Nelson Labs
A Sotera Health company

Looking into the future of Extractable testing to Support Chemical Characterization – What can we learn from NTA

PIET CHRISTIAENS, NELSON LABS

April 26, 2023

Table of Content

Nelson Labs.
A Sotera Health company

PART 1

Introduction

1. Introduction

- **Third Year** after implementation of ISO 10993-18:2020
- Coinciding: reported scattered results of **“Round Robin”** testing for Extractable testing
- A lot of **Learning**, both for **Authorities** as well as for **E/L-Practitioners**
- What was **historically acceptable**, may **not be acceptable now**...
- **Major shifts in thinking** will be discussed
- **Where could it go from here**?

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

PART 2

Observations

2. Observations

- **Interactions with Authorities**

  - **Lack of trust** in Extractables Data (cfr Round Robin)
  - **Increasing Scrutiny** on generated E/L data
  - **Lack of Understanding** of some of the basic concepts
    - *Both with E/L-Labs as with some Regulators*
  - **Lack of Clear Actionable and Achievable Guidance** sometimes leads to:
    - *Unrealistic Expectations*
    - *Adherence to Theoretical Concepts that do not always reflect Scientific Reality*
  - **Feedback from Regulatory Reviews**:
    - *Reviewer Dependent*
    - *Alternatively: "default" list of deficiencies*

2. Observations

- **Existing Guidance: not sufficiently adequate for setting up Proper E-Studies for MD**
  - **ISO 10993-18:2020:** large step forward, but leaves some issues unaddressed
  - **USP<1663>:** Guidance for Identification does not address malpractices
  - **USP<1664>:** Guidance for Quantification in Leachables is adequate for Pharma, no guidance for Quantification for MD Extractables
  - **IN GENERAL:** Guidances for Pharma E/L is not always useful as it is a 2-step approach

- **New Developments**
  - ISO 10993-17 FDIS: Large Spread between **"Toxicological Screening Limit"** versus **"Analytical Evaluation Threshold (AET)"**
  - New Published Information on **Non-Targeted Analysis** (eg BP4NTA) from other industries could (hopefully):
    - introduce some realism into the expectations
    - Introduce new concepts into the E/L world

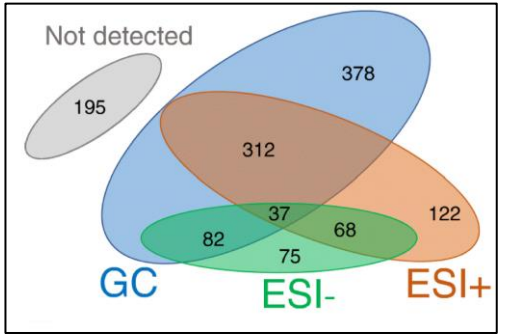
PART 3

Harmonizing Extractable Practices for Medical Devices

3. Harmonizing Extractable Practices for Medical Devices

Already looking into the future

- **Hard to Harmonize** on Methodologies and Instrumentation
  - Every Lab has developed their own testing strategy with supporting Instrumentation
  - Hard to change this post factum
- Therefore: **Harmonizing on OUTPUT** is the next best thing
- **Optimization of Orthogonal and Complementary Testing methodologies**
  - GC/MS detects >66% of all compounds: Which ones are part of the 34%?
  - Optimize other Methods by narrowing the Gap (LC/MS ESI or APCI or other detectors)
  - Know the gaps in your methodologies: allows to finetune the protocols
- **Same Minimal Sensitivity** for the methods Employed (eg LoD<AET)
- However: set **Realistic Expectations for the AET**!



ENTACT Round Robin Study in Environmental Testing: Conclusion

3. Harmonizing Extractable Practices for Medical Devices

When Harmonizing OUTPUT: Think of the Report “USERS”

- Results are further evaluated by **Toxicologists /Risk Assessors**
- Do **not expect further interpretation** of analytical data
- **IDENTIFICATION:** Reported Compounds with Name, Structure and CAS N° will be assessed, regardless how accurate the identifications are
- **QUANTIFICATION:** Quantitative results should be “Protective”
- **Provide Information on the Controls** during sample prep and analysis
  - Examples: Sample Preparation Recoveries
  - Confidence in analytical data!
- **Explain all calculations**
  - DBT (TTC), AET, UF, LoD/LoQ…
  - Allows verification!

