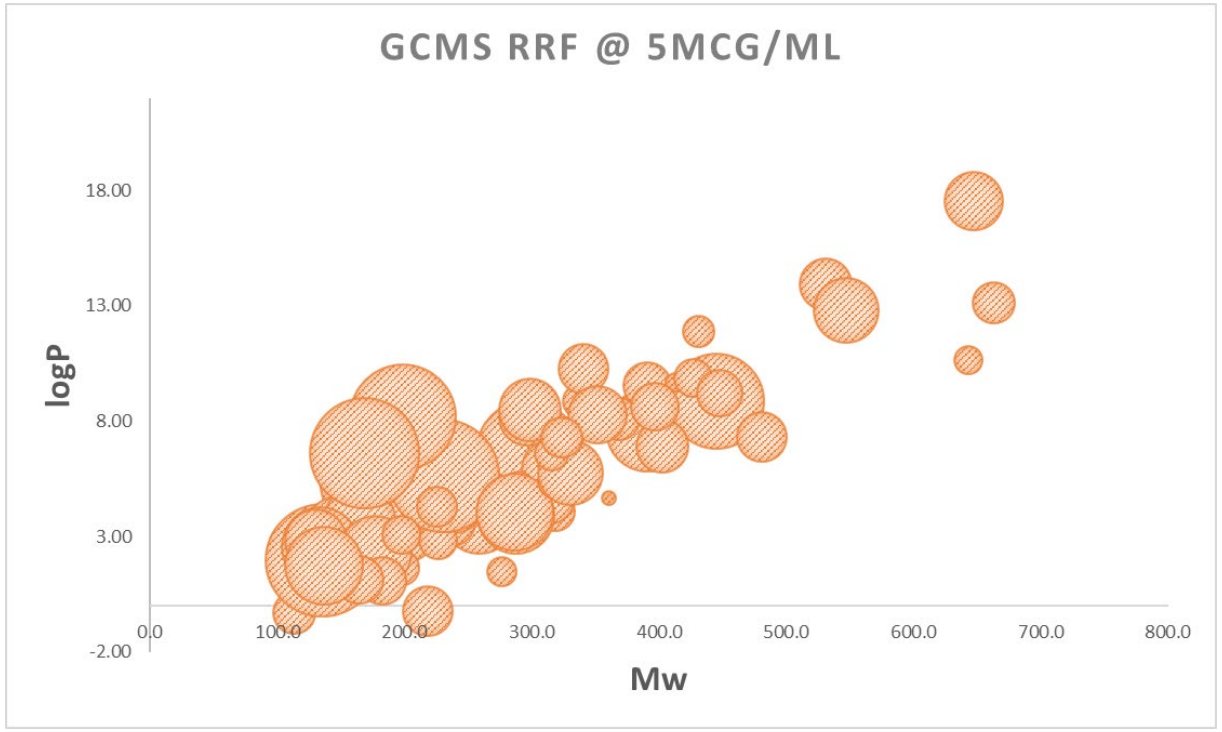
Example Plots Using Selected CLAP List Properties





Example Plots Using Selected CLAP List Properties (cont.)





Discussion: ASCA Coverage Maps for Non-Targeted Analysis

1. *How might coverage data optimally be presented (graphically and/or tabularly)?*
2. *Is use of a coverage map approach feasible?*
3. *How could coverage of complementary techniques (e.g., outside GC and LC detectability) be included?*
4. *What are the appropriate physicochemical properties and ranges?*
5. *How can coverage with respect to cohort of concern chemicals be addressed?*
6. *What could acceptable coverage look like?*

Accreditation Scheme for Conformity Assessment (ASCA) and the Use of Chemical Analysis to Support Biocompatibility of Medical Devices

November 6, 2024

U.S. FOOD & DRUG ADMINISTRATION

Center for Devices and Radiological Health
Division of Standards and Conformity Assessment

ASCA Expansion for Chemical Analysis of Medical Devices

Important considerations for ASCA program inclusion:

- Ability to develop a consistent **general approach**
  - —Define procedures and methods (e.g., SOPs) for FDA review as part of a testing laboratory's *ASCA Accreditation* application instead of reviewing the summary of procedures and methods in each pre-market submission review.
  - —ASCA Summary Test Report describes key test parameters and results that are specific to each test and references only defined procedures and methods (e.g., SOP numbers and revision numbers).
- Personnel **competency evaluation**:
  - —ISO/IEC 17025 requirements + ASCA specifications that are specific for chemical analysis of medical devices
  - —Training
  - —Proficiency Testing

Developing General Approach for Chemical Analysis of Medical Devices

- Study components of chemical analysis of medical devices:
  - — Test article preparation
  - — Test article extraction
  - — Extract processing
  - — Reporting threshold
  - — Extract analysis
  - — Data evaluation (identification and quantification)
- Outside of scope of workshop discussion: information gathering
  - —This should be conducted before chemical analysis of medical devices to collect information about device components, materials, material construction, manufacturing process, etc.
- Devices currently excluded from ASCA for biological testing: absorbable devices, in situ polymerizing devices, liquid devices, creams, gels, hydrogel devices, devices containing nanomaterials, and devices require customized sample preparation/testing methodologies.

Discussion Topics

Time	Topic	Speaker
12:55-1:20 pm	Test Article Preparation	Jennifer Goode
1:20-1:50 pm	Test Article Extraction	Jinrong (Jinny) Liu
1:50-2:25 pm	Extract Processing	Nicholas Keyes
2:25-3:00 pm	Reporting Threshold	Byeong Hwa Yun
3:00-3:15 pm	Break	
3:15-3:50 pm	Extract Analysis	Nicholas Keyes
3:50-4:15 pm	Data Evaluation (Identification and Quantification)	Joshua Young
4:15-4:30 pm	Personnel Competency Evaluation	Shuliang Li
	ASCA Summary Test Report	

Abbreviations and Acronyms

- **ACN**: Acetonitrile
- **AES**: Atomic Emission Spectroscopy
- **AET**: Analytical Evaluation Threshold
- **APCI**: Atmospheric Pressure Chemical Ionization
- **BPA**: Bisphenol A
- **CAD**: Charged Aerosol Detector
- **DBT**: Dose-Based Threshold
- **DCM**: Dichloromethane
- **DEHP**: Di-(2-ethylhexyl)phthalate
- **ELSD**: Evaporative Light Scattering Detector
- **ESI**: Electrospray Ionization
- **EtOAc**: Ethyl Acetate
- **EtOH**: Ethanol
- **FID**: Flame Ionization Detector
- **FTIR**: Fourier Transform Infrared Spectroscopy
- **GC-MS**: Gas Chromatography Mass Spectrometry
- **HS-GC-MS**: Headspace GC-MS
- **ICP-MS**: Inductively Coupled Plasma Mass Spectrometry
- **IPA**: Isopropanol
- **LC-MS**: Liquid Chromatography Mass Spectrometry
- **LOD**: Limit of Detection
- **LOQ**: Limit of Quantification
- **NVOCs**: Non-Volatile Organic Compounds
- **NVR**: Non-Volatile Residue
- **OES**: Optical Emission Spectroscopy
- **PBS**: Phosphate Buffered Saline
- **RF**: Response Factor
- **RRF**: Relative Response Factor
- **RSD**: Relative Standard Deviation
- **RT**: Retention Time
- **S/N**: Signal-to-Noise
- **SVOCs**: Semi-Volatile Organic Compounds
- **TTC**: Threshold of Toxicological Concern
- **UF**: Uncertainty Factor
- **UV**: Ultraviolet
- **VOCs**: Volatile Organic Compounds

Terminology

- **Reference standard:** A substance containing a compound of known molecular structure with high purity (e.g., analytical standard grade, >99.5% purity) suitable for the intended analytical purpose (e.g., targeted analysis, surrogate standard).
- **Internal standard:** A reference standard added to (i.e., spiked into) a solution at a known concentration used to normalize the response of other compounds or reference standards present based on its RF.
- **External standard:** A reference standard present in a solution at a known concentration which is analyzed separately under identical conditions. It is used to facilitate the qualitative identification and/or quantification.
- **Surrogate standard**: A reference standard used to facilitate quantification that minimizes RF variation between the standard itself, and the compound being quantified. It serves as a replacement (or surrogate) for a reference standard which matches the analyte(s) of interest, which is not always available in a screening analysis. It may be used to demonstrate the range of concentrations and chemical properties captured by the steps of an analytical workflow, including sample preparation (e.g., to assess recovery), chromatographic separation, data acquisition, data processing (e.g., for semi-quantification), and analyte identification (e.g., to confirm the identity).

