Essential Principles of Chemical Characterization (Extractables and Leachables) Applied to Small Volume Parenterals (SVPs)

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Presentation Outline

1. Suitability for Use; Drug Products and their Packaging Systems
2. Introduction to Chemical Characterization (Extractables and Leachables)
3. Material Characterization, Selection and Qualification
4. Packaging Systems Characterization and Qualification (Extractables)
   - ✓ Extractable Studies: General Considerations
   - ✓ Extractable Studies: Generating the Extract
   - ✓ Extractable Studies: Analyzing the Extract
5. Packaged Drug Product Characterization and Qualification (Leachables)
6. Simulation Studies when Leachables Studies are not Possible

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1. Suitability for Use; Drug Products and their Packaging Systems

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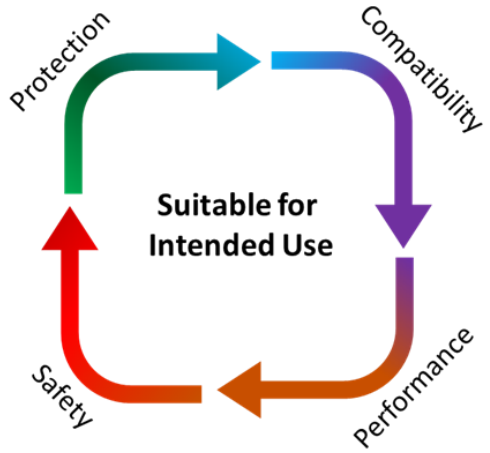
The Essential Expectation for Drug Product Packaging

Every proposed packaging system should be shown to be **suitable for its intended use**:

- It should be adequately **protect the dosage form**;
- It should **be compatible with the dosage form**;
- It should **be** composed of materials that are **considered safe for use with the dosage form** and the route of administration.
- If the packaging system has a performance feature in addition to containing the product, the assembled container closure system should be shown to **function properly**.



Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics.
CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1999

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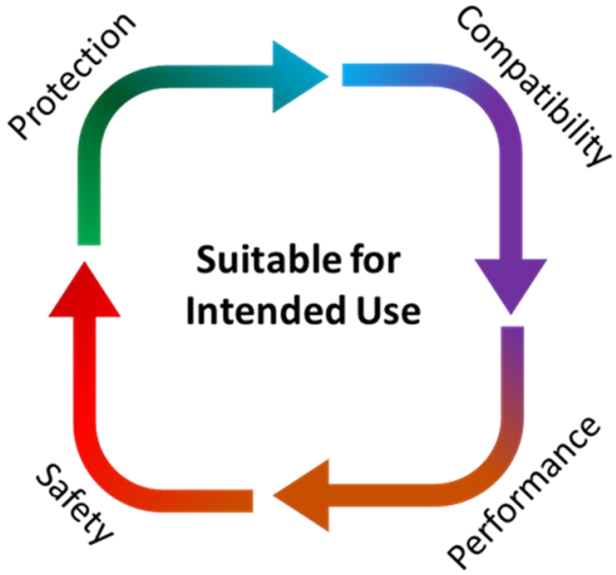
Qualification of Packaging and Packaging Systems

A packaging system is qualified as being suited for its intended use when it has been established that the packaging system is:

- Protective
- Functional
- Compatible
- Safe



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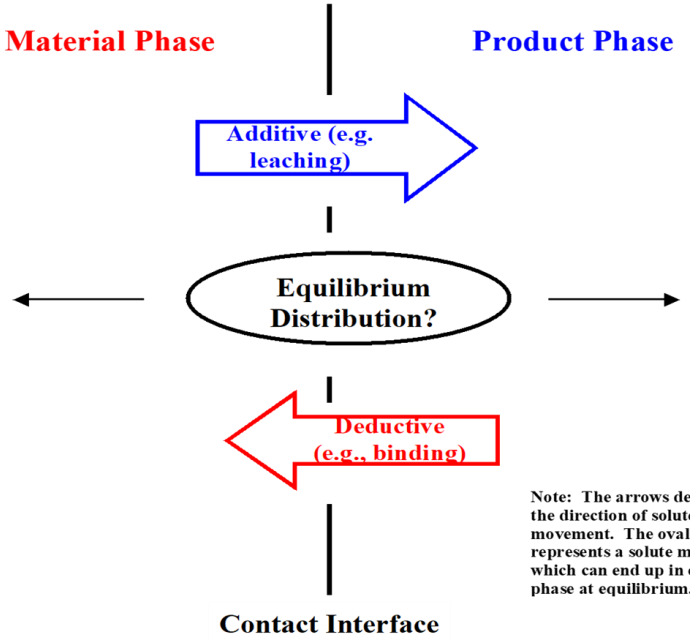
Problem Statement: Suitability for Use

