Best Practices for OINDP Pharmaceutical Development Programs Leachables and Extractables

VII. Characterization of Leachables

PQRI Leachables & Extractables Working Group

PQRI Training Course

12-13 April 2007

Chicago, IL

Course Objectives

- Necessary definitions
- Brief review of historical approach
- Application of the AET for leachables
- Analytical method development for leachables
- Validation of analytical methods for leachables
- Leachables testing on formal stability programs
- Correlation of leachables and extractables
- Summary of PQRI Recommendations
- Conclusion

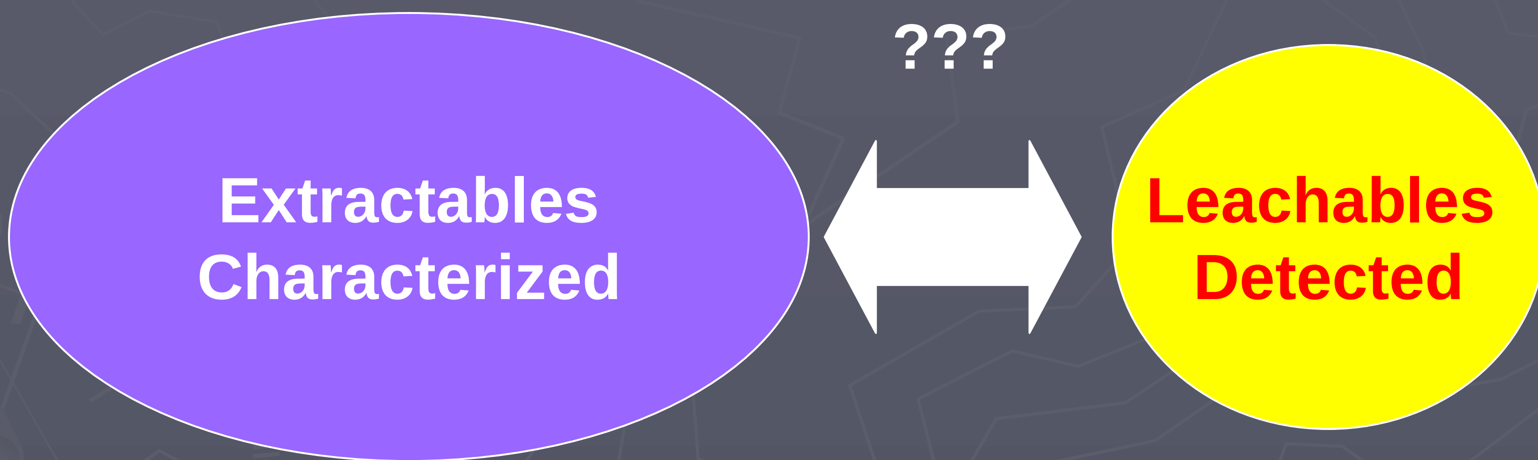
The Grand Tautology

- "Leachables in OINDP are compounds which are present in the drug product due to leaching from container/closure system components."

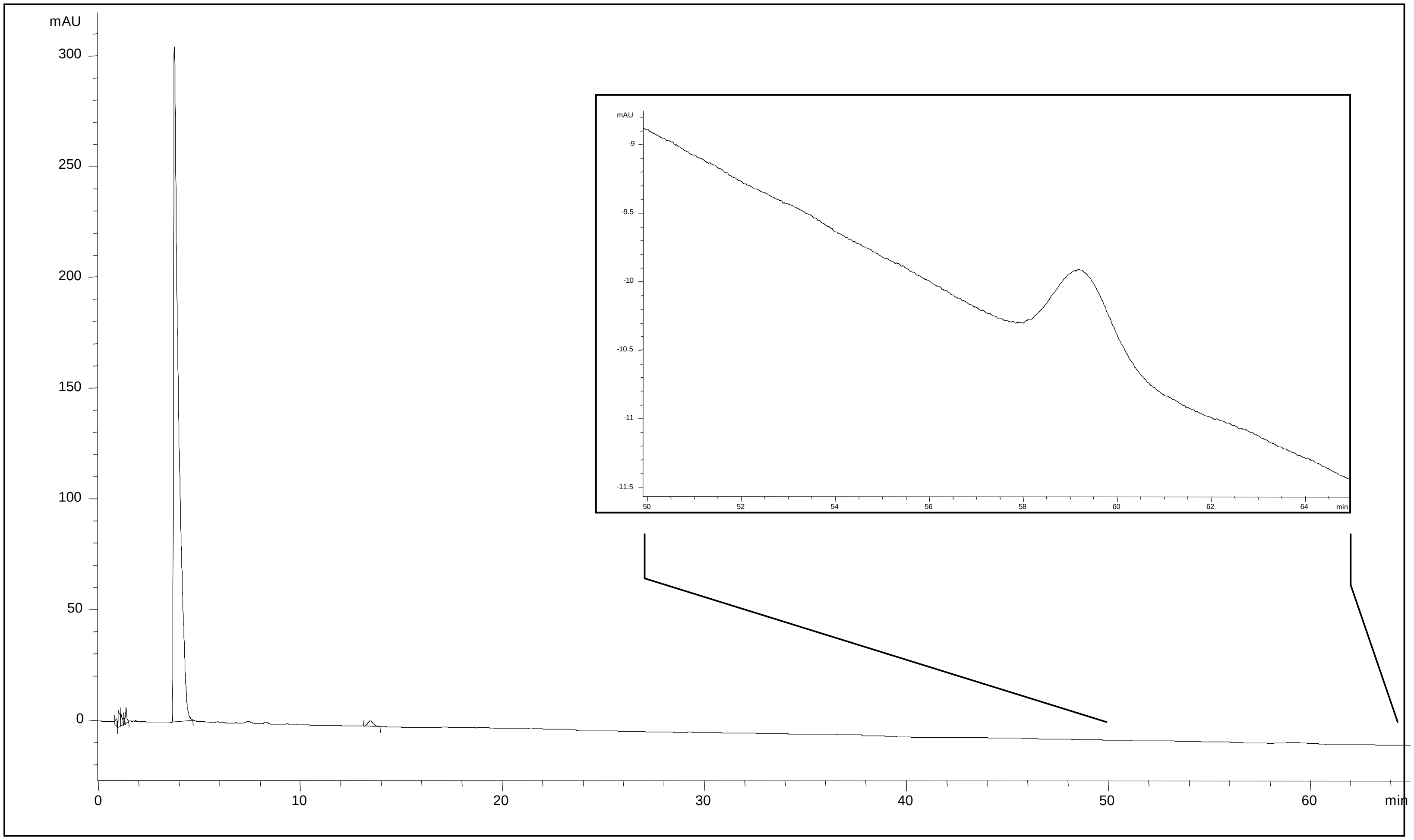
Boolean Leachables

- "Leachables are often a subset of, or are derived directly or indirectly from extractables."

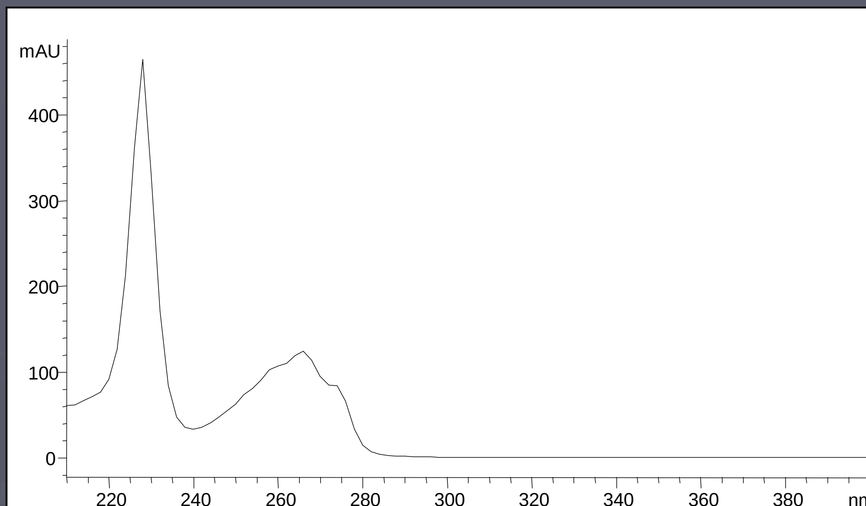
Set Theory and Leachables- Avoiding the Null Set Intersection



Risk Avoidance-
“What’s that new peak?”