3. Harmonizing Extractable Practices for Medical Devices

ULTIMATE GOAL:

REGARDLESS OF THE METHODOLOGIES AND INSTRUMENTATION USED, ALL LABS SHOULD COME WITH

- The same **number of compounds** to be assessed
- The **same identification** for the compounds (be protective!)
  - No Conflicting Identifications
  - Only the Identity Classification can be different
  - Be conservative in assigning identifications (i.e. GC/MS)
- **Reported Concentrations** should be equally **“protective”** across labs

PART 4

The AET: Cornerstone in the Extractable Assessment for Medical Devices

Nelson Labs
A Sotera Health company

Part 4: The AET: cornerstone in the Extractable Assessment for Medical Devices

Cfr. Presentation of Dennis Jenke given earlier

Some Thoughts

- Originally (PQRI) **the AET was concentration based** (expressed in µg/mL or µg/L)
- However, slowly the **AET became "response based".**
- Not Non-Targeted Screening Analysis: **no Universal Detector with Equal Responses** for all analytes exist
  - *Consequence correct the AET downwards with established Uncertainty Factors (accounting for RF variation)*
- However, for **Targeted Methods** (with eg Validated Methods): no need to correct AET with UF
  - No remaining Uncertainty!
- Now **what about Semi-Quantitative Concentration Determinations**?
  - Re-evaluate the Uncertainty of a semi-quantitative concentration determination

WHAT WOULD HAPPEN IF WE WOULD TURN THIS AROUND? => next slide

Part 4: The AET: cornerstone in the Extractable Assessment for Medical Devices

WHAT WOULD HAPPEN IF WE WOULD TURN THIS AROUND?

- **All compounds detected above LoD are converted into concentrations**
- The Nelson Way: **RRF correction** for Compounds in Database (with Experimental RRF)

$$[Ext]_{Semi-Quant} = \frac{Response_{Ext} \,.\, [I.S.]}{RRF_{Ext}\ Response_{I.S.}}$$

- For Compounds with no Experimental RRF: use a “Conservative RRF” that is protective

$$Conservative\ RRF \quad = \frac{Mean_{RRF}}{UF}$$

- Once the Responses are converted into concentration then apply the AET
- **In that case, AET does not need to be corrected anymore with an UF**
  - **The UF is integrated into the Conservative RRF Calculation (RRF_{CON})**
- **This avoids False Positive and False Negative results around the AET**

Part 4: The AET: cornerstone in the Extractable Assessment for Medical Devices

The Divide between the Toxicological Screening Limit and the AET is not sustainable!

TTC Exposure Duration Category	Limited (<24 h)	Prolonged (24 h to 30 days)	Long-term (> 1 month to 1 year)	Long-term (> 1 year – 10 years)	Long-term (>10 years)
Cumulative TTC, µg/person	**120**	240	620	3660	5475
Dose Based Threshold (DBT) basis of AET Calculation (µg/day) (ISO TS 21726)	**120**	**120**	**20**	**10**	**1.5**
TSL/DBT	**1**	**2**	**31**	**366**	**3650**

AET is 3650 more protective than Toxicologically Relevant (TSL)

Toxicological Screening Limit:
cumulative *exposure dose* over a specified time period, to an *identified constituent* that will be without appreciable *harm to health*

TSL

AET

PART 5

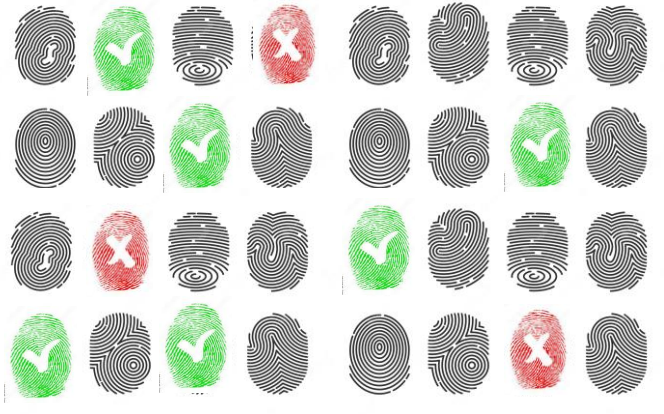
Identifications: need for more and better Guidance

Part 5: Identifications – Need for better Guidance

Initial General Observation:

- **GC/MS: Identifications are given to "lightly" – prone to errors**
  - Often: "Mass Spectral Matching" without any further consideration or evaluation
  - Risk of mistakes in linking the compound to its right toxicity data

- **LC/MS: too many unidentified compounds are reported**
  - Problematic for TRA



Part 5: Identifications – Need for better Guidance

Evaluating the USP<1663> Guidance for the classification of Identification and how it is Practiced

- Although it contains valuable information, the Guidance in the Document **could be "fine-tuned"**
- Additional class for **Partially Identified** Compounds
- **Re-evaluation on the criteria** the classify compounds in an identification class
- **Confusing nomenclature/symantics** of the ID-Classes
  - Eg. **CONFI**rmed versus **CONFI**dent
  - Confusing for Users of Reports

Part 5: Identifications – Need for better Guidance

Will an upgrade of the Identification Classification *(USP<1663> or other regulatory documents)* solve the problem?