- Contact between a drug product and a system (such as its packaging) provides the opportunity for the two to interact.
- When the drug product and the system interact, the interaction may affect the composition of the drug product and/or the system.
- The resultant change in the composition of the drug product and/or system may adversely impact the drug product's (or system's) ability to perform in its desired, necessary and required manner (i.e., produce the expected clinical outcome).



Suitability for Use - Compatibility

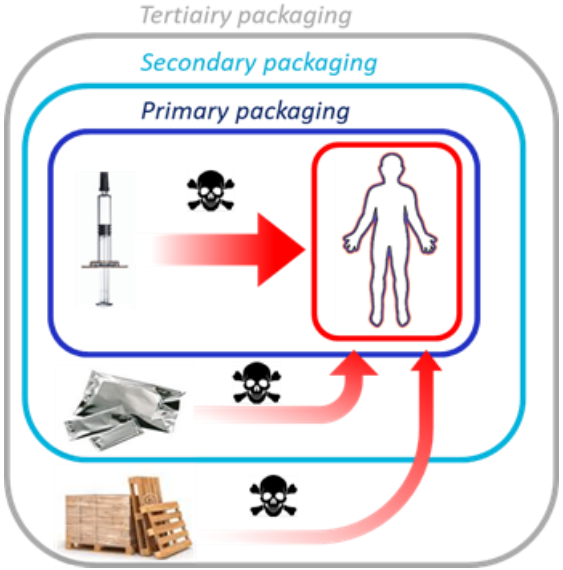
- Packaging components that are compatible with a dosage form **will not** interact sufficiently to **cause unacceptable changes in the quality of** either **the dosage form or the packaging** component.

- Examples of interactions include:

  - loss of potency due to absorption or adsorption of the active drug substance;
  - degradation of the active drug substance induced by a chemical entity leached from a packaging component;
  - reduction in the concentration of an excipient due to absorption, adsorption or **leachable**-induced degradation;
  - precipitation;
  - changes in drug product pH;
  - discoloration of either the dosage form or the packaging component;
  - or increase in brittleness of the packaging component.

Suitability for Use - Safety

- Packaging components should be constructed of **materials** that **will not leach** harmful or undesirable amounts of substances to which a patient will be exposed when being treated with the drug product



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2. Introduction to Chemical Characterization (Extractables and Leachables)

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Introduction to Chemical Characterization (Extractables and Leachables)

Extractable:

- A substance that is extracted from a resin, material, part, component, system or device via a solvent under specified laboratory conditions of contact including temperature, duration, stoichiometry, extraction technique, etc.

Leachable:

- A substance that is present in a finished drug product as a result of its contact with a packaging system under the actual product conditions of distribution, storage and use.

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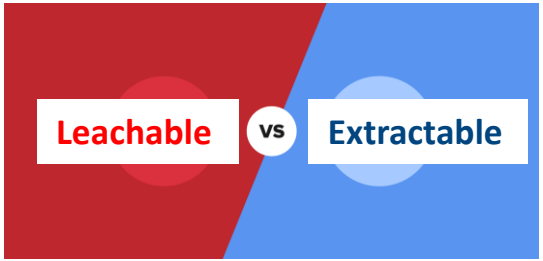
The Relationship between Extractables and Leachables

- The terms **Extractable** and **Leachable** provide clarity in terms of:



✓ The impact of the chemical on the user of the product.

- **Extractable** = potential impact
- **Leachable** = actual impact

✓ The object on which the testing is performed.