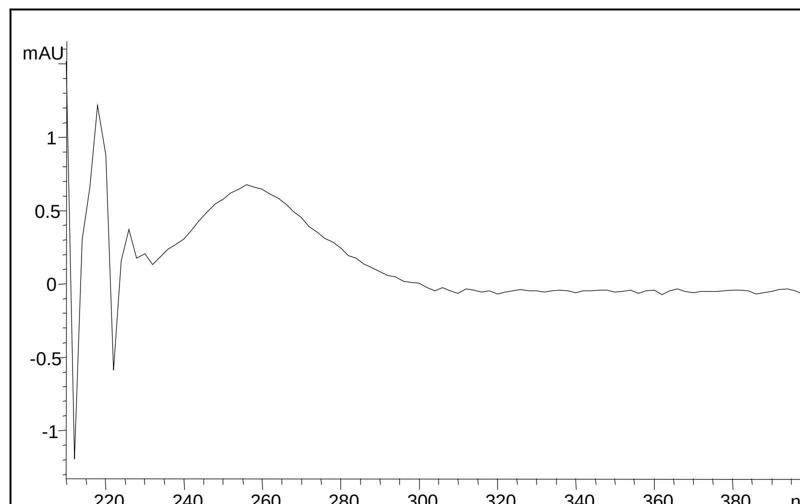


Trace Organic Analysis- Basic Identification

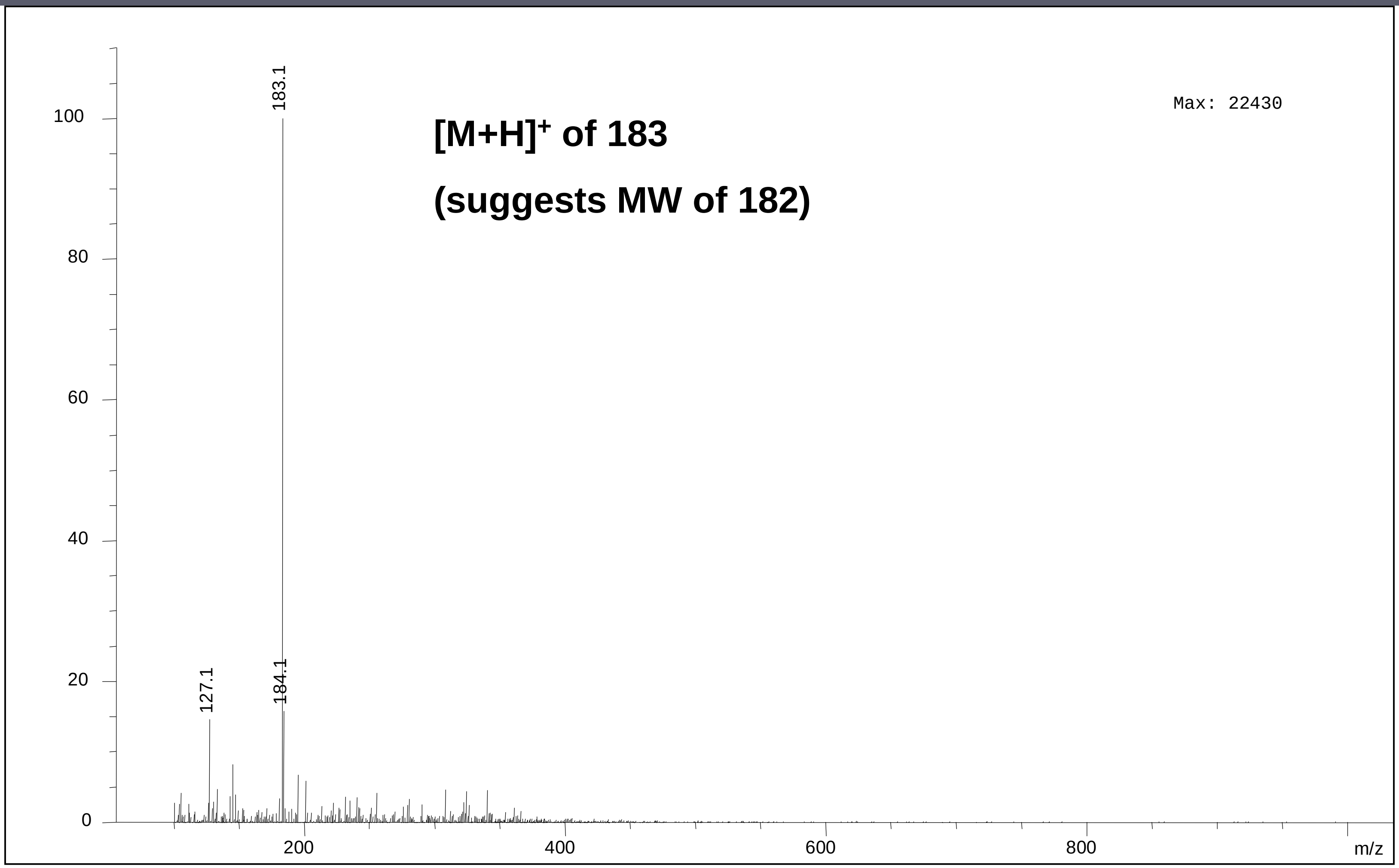


UV Spectrum of API

UV Spectrum of "Noise" or Unknown?

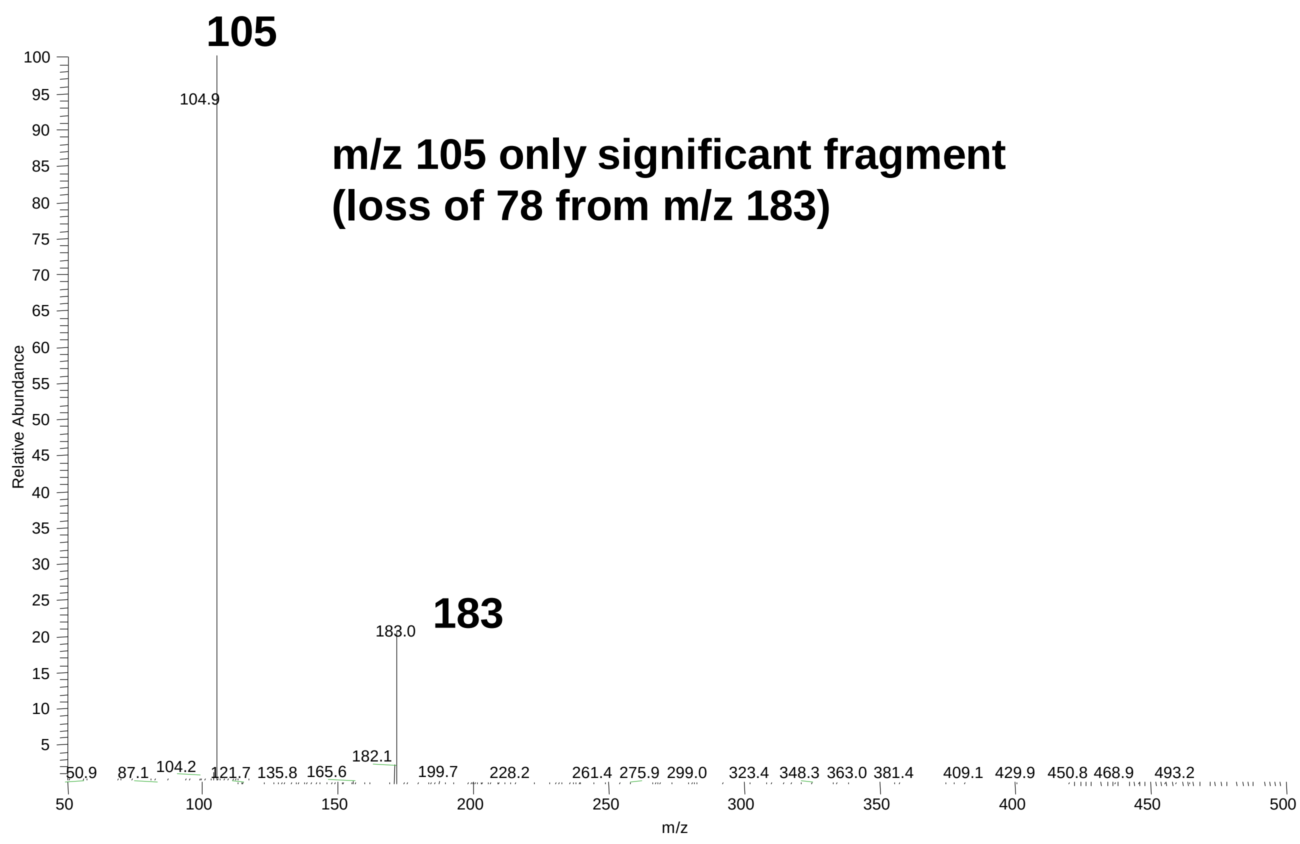


Trace Organic Analysis-Modify HPLC for LC-MS



Trace Organic Analysis-LC-MS^N

LC-MS-MS of m/z 183

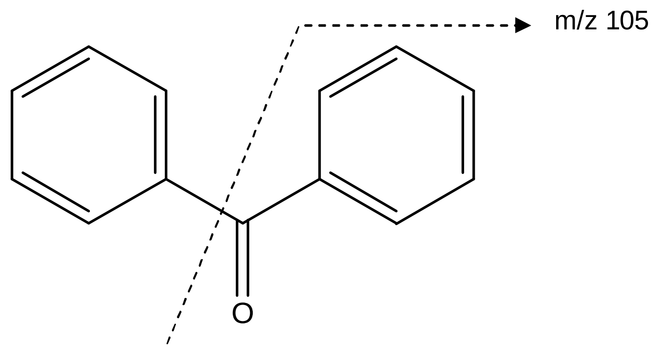


Trace Organic Analysis- Molecular Formula Determination

Accurate Mass Measurement

Performed using a Micromass QToF2 resulting in an exact mass of m/z 183.0801 for $[M+H]^+$.