- Probably not
- the issue is that the Guidance for ID-Classification is not always strictly followed anyways.

Solution?

- **Justify more extensively** the conclusion of an identification in the report.
- **Avoid automatic output** from fits with commercially avaiable Mass Spectral Libraries *("the highest Match wins")*
- Examples:
  - Mirror plot of Mass Spectrum of extractable versus Mass Spectrum of Library hit: visual inspection
  - Additional criteria to come to an ID conclusion: Not only Match Factor!
  - Retention Index, InLib score, Reverse Match factor, Assignment of Mass fragmentation...
- For LC/MS
  - Make the link to GC/MS results (Elemental Formula confirmation with Accurate Mass)
  - ...

PART 6

Quantifications for Non-Targeted Analysis: Realistic Expectations

PART 6: Quantifications for NTA: Realistic Expectations

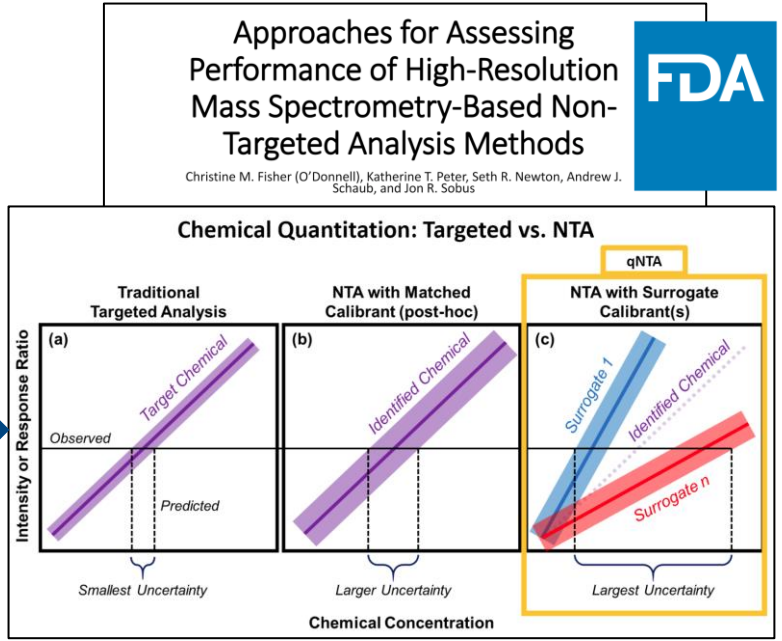
Position of Authorities: Conflict between Expectations and Realism of how Quantitative NTA really is

Feed-back from Authorities:

- Use 3 Surrogates for GC/MS, 5 Surrogates for LC/MS
- Use 5 Point Calibration Curves to quantify all Compounds
- Or, use RRF based on 5-calibration curves
- No Internal Standards, use External Calibration
- ...

Recoveries for compounds monitoring extract handling (Liq/Liq, Concentration Step):

- Expectation: 85 - 115%
- Typical for Trace Analysis: 50% - 200% (eg EPA)
- Consequence:
  - Labs will select compounds that do always give good recoveries
  - Not Necessarily compounds that monitor the quality (eg more volatile compounds to monitor concentration steps)



NELSON RRF APPROACH (only, is is pre-hoc)

FDA SURROGATE APPROACH

PART 6: Quantifications for NTA: Realistic Expectations

Looking at the Future

- **High Accuracy** Analysis and **Non-Targeted** Analysis are **incompatible terms**
- **Avoid Second Pass Targeted Analysis** (with High Accuracy) in every project: not realistic.
- Avoid Frustration

What if... We could move from the term "Accuracy" towards "Protective"?