References:

- *USP <11> Reference Standards*
- *E. M. Sussman, B. Oktem, I. S. Isayeva, J. Liu, S. Wickramasekara, V. Chandrasekar, K. Nahan, H. Y. Shin, J. Zheng, Chemical Characterization and Non-targeted Analysis of Medical Device Extracts: A Review of Current Approaches, Gaps, and Emerging Practices. ACS Biomaterials Science & Engineering 8, 939-963 (2022).*
- *PAC, 1993, 65, 819. (Nomenclature for chromatography (IUPAC Recommendations 1993)) on page 837*

Test Article Preparation

Test Article Preparation

- Proposal: ASCA procedures and training to address:
  - —Use of the final finished device.
  - —Cutting of devices:
    - Minimizing cutting only to the extent necessary.
    - Specifying when to cut and not to cut.
  - —Devices containing multiple components:
    - Specifying when they shall be combined or extracted separately.
      - For example, different types/durations of tissue contact.
  - —Extraction ratio and number of devices to be used per extraction.

Test Article Preparation

Discussion:

- *How do you determine number of devices to be used and the extraction ratio? For example: Use 10993-12 test article surface area to extract volume ratios as a starting point and the goal is to:*
  - *—Meet the AET (i.e., AET ≥ LOQ)*
  - *—Have sufficient volume for extract analysis*
  - *—Anything else?*

Test Article Preparation

Discussion:

- *Do you combine device components with different types/durations of contact for extraction?*
- *What should be considered when combining device components with different types/durations of contact for extraction?*
  - *Exclusion of non-tissue contacting materials/components*
- *Should ASCA chemistry scope exclude any of the following device types?*
  - *—absorbable devices**
  - *—in situ polymerizing devices**
  - *—liquid devices, creams, gels, hydrogel devices**
  - *—devices containing nanomaterials**
  - *—devices containing tissue/biologics*

**excluded from ASCA biological testing*

Test Article Extraction

Test Article Extraction

- Proposal: ASCA procedures and training to address:
  - —Selection of extraction conditions (time, temperature) based on device duration of tissue contact. For example:

Extraction Conditions			
Tissue Contact	Limited (<24 h)	Prolonged (1-30 days)	Long-Term/ Permanent (>30 days)
Duration/Type	Exaggerated extraction or worst-case clinically relevant conditions	Exhaustive extraction or worst-case clinically relevant conditions	Exhaustive extraction
Temperature	50°C or greater than the clinical use temperature	50°C or greater than the clinical use temperature	50°C or greater than the clinical use temperature
Solvents	Polar and non-polar	Polar and non-polar	Polar, semi-polar, and non-polar

Test Article Extraction

- Proposal: ASCA procedures and training to address:
  - —Selection of extraction conditions (solvents), for example:

	Example Solvents	Procedure to address use of alternative solvents
Polar	Water	**Example**: PBS (nitinol-containing devices) for ICP-MS
Semi-polar	Alcohols	**Example**: Aprotic semi-polar solvents (e.g., ethyl/butyl acetate, acetonitrile)
Non-polar	(n-)Hexane	**Example**: Heptane, iso-octane, and cyclic solvents (e.g., cyclohexane)
Solvent Mixture	Procedures to specify defined solvent composition and identify device types/intended uses/material types where solvent mixture may be used*	**Example**: Gas pathway devices that are indicated for use with nebulized medicines may use water/alcohol as extraction solvent, dependent on the drugs solubility, polarity, etc.