- **Extractable** = test the material or package
- **Leachable** = test the finished product

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Regulatory Requirements : What

- Regulatory Aspects - Parenterals*

<1999: 21CFR 211.94(a) “DRUG PRODUCT CONTAINERS AND CLOSURES”

1999: “CONTAINER/CLOSURE SYSTEMS FOR PACKAGING HUMAN DRUGS AND BIOLOGICS” (FDA-Guidance for Industry)
Classification, based on likelihood of interaction and route of administration

2003: EU COMMISSION DIRECTIVE 2003/63/EC, § 3.2.2.2 g
CCS-information is part of the Market Authorization dossier.

2005: “GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS” (EMEA Guideline)
“Decision Tree” what information to provide for different dosage forms

2006: ICH Q8 “PHARMACEUTICAL DEVELOPMENT”, § 2.4 CCS

2014: USP <1663> (Extractables) & USP <1664> (Leachables)

2015: ICH M7: DNA reactive impurities in Pharmaceuticals

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*(Non limitative List)

Regulatory Expectations – US – C/C-Guidance (1999) & USP

Examples of PACKAGING CONCERNS for Common Classes of Drug Products			
Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Components – Dosage Form Interactions		
	High	Medium	Low
Highest	Inhalation Aerosols and Sprays	**Injections and Injectable Suspensions;** Inhalation Solutions	***Sterile Powders and Powders for Injection;*** *Inhalation Powders*
High	Transdermal Ointments and Patches	Ophthalmic Solutions and Suspensions; Nasal Aerosols and Sprays	-
Low	Topical Solutions and Suspensions, Topical and Lingual Aerosols, Oral Suspensions and Solutions	-	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules; Topical Powders; Oral Powders

LYO

Revision of "Table 1" in USP <1664>,
Originally Included into the FDA (Draft) Guidance for Industry (1999):
"Container/Closure systems for Packaging Human Drugs and Biologics"

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Regulatory Expectations – US

The FDA Guidance Document "*Container Closure Systems for Packaging Human Drugs and Biologics*" of **1999**

DOES NOT reflect the current (2022) FDA requirements for E/L Testing and Documentation:

- **Extractables and leachables studies are routinely required for virtually every drug product and every dosage form.**
- **Extractables studies, including simulation studies, are rarely accepted as adequate evidence of suitability for use without also leachables studies.**
- **The expected "level of science" applied to extractables and leachables study is significantly more rigorous and challenging to achieve.**

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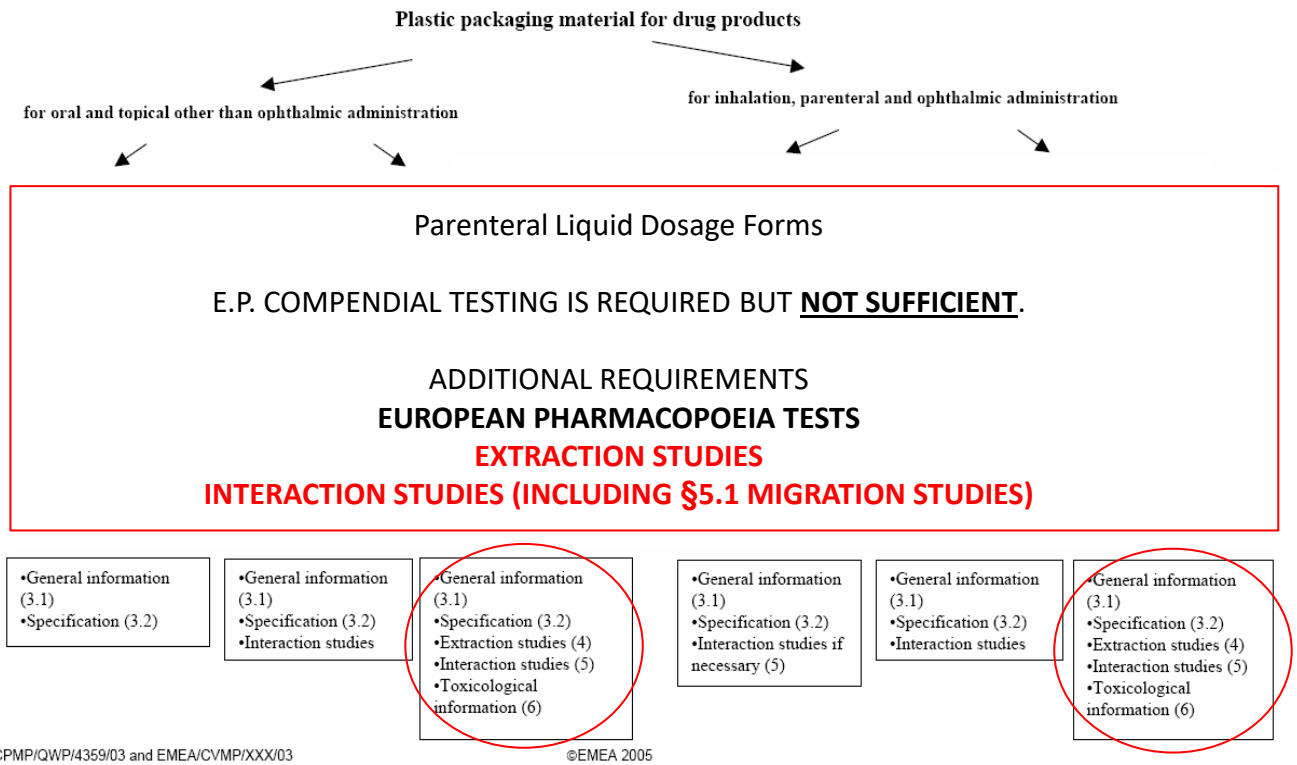
Regulatory Exectations – EU – Plastic Immediate Packaging Materials (2005)