- **Protective**: Reported concentrations are at least equal to higher than the true concentration (eg obtained via Validated Method).
- Using a **"Correction Factor" to correct all detected responses** in a chromatogram
- The Correction Factor should include an **Uncertainty Factor**
- The Uncertainty factor should allow to evaluate the **"Coverage"**
- Define the term "Coverage": minimum number of compounds of which the reported concentration will be equal or higher than the true concentration.

PART 7

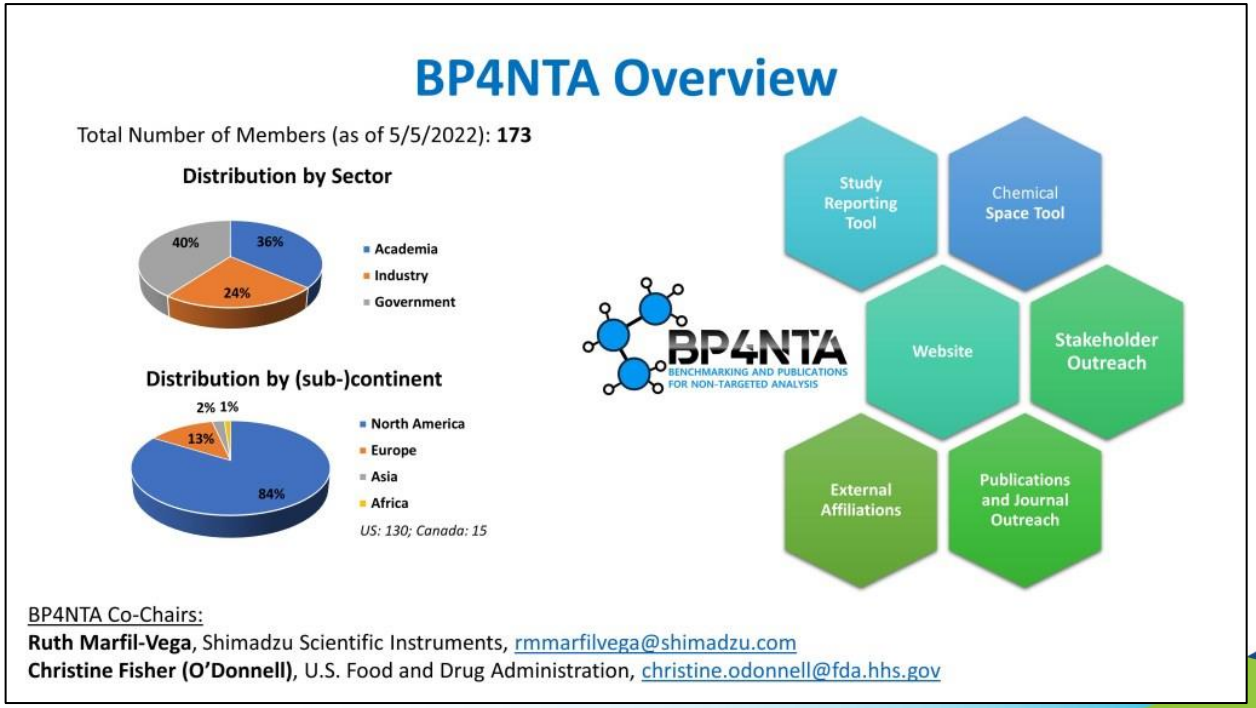
Concepts for Non-Targeted Analysis in Literature (BP4NTA): what can we learn?

Part 7: Non-Targeted Analysis (BP4NTA)

BP4NTA: Benchmarking and Publications For Non-Targeted Analysis

- The Benchmarking and Publications for Non-Targeted Analysis (BP4NTA) Academia and Industry working group was established to address challenges in non-targeted analysis (NTA) studies using mass spectrometry.

- Environmental
- Food
- Forensic
- Cosmetic
- Chemical
- Medical / Pharmaceutical
- ...



Nelson Labs.
A Sotera Health company

Part 7: Non-Targeted Analysis (BP4NTA)

BP4NTA: Benchmarking and Publications For Non-Targeted Analysis

Suspect screening analysis (SSA)

- identification by comparison to a predefined user list or library containing known chemicals of interest.
- acts as a funnel, tightening the scope of the study.
  - at the data acquisition stage
  - at the data analysis stage
- The choice of a suspect screening list may be guided by prior knowledge of expected contaminant class(es) or researcher interest in specific contaminant class(es).

= THE NELSON LABS DATABASE!