**justification for inclusion/exclusion criteria*

Test Article Extraction

- Proposal: ASCA procedures and training to address:
  - —Selection of extraction vessel:
    - Sealed clean inert container (e.g., sealed glass container).
    - Size appropriate for the device being extracted.
  - —Agitation and temperature control.
  - —Complete submersion of device in solvent.
  - —Number of extraction replicates and how replicate analyses will be conducted (e.g., identification and quantification)

Test Article Extraction

- Proposal: ASCA procedures and training to address:
  - —Solvent compatibility with device samples.
    - Can be assessed during exhaustive extraction endpoint determination.
  - —Evaluation and documentation of changes in test articles and extracts (degradation, particulates, color, swelling).
    - Degradation:
      - Procedures to specify what changes are considered degradation. For example, observed damage or destruction of materials of a device after extraction that are not intended to degrade/resorb.
        - Changes are not transient.
        - Changes can be physical or structural and can be visually observed or physically felt.
      - Swelling in silicone or rubber materials by itself is transient (not considered degradation).

Test Article Extraction

- Proposal: ASCA procedures and training to address:
  - —Exhaustive extraction:
    - Specify duration of extraction cycles. Examples:
      - Repeated extract cycles for 72 hours.
      - 24 hour extraction cycles and specify when 24 hour extraction cycles are used (e.g., extract saturation or extractables are reactive/unstable).
    - Determine the exhaustive extraction endpoint.
      - Demonstrate for each solvent used.
      - Gravimetric non-volatile residue (NVR) analysis.
    - Specify whether the same extraction conditions (number of devices, temperature, volume, duration, and number of cycles) are used for generation of extracts for both exhaustive determination and analytical testing.

Test Article Extraction

- Proposal: ASCA procedures and training to address:
  - —Exhaustive extraction (cont):
    - Balance capabilities, for example:
      - Readability: d=10 µg (i.e., d=0.01 mg)
      - Minimum weight of NVR: ≤ 0.5 mg (balance can accurately measure 0.5 mg)
    - Technique for preparation and weighing of NVR, for example:
      - Use entire extract volume in an appropriate drying vessel.
        - Procedures for when extraction volume exceeds the capacity of the drying vessel: e.g., multiple additions of extraction volume into the drying vessel.
      - Evaporate the extract and dry to constant weight.
      - Cool the drying vessel in a desiccator.
      - How do you transfer vessels between the desiccator and balance (e.g., use inert means (tweezers) to transfer vessels between the desiccator and balance).

Test Article Extraction

- Proposal: ASCA procedures and training to address:
  - —Pooling of extracts from each iteration of an exhaustive extraction.
    - Specify if and when you conduct analysis of each iteration.
  - —Extract storage.
    - Specify storage conditions before chemical analysis, including storage duration (for extracts from each iteration, pooled extracts, or extracts after preparation for analysis).

Test Article Extraction

Discussion:

- *What kind of changes do you consider as degradation?*
- *If multiple extraction cycles result in extractable amounts that do not decrease, does this signal dissolution or device degradation, or perhaps that analytical chemistry may not be appropriate for evaluation of endpoints?*
- *How long are extracts usually stored (e.g., up to how many days), before being used for analysis?*
  - *—For example: initiate the analysis as soon as is practically possible after performing the extraction (within 24 hr)?*
- *Storage condition: Room temperature? Refrigerated (4 °C)?*

Test Article Extraction

Discussion:

- *How often do you conduct verification with certified weight sets of your balance for NVR determination?*
- *Are there any other critical considerations for NVR determination that could impact study results?*
- *How much volume do you usually use for NVR determination?*

Extract Processing

Extract Processing

- Proposal: ASCA procedures and training to address:
  - —Extract Solvent Exchange:
    - Specify when solvent exchange will be performed.
    - Describe solvent exchange methodology(ies).
    - Recovery qualification (for each methodology).
      - Specify number and identity of reference standards used for spike and recovery.
      - For liquid-liquid extraction, recovery rate is dependent on:
        - The physiochemical properties of solvents and reference standards.
        - Number of solvent exchange cycles performed.
        - Volume ratio of two solvents during each solvent exchange cycle.
      - Specify acceptable recovery rate (e.g., 80-120% or justification if outside this range).