A tentative empirical formula of $C_{13}H_{11}O$ was proposed with a mass accuracy of 4.9 ppm.

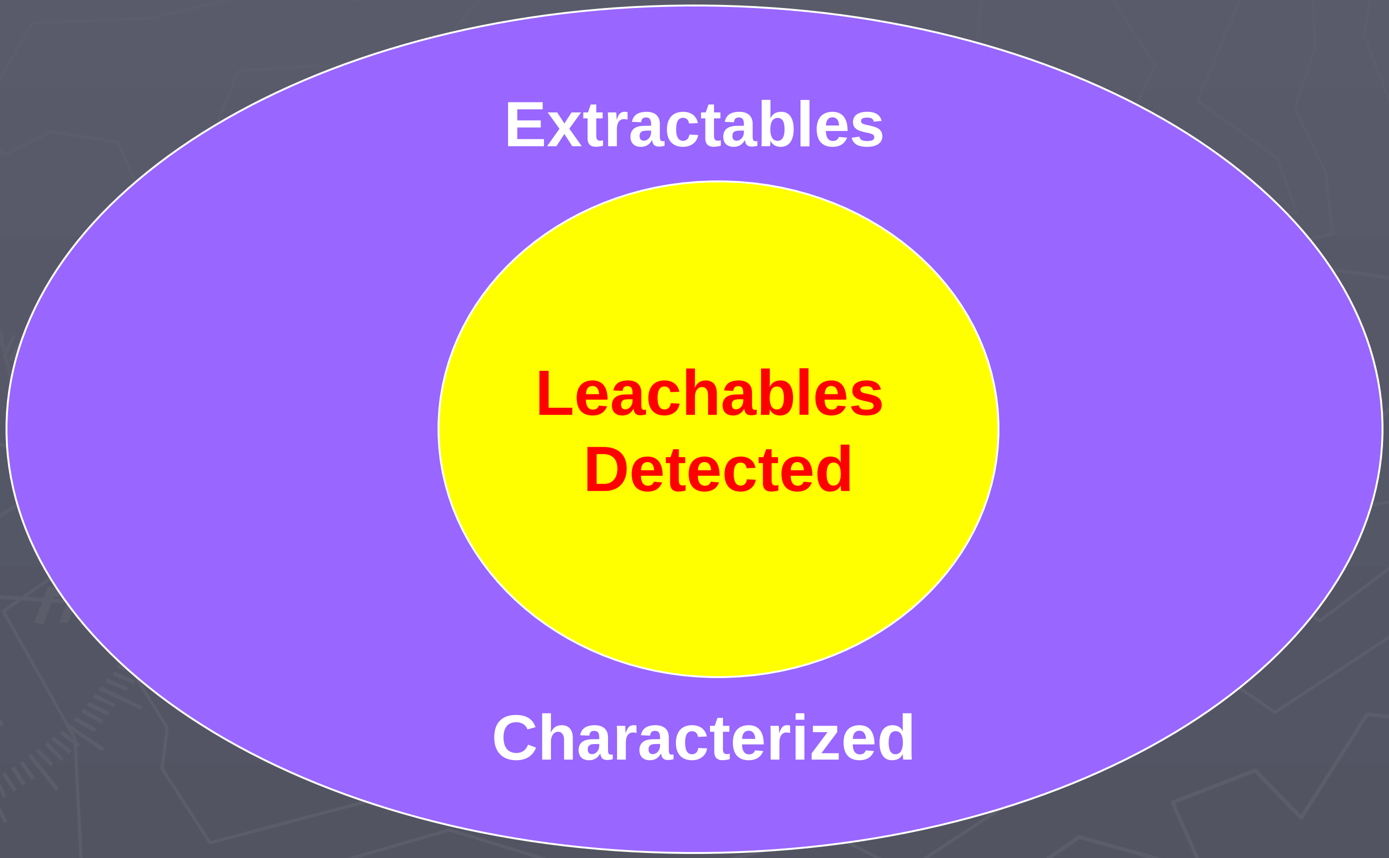


Timing is Everything

If not adequately characterized prior to filing, what can possibly happen?

Delays

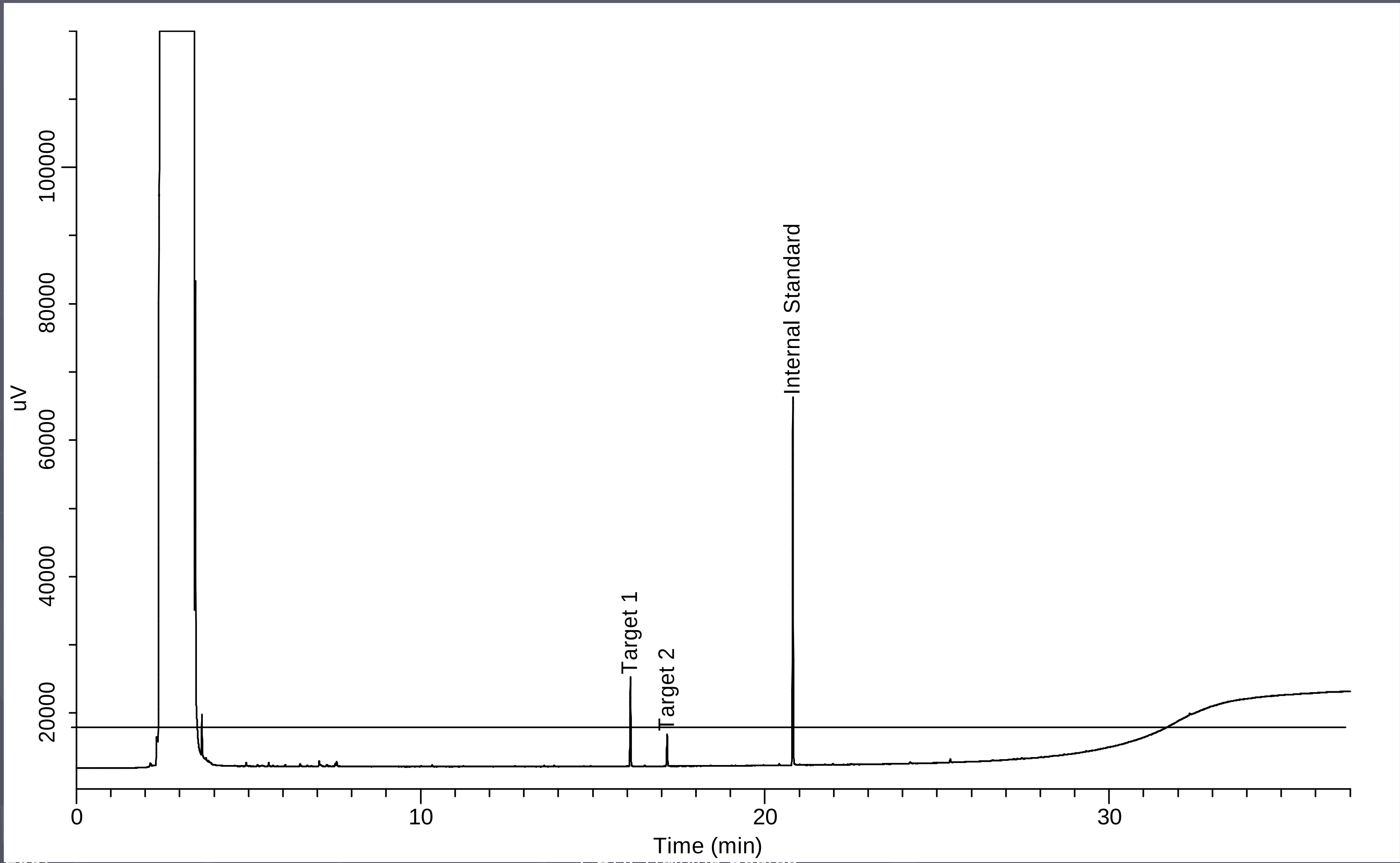
Set Theory and Leachables-Leachables as Subset