Part 7: Non-Targeted Analysis (BP4NTA)

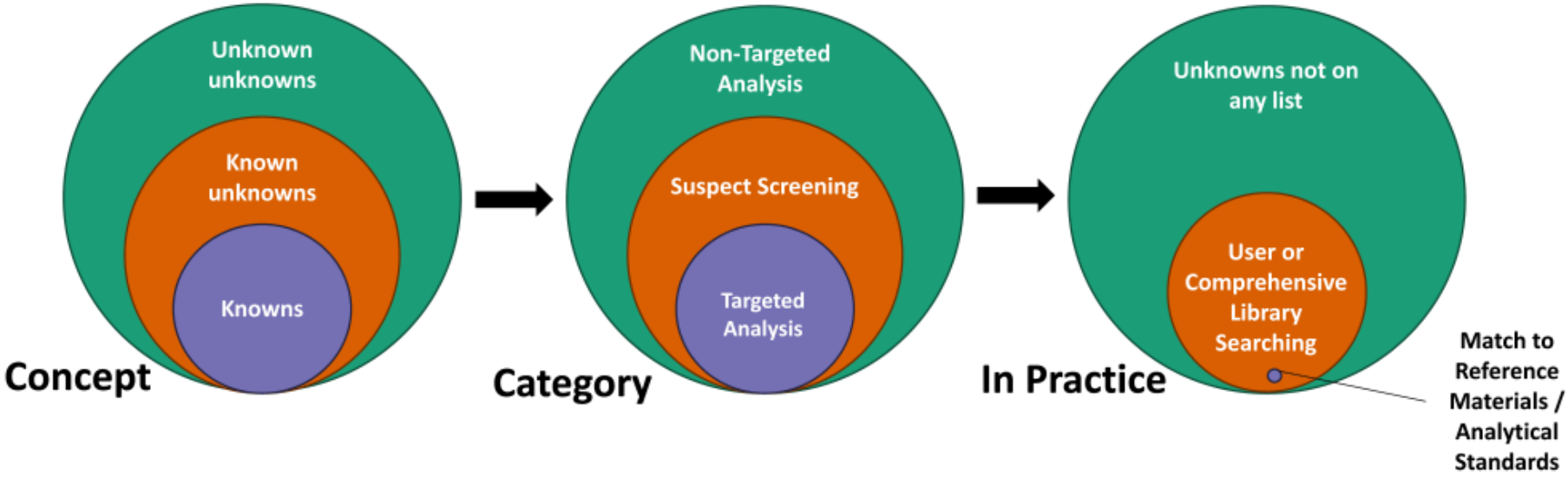
Non-Targeted Analysis (NTA),

- “non-target screening” and “untargeted screening”
- characterization without the use of a priori knowledge regarding the sample’s chemical content.
- The resulting detections may be used to classify samples (using the entire chemical profile), and/or subsequent analyses may focus on the identification of individual chemicals.
- Typically, “true” NTA annotation and identification efforts are focused on chemicals that are unknown from two perspectives:

  1) the chemicals are not included in established libraries or databases

  2) presence of the chemical in the sample is not known a priori.

Part 7: Non-Targeted Analysis (BP4NTA)



Part 7: Non-Targeted Analysis (BP4NTA)

Other Guidance in BP4NTA (non-limitative list):

- **How to set-up an NTA study, eg**
  - On the instrument: the Analytical Sequence
  - QA/QC-Metrics
- **Annotation and Identification**
  - Identification and Confidence Levels
- Differentiating **Databases** versus **Libraries**
- The **Confusion Matrix**
  - True Positives
  - False Positives
  - True Negatives
  - False Negatives
- The **NTA Reporting Tool**!!
- …

Reporting Analytical Data for Regulatory Submissions: A CRO Perspective on Implementing the BP4NTA Study Reporting Tool in the Healthcare Industry

Nicole Dunn[1], **Anna Michelson**[1], **Louis Fleck**[1], **Gyorgy Vas**[1,2,*]

Nelson Labs.
A Sotera Health company

PART 8

Conclusion

Part 8: Conclusion

- Extractable & Leachable Testing for Medical Devices is **gaining maturity**
- However, some **basic concepts** are still **not well understood**
  - From partitioners side
  - From Authorities side: realistic expectations
- Call for **Harmonization on the Outcome**
  - Identification: Better Guidance
  - Quantification: “accurate” versus “protective”
- What can we **Learn from Other Industries practicing Non-Targeted Analysis**?
  - BP4NTA

Questions?

Dr. Piet Christiaens, Scientific Director - Nelson Labs Europe
e-mail: pchristiaens@nelsonlabs.com
Tel: +32 16 40 04 84