- Going through the decision tree: **liquid dosage forms – strictest requirements**



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Regulatory Exectations – EU – Plastic Immediate Packaging Materials (2005)

Some Side Notes to the EMA Immediate Packaging Guideline (2005)

- ✓ Not for Elastomers (?) = > In reality: **ALSO** used for rubber items such as closures.
- ✓ If a Material is described in the E.P. and if it complies with the specifications therein, no Extractable testing may be needed.
  - ➢ **Not the actual position of European regulators, who almost certainly require extractables studies.**
- ✓ If Extractable Testing shows only compounds with low risk (at low concentrations) no Leachable study is necessary.
  - ➢ **Not the actual position of European regulators, who almost certainly require leachables studies.**

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Essential Resources for Packaging and Packaging System Qualification

- **For Packaging Systems:**
  - USP <661.1> Plastic Materials of Construction
  - USP <661.2> Plastic Packaging Systems for Pharmaceutical Use
  - USP <1661> Evaluation of Plastic Packaging Systems and Their Materials of Construction With Respect to Their User Safety Impact
  - USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
  - USP <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery systems
  - PQRI PDP Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral (Intravenous, Subcutaneous, and Intramuscular) Drug Products
  - PQRI Principles for Management of Extractables and Leachables in Ophthalmic Drug Products. C. Houston, et al. PDA Journal of Pharmaceutical Science and Technology February 2022, pdajpst.2022.012744; DOI: https://doi.org/10.5731/pdajpst.2022.012744
  - ICH Q3E Guideline for Extractables and leachables (in preparation)
- **For Medical Devices:**
  - ISO/FDIS 10993-18: Biological evaluation of medical devices -- Part 18: Chemical characterization of medical device materials within a risk management process
  - E.M. Sussman et al. Chemical Characterization and Non-targeted Analysis of Medical Device Extracts: A Review of Current Approaches, Gaps, and Emerging Practices. *ACS Biomater. Sci. Eng.* doi=10.1021/acsbiomaterials.1c01119. 2022. (**Note that this is a scientific article not to be construed as Agency Guidance**).
- **For Components used in Manufacturing Systems:**
  - USP <665> Polymeric Components and Systems Used to Manufacture Pharmaceutical and Biopharmaceutical Drug Substances and Drug Products
  - USP <1665> Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products

3. Material Characterization, Selection and Qualification

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Material Screening and Selection

- **Test Article:** Materials of Construction
- **Purpose:** Establish the material‘s composition
- **Test Strategy:** Characterize the test article for ingredients (composition), biocompatibility and general chemical properties.
- **Typical Approach:** Exhaustive/aggressive extraction. Target and screening analysis.
- **Impact Assessment:** During the development of a packaging system, potential materials of construction are characterized and screened for use based on their characteristics. Unsuited materials are rejected, suitable materials are adopted.
- **Value Proposition:** The best means of insuring packaging suitability is to use suitable materials of construction.