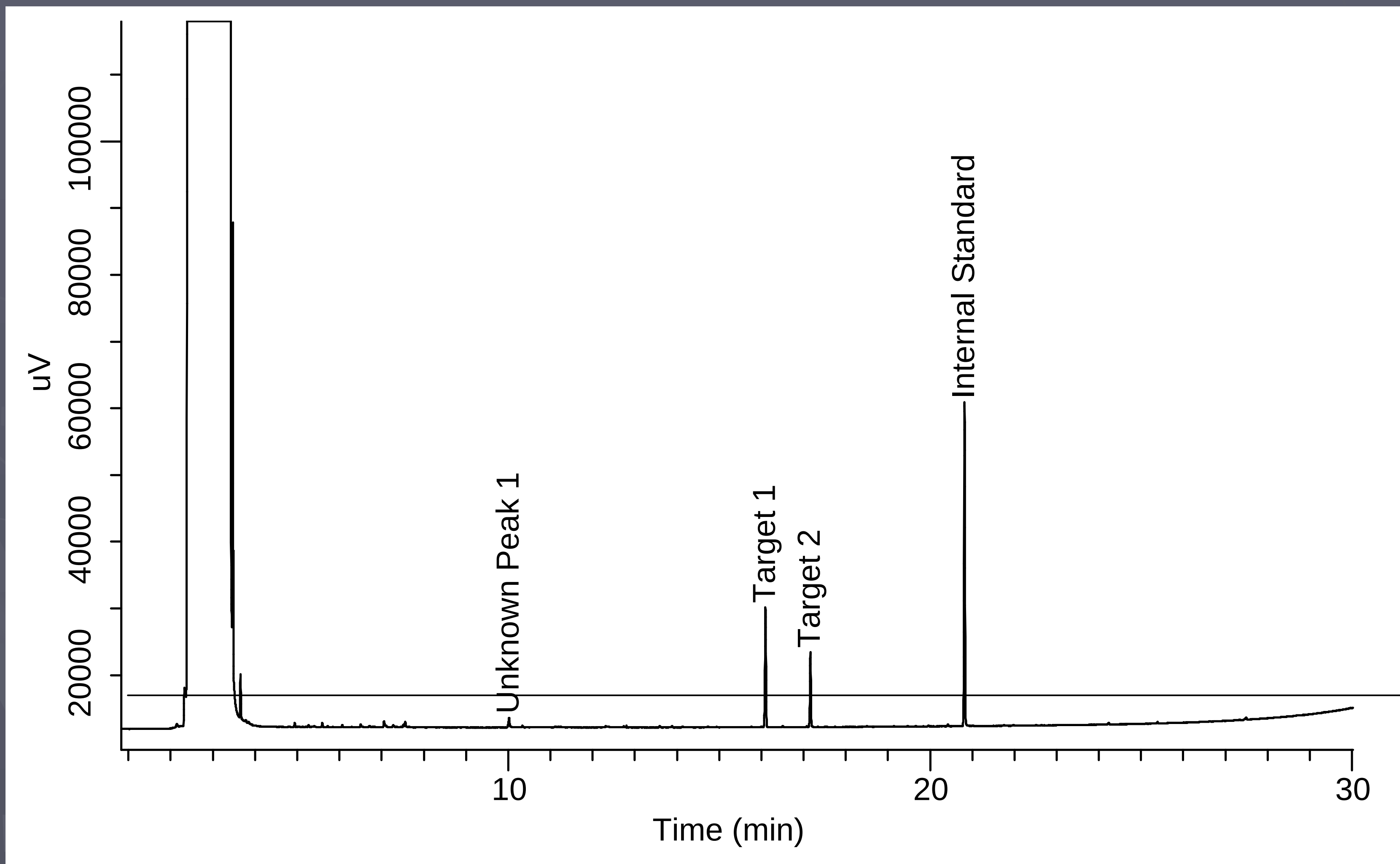
Mechanistic Explanation

- "Due to the time-dependent nature of the leaching process, leachables appear in an OINDP formulation over the shelf-life of the product as determined during appropriate stability and accelerated stability studies."

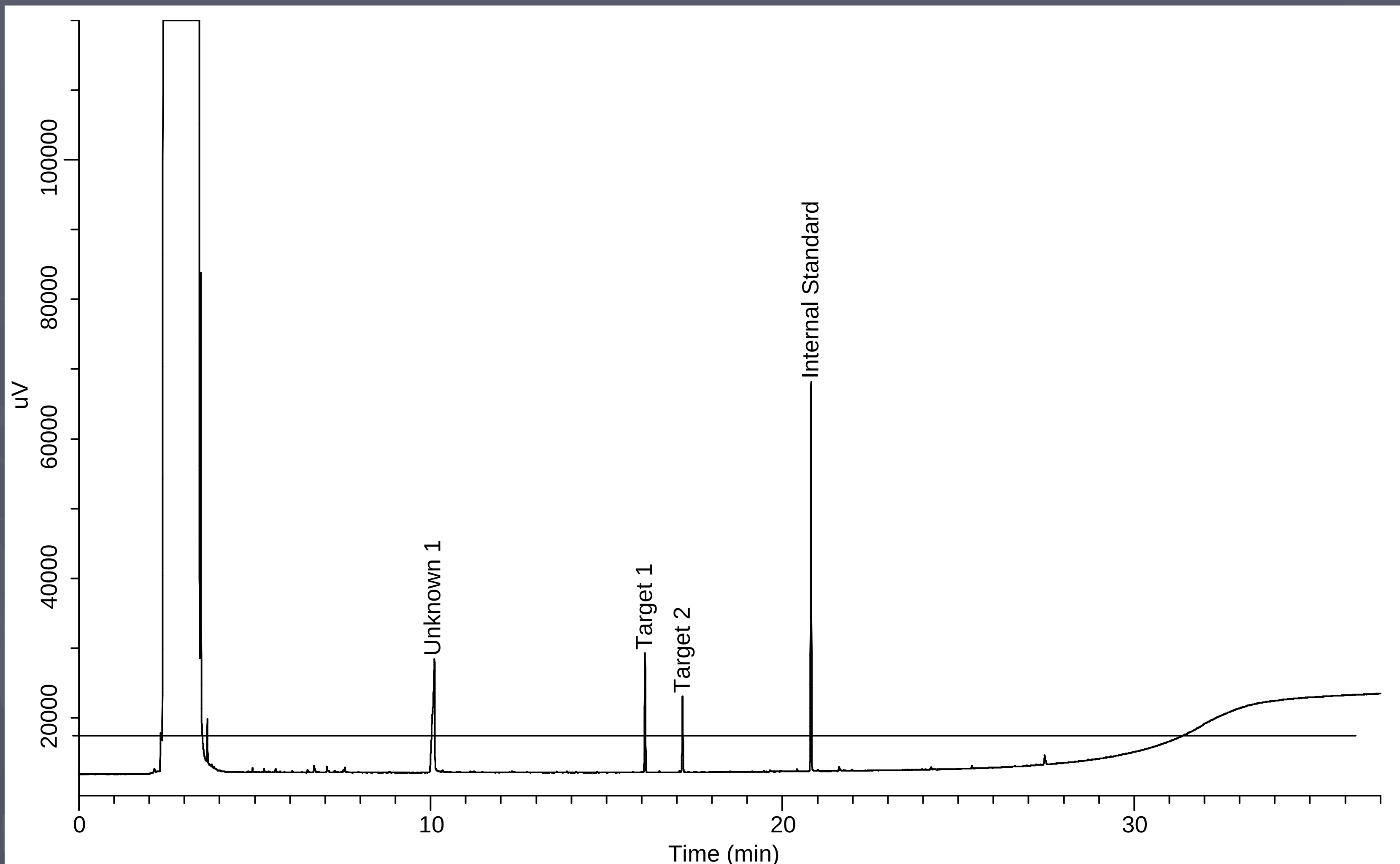
Time Dependence Example- Accelerated Drug Product



Time Dependence-
1 Month



Time Dependence- 3 Months



Formation of Pharmaceutical Development Team

It's not any one function's responsibility

- Not Engineering
- Not Marketing
- Not Manufacturing
- Not Toxicology
- Not Regulatory
- Not Analytical Chemistry

It's EVERYONE'S responsibility

Function of Pharmaceutical Development Team

- Investigate ALL possible sources
- Anticipate ALL possible changes
- List ALL possible targets

- Avoid the “universal method” syndrome

"Universal Method Syndrome"

Variations on:

"Just develop and validate a leachables method; we'll figure out what to do if we see anything"

"Develop so we can quantitate all peaks at the LOQ."