Extract Processing

- Proposal: ASCA procedures and training to address:
  - —Extract Concentration:
    - Specify when concentration will be performed.
    - Describe concentration methodology(ies).
    - Recovery qualification (for each methodology).
      - Specify number and identity of reference standards used for spike and recovery.
      - For evaporative concentration, recovery rate is dependent on:
        - The physiochemical properties of solvents and reference standards.
        - Temperature of concentration conditions.
        - Extent of concentration (e.g., concentration factor).
      - Qualification to the greatest concentration factor for a given solvent/condition. (e.g., a process qualified for a 10-fold concentration would be unable to justify a 50-fold extract concentration).
      - Specify acceptable recovery rate (e.g., 80-120% or justification if outside this range).

Extract Processing

- FDA research: recovery qualification
  - —FDA is working on a predictive tool for recovery based on an Abraham solvation model for liquid-liquid extraction and evaporative concentration.
    - The tool may provide a means to predict compounds that are appropriately challenging candidates for spike and recovery but not impractical.
    - The tool is **not intended to replace experimental verification**.
  - —Preliminary results suggest a small list of worst-case compounds may be definable for recovery qualification.
    - Work currently ongoing.
    - Direct evaporation of aqueous solvents (water) is **not recommended**, consistently showing poor recovery (i.e., 0%) for most volatile and semi-volatile compounds.

Extract Processing

- Model examples*
  - —Input Variables:
    - Liquid-Liquid Extraction: volume ratio, number of exchange cycles, pH.
    - Evaporative Concentration: concentration factor, temperature.

Compound	Solvent Exchange (Liquid-Liquid Extraction)		Concentration (Evaporation)						
	EtOAc	DCM	Water	EtOAc	DCM	Hexane	IPA	EtOH	ACN
2,4-Di-tert-butylphenol	100 %	100 %	0 %	100 %	100 %	99 %	100 %	100 %	100 %
Caprolactam	82 %	98 %	35 %	97 %	100 %	34 %	91 %	94 %	95 %
D6 Siloxane	100 %	100 %	0 %	93 %	100 %	98 %	89 %	86 %	48 %
Benzotriazole	100 %	95 %	18 %	100 %	100 %	82 %	100 %	100 %	100 %
Naphthalene	100 %	100 %	0 %	54 %	96 %	71 %	27 %	35 %	64 %

*These examples should not be interpreted as recommendations (comprehensive or partial) for use in recovery qualification.

Extract Processing

- Proposal: ASCA procedures and training to address:
  - —Extract Dilution:
    - Describe when and how dilution is performed.
      - E.g., when the concentration of extractables are above the calibration linear dynamic range.
  - —Particulates and precipitates:
    - Describe when and how particulate source and chemical composition are characterized
      - E.g., particulates from device due to saturation and precipitation are characterized by FTIR.
    - Describe when and how particulates and precipitates are removed.
      - If particulates are believed to be precipitated extractables, describe how these will be accounted for in the total quantity of extractables released by the device.
        - E.g., Re-dissolution of particulates or precipitates and analysis.
      - If centrifugation or filtration are used to remove particulates or precipitates, describe how this will be performed and the impact on the test article extract.

Extract Processing

Discussion:

- *Would a list of chemicals recommended by FDA for use in qualification of recovery be useful?*
- *How many chemicals do you believe are necessary to use in spike and recovery testing?*

Reporting Threshold

Reporting Threshold

- Proposal: ASCA procedures and training to address:

  Calculation of the AET:

$$AET = DBT \times \frac{A}{BCD} \times \frac{1}{UF}$$

  - A is the number of devices extracted
  - B is the extraction volume (in mL)
  - C is the number of devices to which a patient would be exposed in a day during clinical use.
  - DBT is the dose-based threshold (in µg per day)
  - UF is the uncertainty factor
  - D is the dilution or concentration factor (i.e., $D=V_{final}/ V_{initial}$)

Reference: ISO 10993-18: 2020, Annex E

Reporting Threshold

- Proposal: ASCA procedures and training to address:
  - —RRF database / calculation of UF
    - Generate an RRF database for each detector/detection technique.
      - E.g., ESI+/- and any other detectors used in LC-MS.
    - Establish RRF database with chemicals across a broad range of physicochemical properties and are relevant to medical devices.
    - RRF database established by each test lab performing extractables testing (i.e., not using RRF database data developed by other test labs, as variations in methods can impact results).
      - Default UF: GC-MS UF=4, LC-MS UF=10, HS-GC-MS UF = 10 (?)