Before you run to the lab...

- Collect available safety information from the material's vendor:
  - ✓ Compendial Compliance
  - ✓ Biological Reactivity Testing
  - ✓ Use in Food Contact Applications
  - ✓ Conformance to Compositional Standards
  - ✓ Formulation
  - ✓ Processing
  - ✓ Extraction testing

- Oftentimes, the above information alone may be sufficient to support a selection decision.
- Furthermore, these types of information create a preponderance of evidence, which may make up for gaps in extractables or leachables testing when making and supporting a claim of safe for its intended use.

Important Note: Material information, especially when used to support material selection, is rarely required in a regulatory submission and is almost never adequate to qualify packaging.

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Pillars of Evidence that a Material of Construction is Safe

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The Importance of Material Characterization

Materials cannot be qualified as being inherently safe and therefore there is no regulatory value escribed to material characterization.

However

- If the materials of construction are well-characterized and an assessment of the characterization data suggests that they are suitable for their intended use,

Then

- It is likely that the packaging system assessment will be favorable (less likely that there will be unpleasant surprises during E&L and biocompatibility studies).

Additionally

- Material Characterization data may be the proper basis of managing change control.

4. Packaging System Characterization and Qualification - Extractables

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4a. Extractable Studies: General Considerations

Acceptable Practices

- **USP <1663> Monograph**

  "Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems"

  This is an **INFORMATIONAL** monograph.

- PQRI – **Parenteral & Ophthalmic Drug Products (PDP and ODP)**

  Best Demonstrated Practice Recommendations: **Chemistry** & Toxicology

  These are **RECOMMENDATIONS.**

As was noted earlier, the official regulatory Guidance and Guidelines DO NOT reflect current regulatory requirements and thus provide little direction in terms of the proper design and execution of extractables studies. One learns what the current regulatory requirements are by experiance secured in regulatory deficiency letters and the like.

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Acceptable Practices

- These two documents are either **INFORMATIONAL** or **RECOMMENDATIONS**

  ✓ **Allow flexibility in design**

  What is the intent? => **Strategy** of testing

  How to design the study for the envisioned intent? => **Tactics**

  ✓ **However, justification is needed**

  Both **identifying the necessity** for an extraction study,

  as well as **justifying the design**,

  is the responsibility of the holder of the NDA.

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What is the PURPOSE of an Extraction Study?

- Material characterization of the packaging components (as noted previously)
- "Impurities profiling" of the materials
  - ✓ Identify as many compounds as possible
  - ✓ Identify "bad actors" in the materials
  - ✓ Establishes the worst case that "it all comes out"
- Forecast leachables profile; extractables as probable leachables
- Establish leachables – extractable correlations
- Extablish target compounds to be monitored as leachables in leachables studies
  - ✓ Toxicity
  - ✓ Concentration in the materials
  - ✓ Risk for migration
- In certain cases (more applicable to OINDP): Facilitates extractable specifications for incoming raw materials.

The purpose of an extraction study dictates it design.

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Design Space for an Extractables Study

- **Factors** that impact the design of an extractables study

  - ✓ The **classification & specific requirements** per drug product
    - Table 1 in FDA C/C-Guidance (1999)
    - Decision tree in the EMA-Guideline (2005)
  - ✓ The **composition of the DP,** in contact with the C/C system
  - ✓ The **type of contact** between the DP and the C/C system
    - Primary packaging
    - Secondary packaging (e.g. needle shield, label,...)
  - ✓ The C/C's **materials on construction**
    - e.g., rubber versus polyolefin for BFS
  - ✓ The **knowledge of the composition** of materials (from vendor)
    - Additives, catalysts, oligomers, colorants,...
  - ✓ The **use of the data**
    - Only for this particular application, or also for other DP?