- Finding needles in haystacks is hard!
- Needles are sharp!

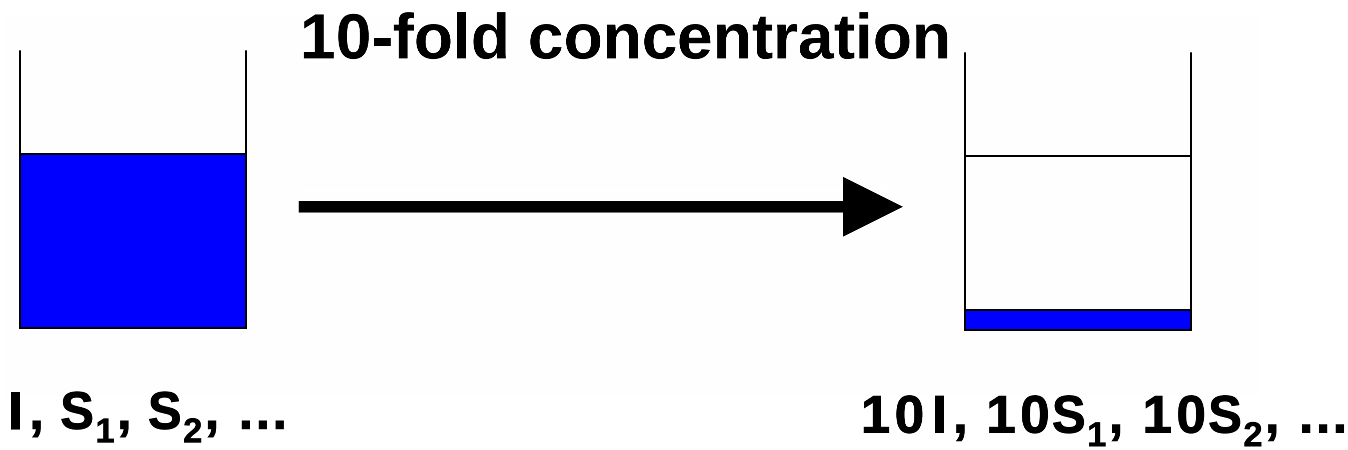
Developing a Useful Leachables Method

- Pick targets (extractables)
- Use multiple techniques if necessary
  - Choose a good internal standard if necessary
- Calculate the AET
- Set the AET > LOQ

Internal Standards

- For less stable techniques, corrects for method variabilities
  - *Sample preparation/extraction*
  - *Injection*
  - *Detection*

Preparation Variation Control by Internal Standards



$$\frac{S_1}{I} = \frac{10S_1}{10I}$$

Injection-to-Injection Variation Control by Internal Standards

	Internal Standard Area	Target Area	RF
Injection #1	16829.81017	10334.64888	0.61406806
Injection #2	10310.14813	7174.591338	0.69587665
Injection #3	11278.75411	5828.721237	0.516787686
Injection #4	12081.30852	6701.71641	0.554717761
Injection #5	13699.56179	8227.185641	0.600543708
Injection #6	10577.04126	7597.389031	0.718290573
Injection #7	16987.86803	10985.23999	0.646652068
Injection #8	12713.30506	8727.207324	0.686462512
Injection #9	10244.0203	7281.174188	0.710773112
Injection #10	15756.64909	9919.311478	0.629531788
%RSD	20.31%	20.38%	10.61%

Choosing "Good" Internal Standards

- Technique compatible
- "Well-behaved"
  - stable in the analytical matrix.
- No interferences
- Similar response factor to targets
- "Goldilocks" concentration
  - *not too high*
  - *not too low*

Picking Targets

Example Extractables:

- Irganox 1010
- 2-ethyl hexanol

Widely varying polarities, volatilities suggest two methods for leachables

Culling Targets

Refining Example:

Inhalation Solution, no Irganox 1010 in formulation extracts, then

- 2-ethyl hexanol

would be the only target

Target Selection Justification

- Just because an extractable is detected, doesn't necessarily mean that a leachable method should be developed for that extractable

No Leachables Studies Required if

"a. Aqueous and/or drug product formulation extracts of Inhalation Solution direct formulation contact container closure system materials yield no extractables, under appropriate stress conditions, at Final AET levels, or no extractables above final AET levels with safety concern;

AND

b. There is no evidence for migration of organic chemical entities through the unit dose container or protective packaging components into the drug product formulation."

Analytical Uncertainty

The Working Group proposes and recommends that analytical uncertainty in the Estimated AET be defined as one (1) %Relative Standard Deviation in an appropriately constituted and acquired Response Factor database OR a factor of 50% of the Estimated AET, whichever is greater.

Response Factors

Analyte ID	RF Value	RRF Value
BHT	19.28	0.95
Irganox 1076	7.4	0.35
p-terphenyl-D14	17.40	0.88
Bis (2-ethylhexyl) phthalate	14.38	0.71
2,6-d-tert-butylphenol	19.96	0.96
Eicosane	15.73	0.77
Diphenylamine	21.91	1.05
Dibutyl phthalate	12.54	0.61
Mean	**16.08**	**0.79**
Standard Deviation	**4.66**	**0.23**
%RSD	**28.98**	**29.00**

Estimate AET-
MDI Example

For MDIs the Working Group recommends setting the AET = SCT (0.15 µg TDI)

Consider Example MDI

- 200 actuations per canister
- 12 actuations per day

FINAL AET

Final AET =

Estimated AET x (1- analytical uncertainty)

Where analytical uncertainty = Max (%RSD or 0.5)

Final AET-
MDI Example

$$\text{FINAL AET} = \frac{0.15\ mg}{\text{day}} \times \frac{200\ \text{actuations}}{\text{canister}} \times \frac{1\ \text{day}}{12\ \text{actuations}} \times (1 - \text{uncertainty})$$

$$\text{Final AET} = \frac{2.5\ mg}{\text{canister}} \times \left(1 - 0.29\right) = \frac{1.8\ mg}{\text{canister}}$$

$$\text{Final AET} = \frac{2.5\ mg}{\text{canister}} \times (1 - 0.5) = \frac{1.3\ mg}{\text{canister}}$$

Detection Method Comparisons (Rough)

HPLC-UV	1-10 ng per 25 µL injection
GC-MS	0.01-2 ng per 1 µL injection
GC-FID	0.01-1 ng per 1 µL injection

Final AET Preparation Concentrations-MDI Example

HPLC-UV	0.1-0.4 µg/mL or ~3 canisters per mL
GC-MS	0.01- 2 µg/mL or ~2 canisters per mL
GC-FID	0.01-1 µg/mL or ~1 canister per mL

Estimate AET- Nasal Spray Example

For Nasal Sprays, the Working Group recommends setting the
AET = SCT (0.15 µg TDI)

Consider Example Nasal Spray Drug Product

- 120 labeled actuations per container
- 4 actuations per day
- 10 mL fill volume

Final AET-
Nasal Spray Example

$$\text{FINAL AET} = \frac{0.15\ mg}{\text{day}} \times \frac{120\ \text{actuations}}{\text{container}} \times$$

$$\frac{1\ \text{day}}{4\ \text{actuations}} \times \frac{1\ \text{container}}{10\ \text{mL per container}} \times (1 - \text{uncertainty})$$

$$\text{Final AET} = \frac{0.45\ mg}{\text{mL}} \times (1 - 0.29) = \frac{0.32\ mg}{\text{mL}}$$