Reporting Threshold

- Proposal: ASCA procedures and training to address:
  - —RRF database / calculation of UF, for example:
    - Demonstrate that the techniques can detect chemicals across a broad set of physicochemical properties of chromatographic/mass spectrometric importance.

Reporting Threshold

Discussion:

- *What criteria do test laboratories employ to select compounds for inclusion in their RRF databases?*
- *How receptive would test laboratories be to a defined, minimum composition for an RRF database (potentially >100 compounds) to remove subjectivity in database population?*
- *What UF have you determined or default UF do you apply for your HS-GC-MS method?*

Extract Analysis

Extract Analysis

- Proposal: ASCA procedures and training to address:
  - —Analytical Methods:
    - GC-MS, LC-MS:
      - Detector types (e.g., EI for GC-MS and ESI+ and ESI- for LC-MS).
      - Additional supplemental detectors used (e.g., UV, CAD, APCI, FID).
    - ICP-MS:
      - Alternative detectors (e.g., OES or AES).
    - HS-GC-MS
      - Complementary technique for evaluation of volatile compounds not detectable by GC-MS due to low boiling point (e.g., D3 siloxane, halogenated solvents).
      - Comprehensiveness of the analysis is strongly dependent on the manner of testing.
        - Establish criteria for when analysis might be performed on aqueous extracts or directly on the device (i.e., solvent-free).

Extract Analysis

- Proposal: ASCA procedures and training to address:
  - —Analytical Methods (Cont):
    - Parameters, method qualification, and justification of the selected complement of analytical methods for extract analysis (e.g., HS-GC-MS, GC-MS, LC-MS, ICP-MS).
    - Selection and justification of detection methods:
      - Primary detectors and complementary detectors.
      - Rules for reporting compounds detectable by more than one detector type (e.g., ESI and UV).
      - HRMS mass accuracy for identification (e.g., 5 ppm mass tolerance).
    - Documentation of the coverage and potential gaps in the detection of the overall orthogonal methodology.

Extract Analysis

- Proposal: ASCA procedures and training to address:
  - —Surrogate Standard Selection
    - Number of surrogate standards, for example:
      - LC-MS: 5 (e.g., 5 responsive in positive ionization, 5 responsive in negative ionization)
      - GC-MS: 3
      - HS-GC-MS: 5(?)
    - Breadth of surrogate standards, for example:
      - Bracket the expected retention time range of extractables.
      - Representative of a range of chemical properties (e.g., molecular weight, polarity, vapor pressure, solubility).
      - Representative of the response variation in RRF database/coverage map.

Extract Analysis

- Proposal: ASCA procedures and training to address:
  - —System Suitability Tests and Criteria:
    - Frequency of testing (e.g., at the time of analysis for each analytical sequence/batch/run).
    - Types of tests performed (e.g., Annex G.6 of ISO 10993-18).
    - How those tests are performed and the criteria for those tests.
    - Reporting of test results.
    - References for Possible System Suitability Tests and Criteria:
      - ICH Q2R2 (Validation of Analytical Procedures) (https://www.fda.gov/media/161201/download)
      - USP <1225> (Validation of Compendial Procedures)
      - FDA Bioanalytical Method Validation Guidance for Industry (https://www.fda.gov/media/70858/download)
      - FDA Analytical Procedures and Methods Validation for Drugs and Biologics (https://www.fda.gov/media/87801/download)
      - USP <621> (Chromatography)

Extract Analysis

- Proposal: ASCA procedures and training to address:
  - —System Suitability Tests and Criteria
    - **Precision**, for example:
      - Measurement: Analysis of 5-6 injections of a reference standard solution within the method range.
      - Criterion: Area %RSD ≤ 15%, Area %RSD ≤ 20% if performed at method LOQ.
    - **Linearity/Curve Fit** (Calibration), for example:
      - Measurement: Analysis of (at least) 1 injection at 5 separate, non-zero concentrations which define the method range.
      - Criterion: Concentration of each point compared to the theoretical concentration calculated from the curve fit. Accuracy within 80-120%.