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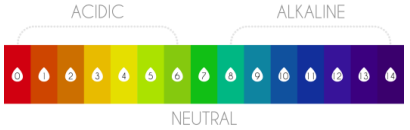
4b. Extractable Studies: Generating the Extract

Design of an Extractables Study: Extraction

Extraction Solvents

Polarity,...

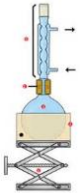


pH

Extraction conditions

Time & Temperature

Autoclave



Reflux

Incubation (shaking)

Extraction ratio

Surface area to solution volume

Extraction Solvents

UPW	UPW	UPW/IPA	IPA	Hexane
pH 2.5	pH 9.5	(50/50)		
Acidic, polar extractables	Basic, polar extractables	Intermediate polarity	→	Non-polar

SIMULATION

MATERIAL CHARACTERIZATION & SIMULATION (NON AQUEUOUS DP)

Recommendations:

- It is not mandatory to always include these 5 solvents
- The solvents should be adjusted to the physico-chemical properties of the DP
- Justifications!!

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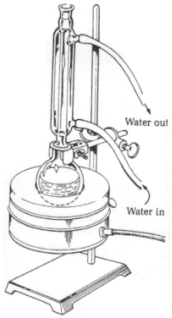
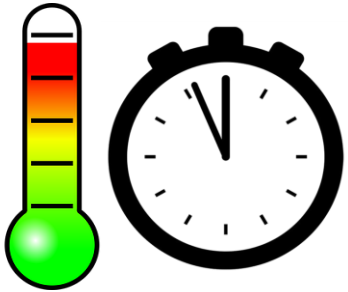
Extraction Time and Temperature

- USP<1663> “Generating the extract” section “Extraction time and temperature”

  - ✓ The combination of extraction time and temperature establishes the magnitude of the driving force and the degree to which equilibrium is achieved

  - ✓ Time and temperature are closely linked to the extraction technique that is used





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Extraction Time and Temperature

- **Possible temperature / time combinations:**
  - ✓ Reflux with organic solvents:
    - ➢ Boiling temperature, 8 h
  - ✓ Soxhlet with organic solvents:
    - ➢ Boiling temperature, 24 h
  - ✓ Sonication:
    - ➢ Room temperature, ½ to 1h
  - ✓ Sealed vessel and “in situ” extraction:
    - ➢ 50°C, 72 h (ISO 10993-12 which is for medical devices and NOT packaging)
    - ➢ 24h below boiling point of extraction solvent = equivalent to 8h reflux
  - ✓ Headspace enrichment:
    - ➢ 40 minutes, temperature is selected based on the type of material (from 70°C for LDPE up to 150° for rubbers / elastomeric material)
  - ✓ Dynamic Extractions:
    - ➢ Extraction conditions are determined based upon the conditions of use

Extraction Stoichiometry

- **Stoichiometry: physical mass/surface area to volume**

✓ Can be based on

- ➢ Known chemical ingredients in a component/material
- ➢ Safety based thresholds for DP leachables
- ➢ Known sensitivities of the analytical instrumentation

✓ Stoichiometry can be manipulated to produce a more concentrated extract

REMARK: beware of solubility of extractables in extraction medium when “back extrapolating” to original ratio’s!

✓ Physical state can be altered (cut, ground, altered in size...)

Extraction Stoichiometry

- Try to stay as close as possible to the ratio's of the actual use of the container

  Example

  A rubber plunger for a 10 mL PFS could be extracted at a ratio of 1 plunger per 10 mL of solvent

- For raw materials, a reasonable ratio is 1g/10mL

- For certain container closure systems (e.g., larger fill volume SVP), the final AET that may need to be considered as it might impact the extraction ratio

  Example

  For a 100 mL bag (bag weighs 10g), the unadjusted AET for a chronically administered DP is 15 µg/L. This AET may not be analytically achievable unless the extracted surface area to solution volume ratio is changed (for example, underfilling the bag).

4c. Extractable Studies: Analyzing the Extract

Analyses of the Extracts

- What has come out of the material?