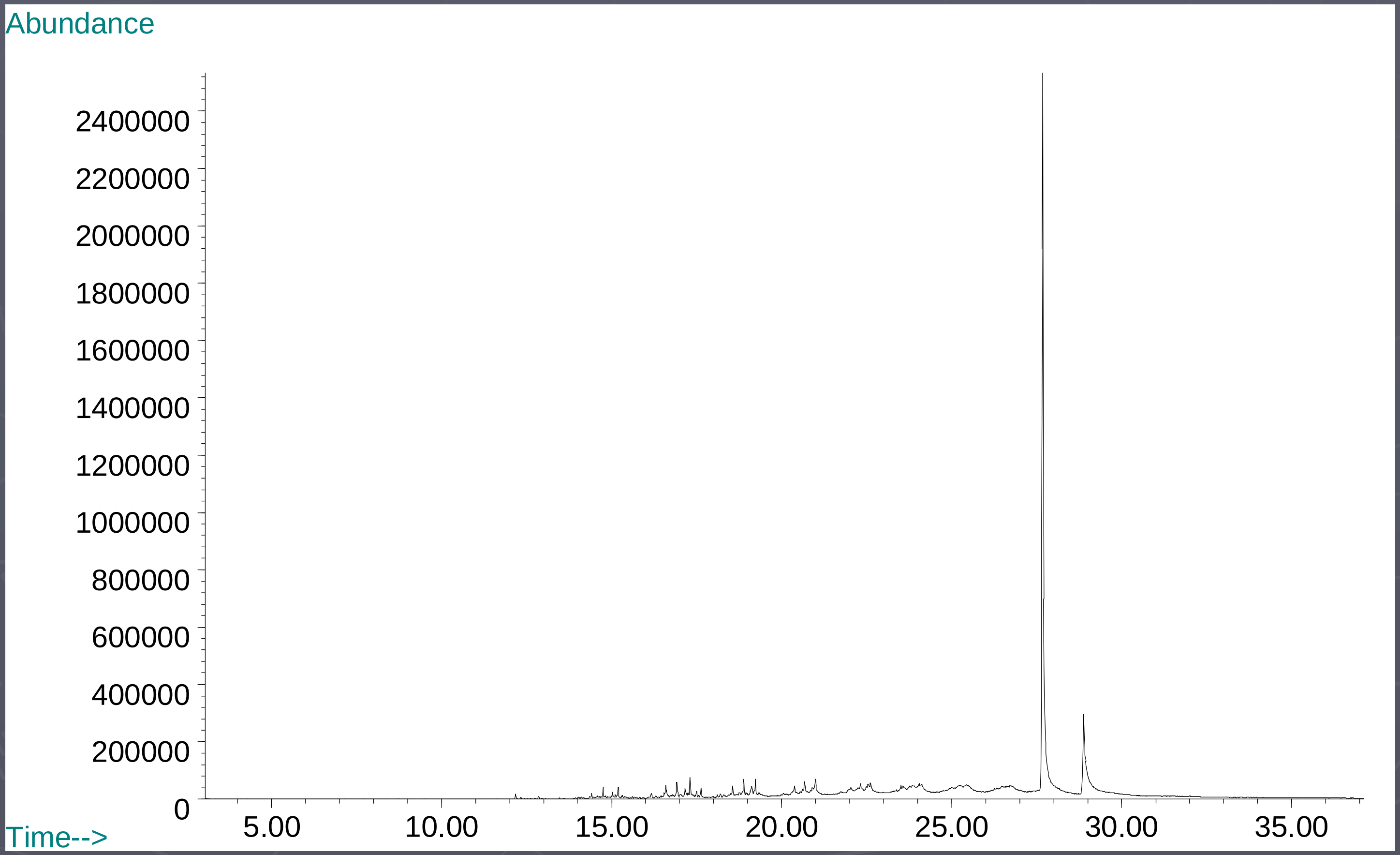
$$\text{Final AET} = \frac{0.45\ mg}{\text{mL}} \times (1 - 0.5) = \frac{0.23\ mg}{\text{mL}}$$

Final AET Preparation Concentrations-Nasal Spray Example

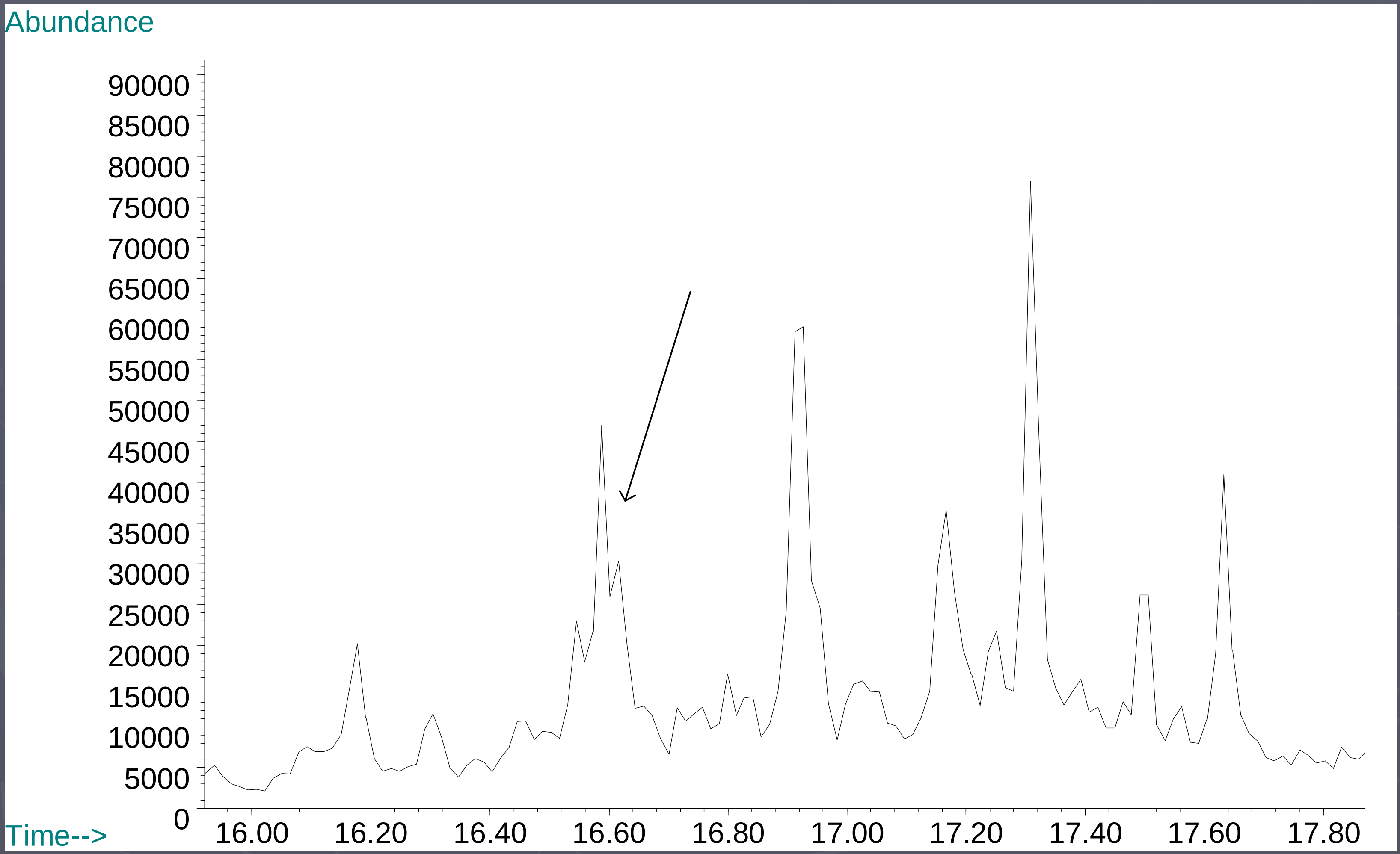
HPLC-UV	0.1-0.4 µg/mL or ~2x concentration
GC-MS	0.01- 2 µg/mL or ~10x concentration
GC-FID	0.01-1 µg/mL or ~4x concentration