Extract Analysis

- Proposal: ASCA procedures and training to address:
  - —System Suitability Tests and Criteria
    - **Sensitivity**, for example:
      - Measurement: Analysis of 1 injection of a reference standard solution at the method LOQ.
      - Criterion: Accuracy within 80-120% (see Linearity) OR S/N ≥ 10.
    - **Specificity**, for example:
      - Measurement: 1 injection of a solvent blank and extract control.
      - Criterion: No significant interference observed.
        - E.g., interferences below the calibration range or appropriately mitigated using deconvolution software.

Extract Analysis

- Proposal: ASCA procedures and training to address:
  - —System Suitability Tests and Criteria
    - **Bracketing/Drift**, for example:
      - Demonstration of continuous method performance throughout the analytical sequence/batch/run (e.g., internal standards to monitor drifting precision or sensitivity when included in injections with external standards).
      - Measurement: Analysis of 1 injection of a reference standard solution within the method range periodically throughout the analysis (minimally once at the end of the analysis)
      - Criterion: Accuracy within 80-120% (see Linearity) OR Overall area %RSD ≤ 15% (when included with initial precision)

Extract Analysis

Discussion:

- *HS-GC-MS:*
  - —*How many surrogate standards do you use for HS-GC-MS semi-quantification, if performed?*
  - —*How frequently do you encounter reportable extractables in HS-GC-MS analysis when performed on aqueous extracts of medical devices?*
- *For semi-quantification, do you use the same set of surrogate standards for all devices or regularly choose device-specific surrogate standards?*
- *What should be considered in selecting surrogate standards for semi-quantification?*
  - —*Number of surrogate standards?*
  - —*Breadth of physiochemical properties of surrogate standards?*

Extract Analysis

Discussion:

- *What types of system suitability tests do you use to evaluate the performance of your analytical methods?*
- *What guidelines do you follow for deciding what types of system suitability tests to develop for your analytical methods?*
- *Do you have any comments on the proposed system suitability tests and criteria?*

Data Evaluation
(Identification and Quantification)

Data Evaluation (Identification and Quantification)

- Proposal: ASCA procedures and training to address:
  - —Identification of all analytes at or above the AET, for example :
    - Match score calculation and how it is used.
    - Spectral reference library/software information.
    - Instrument mass accuracy and mass resolution for every mode of operation.
    - How supporting information is used for identification.
    - Methods to check that proposed identifications are plausible and that identifications are not missed.

Data Evaluation (Identification and Quantification)

- Proposal: ASCA procedures and training to address:
  - —Supporting Information, for example:
    - Molecular formula generation (based on accurate mass) and/or confirmation (with an authentic reference standard of the candidate structure or a close structural analog).
    - Retention time or retention index matching.
    - Isomer assignment based on interpretation of data.
    - Fragmentation spectra interpretation based on data (e.g., for EI-based MS spectra).

Data Evaluation (Identification and Quantification)

- Proposal: ASCA procedures and training to address:
  - —Procedure to define identification levels and information used to support each level of identification, for example :
    - Confirmed
    - Confident
    - Tentative
    - Unknown
  - —Identified cohorts of concern, for example:
    - Investigation of cohort of concern compounds if known or suspected to be present.
    - Procedure to define when and how to look for suspected cohort of concern or potent toxicants if identified by the manufacturer (e.g., low MW aldehydes, halogenated solvents, polynuclear aromatic hydrocarbons, nitrosamines).

Data Evaluation (Identification and Quantification)

- Proposal: ASCA procedures and training to address:
  - —Semi-quantification methodology, for example:
    - Describe the semi-quantification method and justify the method for estimation and/or calculation of the concentration of analytes.
    - Report the final concentration and convert to mass/device or appropriate unit (e.g., µg/g for powder device or µg/mL for liquid/gel device).
    - Specify detection modality.
    - Reference standards used to perform quantification.
      - How their RFs are implemented for semi-quantification for a specific analyte.
      - Justification for the selected reference surrogate standards (e.g., nearest retention time, worst case RF, similarity in chemistry between the surrogate reference standard and the analytes.
    - Refinement of estimates using other reference standards.