Packaging Material

Extraction Solvents

Extraction conditions

Extraction ratio

Analyses of the extracts

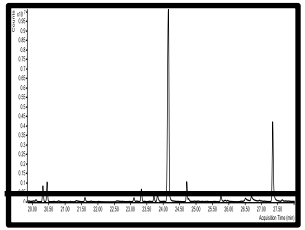
CHROMATOGRAPHIC SCREENING FOR ORGANIC EXTRACTABLES

DISCOVER ALL COMPOUNDS

ABOVE A TOX THRESHOLD (AET)

IDENTIFY ALL COMPOUNDS

(SEMI-)QUANTIFY ALL COMPOUNDS



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CHROMATOGRAPHIC SCREENING FOR ORGANIC EXTRACTABLES

DISCOVER
ALL COMPOUNDS

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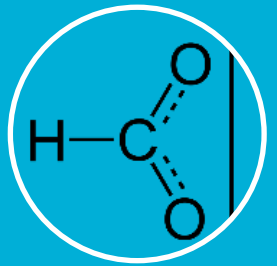
Analyses of the Extracts

Discover all extractable compounds: Orthogonal and complementary methodes

VOC	SVOC	NVOC		
				
HS-GC/MS	GC/MS	UPLC/MS	ICP/OES	IC
Screening Volatiles	**Screening Semi-Volatiles**	(LC/UV, LC/CAD etc.) **Screening Non-Volatiles**	ICP/MS GF/AAS **Extracted Elements**	**Extracted anions**

Extractables Profile : Potentially Leaching Compounds of Concern

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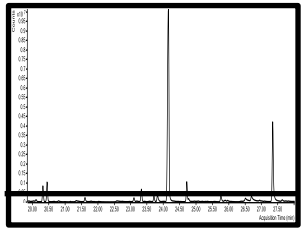
CHROMATOGRAPHIC SCREENING FOR ORGANIC EXTRACTABLES

DISCOVER
ALL COMPOUNDS

ABOVE A TOX
THRESHOLD (AET)



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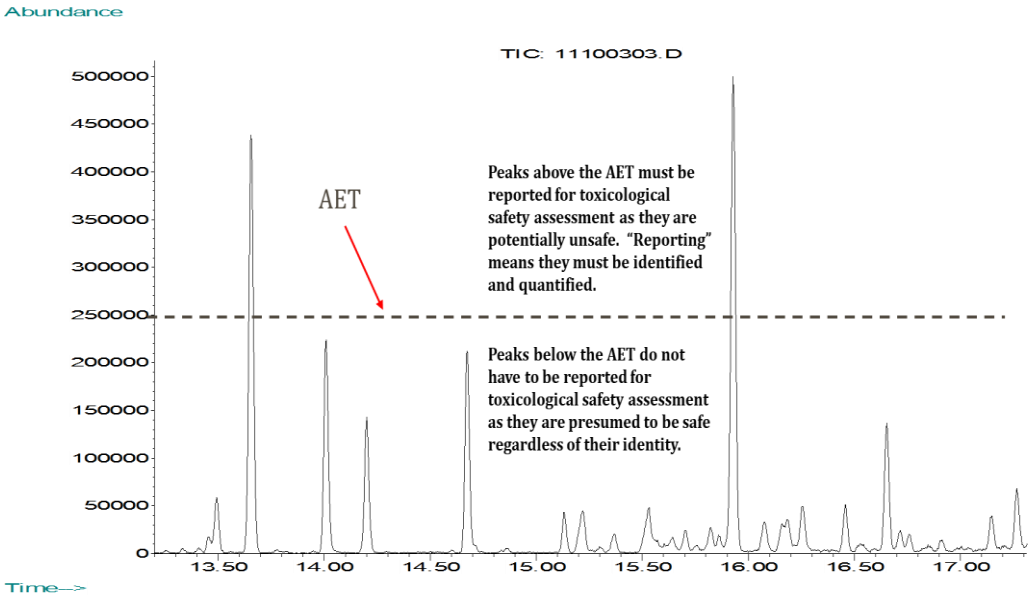
Discover all extractable compounds: Above a Relevant Threshold

The AET Concept



The Analytical Evaluation Threshold (AET): that concentration of an extractable or leachable below which the compound does not have to be reported for safety assessment as its adverse effect on safety is negligible.