Pick the “Right” Technique

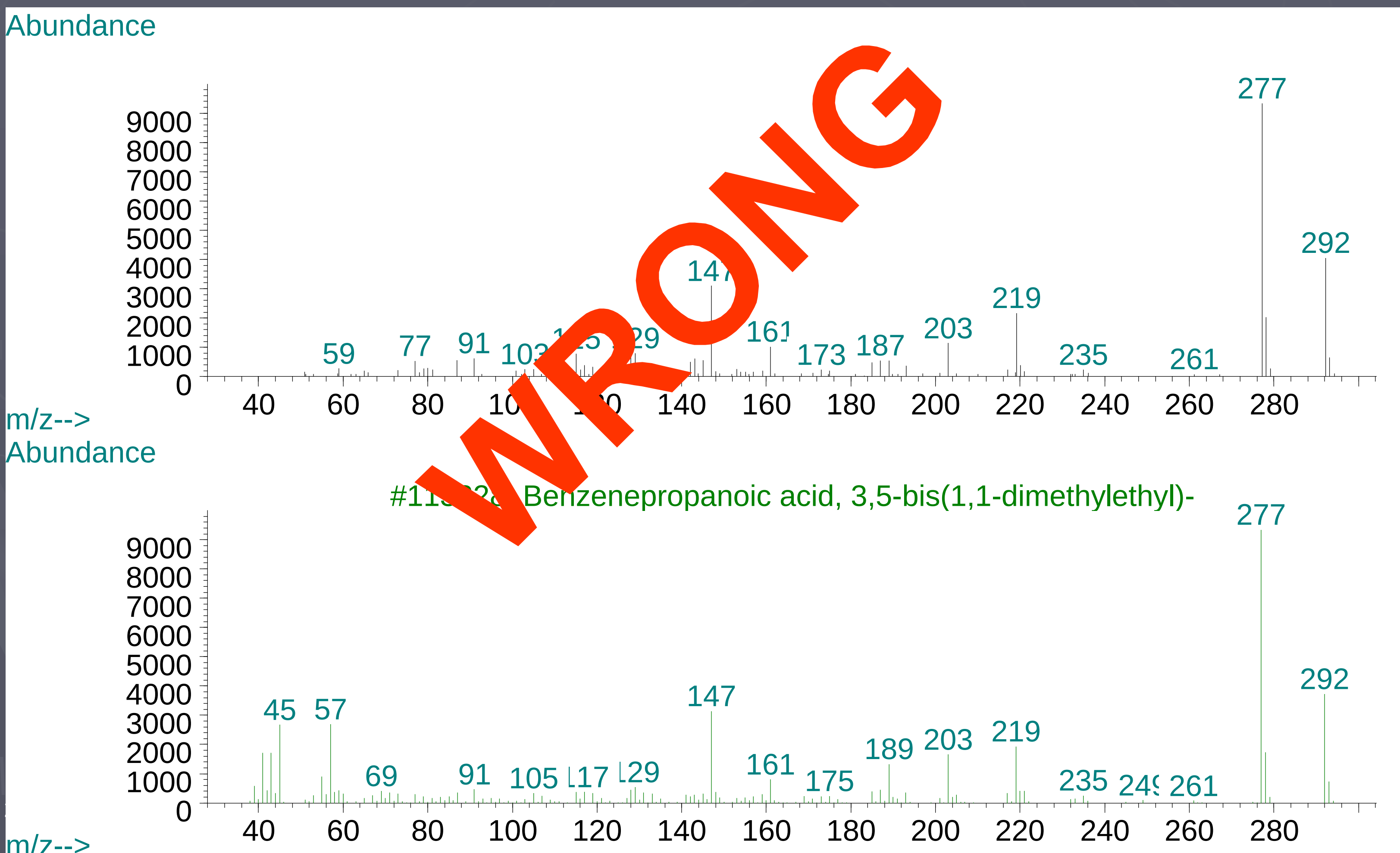
- GC-MS



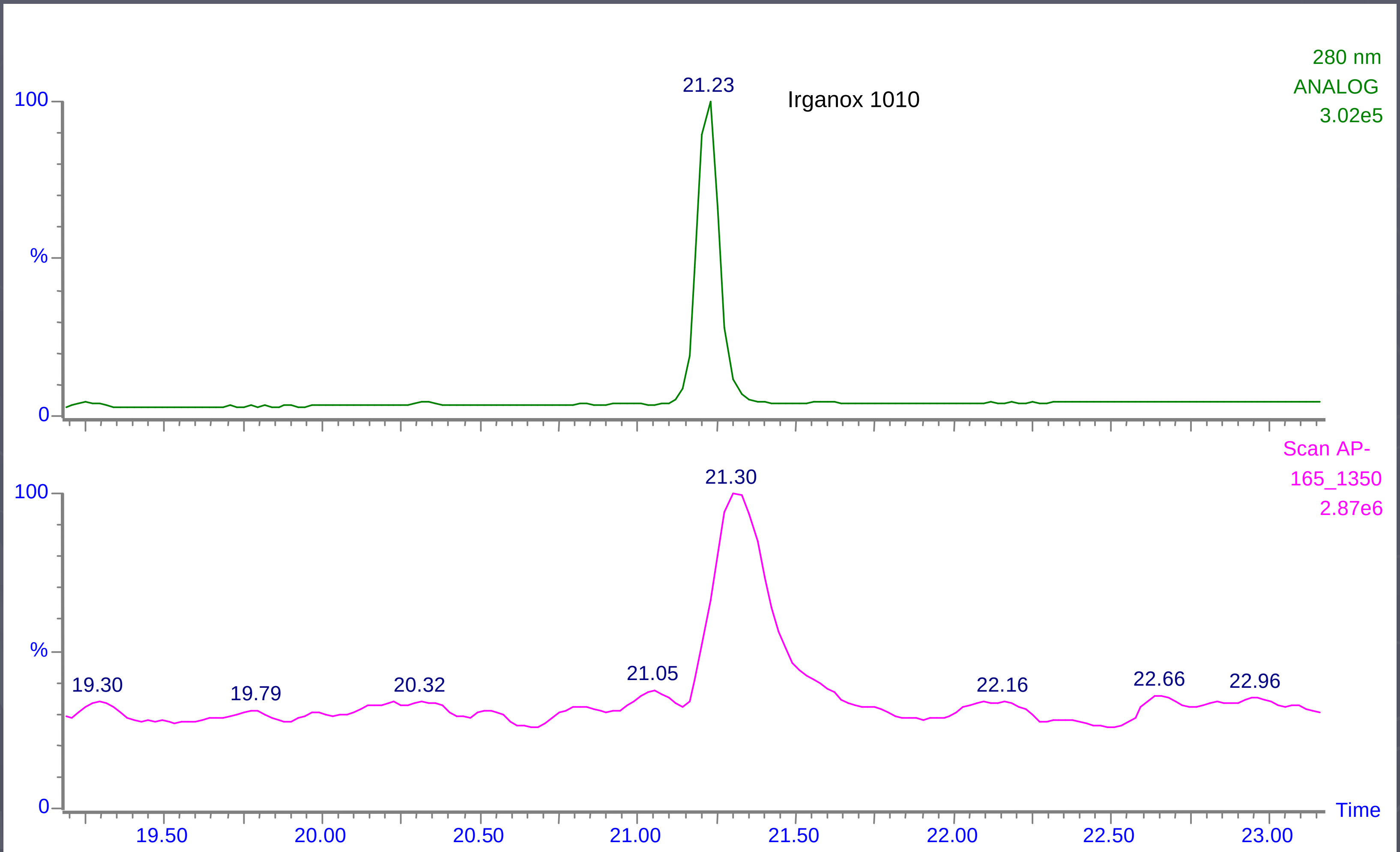
Digging in the GC-MS Baseline



Identify your New Leachable



Better Technique



Validate

Typically use same validation criteria as impurity methods depending on situation

- Quantitative
- Limits Test

What Type of Validation?

Type of Tests / Characteristics	Identification	Testing for Impurities Assay		AssayDissolution (Measurement Only), Content/Potency	Specific Tests
		Quantitative	Limit		
Accuracy	-	+	-	+	+4
Precision-Repeatability	-	+	-	+	+4
Precision-Intermediate Precision	-	+1	-	+1	+4
Specificity	+2	+	+	+5	+4
Detection Limit	-	-3	+	-	-
Quantitation Limit	-	+	-	-	-
Linearity	-	+	-	+	-
Range	-	+	-	+	-
Robustness	-	+	-3	+	+4

NOTE:
- Signifies that this characteristic is not normally evaluated.
+ Signifies that this characteristic is normally evaluated.
1 In cases where reproducibility has been performed, intermediate precision is not needed.
2 Lack of specificity for an analytical procedure may be compensated for by the addition of a second analytical procedure.
3 May be needed in some cases.
4 May not be needed in some cases.
5 Lack of specificity for an assay for release may be compensated for by impurities testing.

Validation Criteria

- Mass concentrations (mass of target divided by mass of whole sample) usually sub ppm range

- Horwitz Curve suggests Inter-Laboratory Agreements ≥16%

- Criteria for Assay NOT appropriate and not justified

Samples

Consistent samples are usually not available

Create by spiking samples to be used for:

1. Repeatability
2. Intermediate Precision
3. Accuracy
4. Sample Solution Stability (solution stability)
5. Specificity

Leachables Testing-
Stability Testing

- Best if drug product used same lots of components as investigated under Controlled Extraction Study
- Can be part of registration stability
- 3 lot minimum recommendation

Leachables Testing-Goals

1. To help establish an extractables/leachables correlation.
2. To understand the trends in drug product leachables levels over the shelf-life of the product.
3. To determine maximum leachables levels up to the proposed shelf-life.
4. To support a comprehensive safety evaluation of the drug product leachables.
5. To establish leachables specifications and acceptance criteria as required.