Data Evaluation (Identification and Quantification)

Discussion:

- *How can the appropriateness of identification confidence be evaluated?*
- *How do you determine when confident/confirmed identification is necessary (e.g., when tentative identification is proposed)?*

Personnel Competency Evaluation

Personnel Competency Evaluation

- Education
- Experience
- Training and competency evaluation:
  - —Sample preparation
  - —Extraction
  - —Extract processing
  - —Identification and quantification
  - —Data record and reporting
- Proficiency testing

ASCA Summary Test Report

ASCA Summary Test Report

Proposed ASCA Summary Test Report to include:

I. Administrative information
II. Test article preparation and extraction
    a. Test article preparation
    b. Extraction condition
    c. Extraction solvent
    d. Extraction parameters
    e. Test and control article and extract appearance
    f. Exhaustive extraction NVR analysis (if applicable)
III. Extract processing
    a. Summary table of extract processing
IV. AET calculation
    a. Summary of AET calculation
V. Results
    a. Summary table of system suitability test results
    b. Summary table of instrument analysis (GC-MS, LC-MS, ICP-MS) results
VI. Signature and date

We will only discuss the section in red today, but you can review our general approach for the biocompatibility test methods in the draft guidance document (link: https://www.fda.gov/media/182026/download)

Proposed ASCA Summary Test Report (Example: NVR Analysis)

Extraction Parameters for Non-volatile Residue (NVR) Analysis

Extraction Solvent	**Extraction vessel (e.g., glass container, polypropylene test tube)**	**Number of extraction replicates**	**Test article amount (cm^2 or g, or mL)**	**Solvent Volume (mL)**	**Extraction ratio [specify cm^2/mL or g/mL]**	**Number of devices extracted per replicate**	**Duration or Cycles [specify cycle number and duration]**	**Extraction Temperature**
Polar: [insert solvent name]	[e.g., 50 mL glass jar]	[e.g., 1]	[e.g., 6 cm^2]	[e.g., 2 mL]	[e.g., 3 cm^2/mL]	[e.g., 1]	[e.g., exhaustive, 3 cycle, 72 hr per cycle]	[e.g., 50 °C]
Semi-polar: [insert solvent name]								
Non-polar: [insert solvent name]								
INSERT ROWS IF NEEDED								

Proposed ASCA Summary Test Report (Example: NVR Analysis)

Exhaustive Extraction NVR analysis (if applicable):

☐ Exhaustive endpoint determination and NVR analysis SOP #:*[SOP ASCA_NVR (date/revision]*

Specify if NVR analysis is conducted by using:

☐ Entire volume of extracts (i.e., all iterations).

☐ Aliquot of extract*: [specify volume of extract]

*If only an aliquot of extract is used for NVR analysis, provide a justification (e.g., There is a sufficient quantity of extractables that 10% of the initial weight can be accurately measured gravimetrically.)

NVR Analysis Results:

Polar Solvent [e.g., Water]			
Iteration	**NVR (mg)**	**NVR (mg/device)**	**% of 1st iteration**
1			
2			
3			
[Insert row if more cycle of extraction is conducted to reach exhaustive extraction endpoint]			
Semi-polar Solvent [e.g., ethanol]			
1			
2			
3			
[Insert row if more cycle of extraction is conducted to reach exhaustive extraction endpoint]			
Non-polar Solvent [e.g., hexane]			
1			
2			
3			
[Insert row if more cycle of extraction is conducted to reach exhaustive extraction endpoint]			

Personnel Competency Evaluation

Discussion:

- *Education and experience: What level of education and experience is needed?*
- *Do different study components (e.g., sample preparation, extraction, extract processing, instrument analysis, identification and quantification) need different levels of education and experience?*
- *Training and competency evaluation: How does your test lab evaluate analyst competency?*

ASCA Summary Test Report

Discussion:

- *What other elements should be considered for inclusion in ASCA summary test report?*

Thank You

Please email us at ASCA@FDA.HHS.GOV with any additional input