Correlation of Leachables and Extractables

- Can be both *qualitative* and *quantitative*

- *Qualitative* correlation can be established if all compounds detected in validated leachables studies can be linked, either **directly** or **indirectly** to an extractable identified in the Controlled Extraction Study

Direct Correlation- Example

I. Stearic acid is a known ingredient in an MDI valve
II. Stearic acid is *confirmed* by GC/MS analysis of methylene chloride extracts of valves.
III. Stearic acid is *confirmed* by a validated leachables method in drug product batches.

Indirect Correlation-Example

I. Stearic acid is a known ingredient in an MDI valve
II. Stearic acid is *confirmed* by GC/MS analysis of methylene chloride extracts of valves.
III. Ethyl stearate is *confirmed* by a validated leachables method in drug product batches.
IV. The MDI formulation contains ethanol which can react with stearic acid to form ethyl stearate.

Quantitative Correlation

- Can be made if the level of the leachable is demonstrated to be consistently less than that of the extractable(s) to which it is qualitatively correlated.
- Best accomplished using data from significant numbers of component batch analyses using validated Routine Extractables Testing analytical methods.

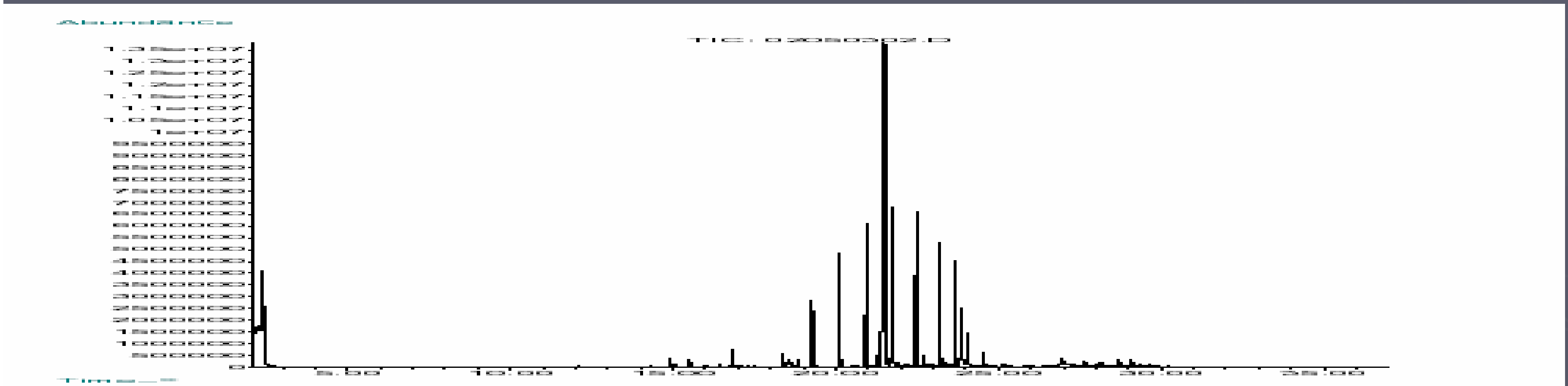
Quantitative Correlation- Example

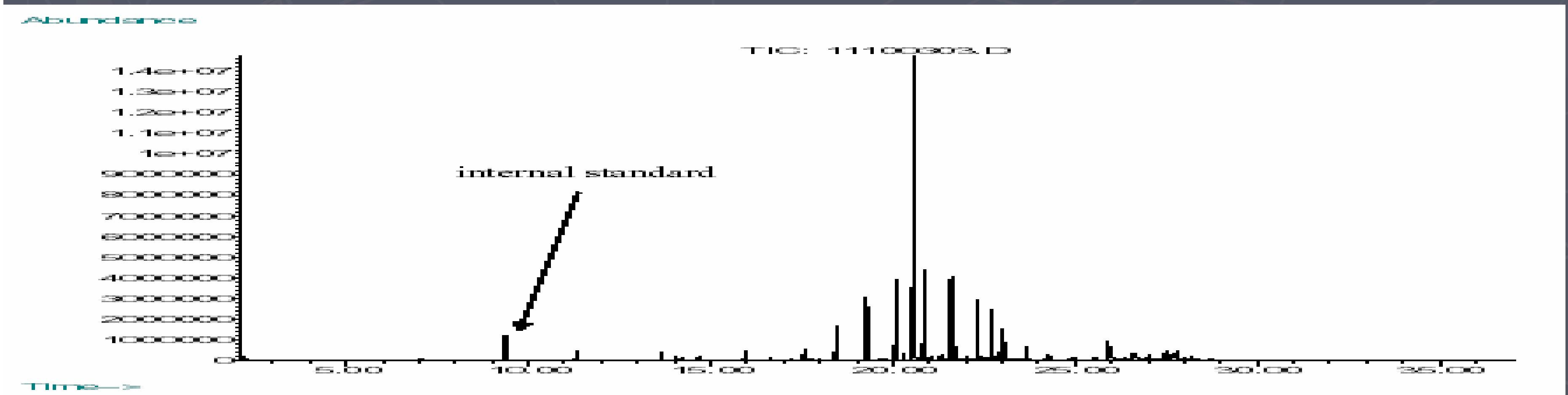
I. Stearic acid has been shown to have a qualitative leachables/extractables correlation.
II. Comprehensive Leachables Studies show the maximum level of stearic acid in drug product is 50 µg/canister; across all registration batches, storage conditions, orientations through proposed end of shelf-life.
III. Analysis of 50 batches of components using validated Routine Extractables Testing method quantitates stearic acid at 800 µg/g with 12.5% RSD.
IV. Given that there is one 150 mg critical component per valve, the anticipated maximum level of stearic acid would be 120 ± 15 µg/canister.

Appropriate Analytical Methods

- "Analytical methods for the qualitative and quantitative evaluation of Leachables should be based on analytical technique(s)/method(s) used in the Controlled Extraction Studies. "

Similar Methods Ease Correlation Establishment





Use the AET

- “Leachables Studies should be guided by an Analytical Evaluation Threshold (AET) that is based on an accepted safety evaluation threshold.”

Determine Final AET

- Determine Estimated AET by converting SCT to units relative to an individual OINDP (e.g, µg/canister, µg/gram component, etc.).
- Evaluate analytical uncertainty and Final AET:

Final AET =

Estimated AET x (1- analytical uncertainty)

Where analytical uncertainty = Max (%RSD or 0.5)

Establish Correlations

- "A comprehensive correlation between extractables and leachables profiles should be established."

Set Leachables Specifications

- "Specifications and acceptance criteria should be established for leachables profiles in OINDP. "

- ***"if tested will comply"***

Validate Methods

- "Analytical methods for Leachables Studies and Routine Extractables Testing should be fully validated according to accepted parameters and criteria."

Special Cases are “Special”

- “Polyaromatic Hydrocarbons (PAH’s; or Polynuclear Aromatics, PNA’s), N-nitrosamines, and 2-mercaptobenzothiazole (MBT) are considered to be “special case” compounds, requiring evaluation by specific analytical techniques and technology defined thresholds for Leachables Studies and Routine Extractables Testing.”

Controlled Extraction Studies are Crucial for Correlation

- "If a qualitative and quantitative correlation cannot be established, the source of the problem should be determined and corrected. Potential sources include excessive variability in component composition and/or manufacturing processes, changes in drug product formulation, inadequate Controlled Extraction Studies, and inappropriate or poorly validated leachables and extractables methods."

Specifications and Acceptance Criteria

- Leachables specifications should include a fully validated analytical test method. The acceptance criteria for leachables should apply over the proposed shelf-life of the drug product, and should include:
  1. Quantitative limits for known drug product leachables monitored during product registration stability studies.
  2. A quantitative limit for “new” or “unspecified” leachables not detected or monitored during product registration stability studies.

Leachables Specifications

- "The Working Group emphasizes that the requirement for establishment and implementation of leachables specifications and acceptance criteria for any particular OINDP is a regulatory policy matter, and therefore considered to be outside the scope of the Working Group's consideration. "

Conclusion

- Development is a Process
- "Qualitative and quantitative leachables profiles should be discussed with and reviewed by pharmaceutical development team toxicologists so that any potential safety concerns regarding individual leachables are identified as early as possible in the pharmaceutical development process."