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Discover all Extractable Compounds: Above a Relevant Threshold

The AET Concept

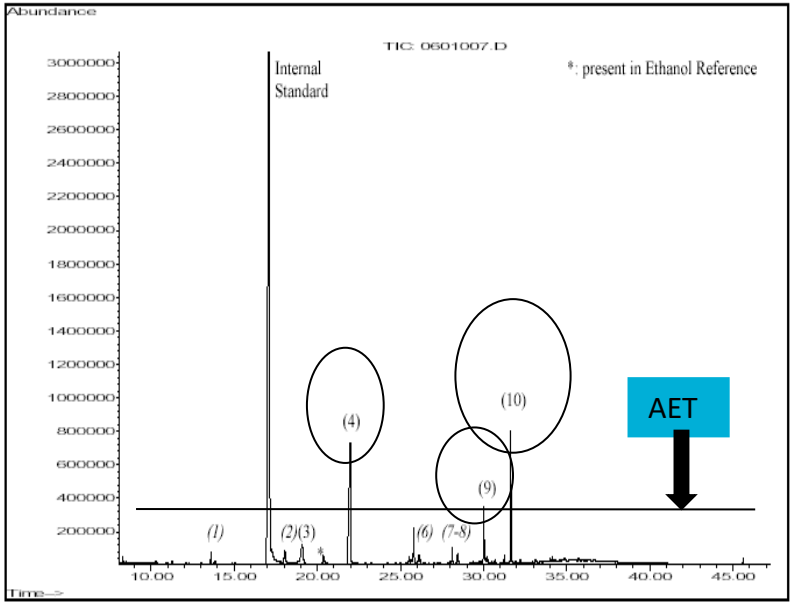
AET: Analytical Evaluation Threshold

Translate SCT

↓

into Analytical Threshold
for Extractable Studies

Taking into account:
- *Total N° of doses / packaging*
- *Max. N° of doses administered / day*



AET = ACTION LIMIT

ACTION = IDENTIFY and (SEMI-) QUANTIFY all compounds above the AET

Analyses of the Extracts

Discover all extractable compounds: Above a Relevant Threshold

The AET Concept

SCT: **S**AFETY **C**ONCERN **T**HRESHOLD

"Threshold below which a leachable would have a **dose so low** as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects"

PQRI for **OINDP's**: SCT = 0,15 µg/day

PQRI for **PDP's**: SCT = see next slide

Exceptions: MBT, Nitrosamines, PNA's and "coherts of concern": as low as possible!

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Discover all Extractable Compounds: Above a Relevant Threshold

The AET Concept

SCT: **For Parenteral Drug Products (PDP's)**

Tox Endpoint	Others	Sensitizer & Irritant	Carcinogen
Class	Class I	Class II	Class III
Threshold Level (µg/day)	50	5	1.5

SCT for Non-Chronic Treatments

SCT for Chronic Treatments

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Discover all Extractable Compounds: Above a Relevant Thrshold

The AET Concept

Non-Chronic Treatment

Example :
1 Dose per day, administered to the Patient
Vial containing 1 Dose
1 vial = 1 stopper (ext study on stopper)
Uncertainty factor UF (here; 2 as an example)

Extractables AET	Leachables AET

For SVP: try to extract the components with a solvent volume = volume of the DP in contact with the C/C-system

1 stopper extracted in 10 mL of **solvent** ***Assessment of Extractables of the Rubber Stopper***	Per vial, 10 mL of Drug Product is stored ***Assessment of the Leachables in Drug Product***

$$\text{AET} = \frac{\textbf{5 µg/day}}{\text{1 Dose/day}} \cdot \frac{\text{1 Dose}}{\text{vial (lea) or stopper } (ext)} \cdot \frac{vial\ (lea)\ or\ stopper\ (ext)}{10mL} \frac{1}{2\ (=\text{UF})} = 250\ \mu g/L$$

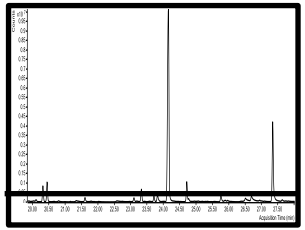
Although not mandatory, it is advisable or "good practice" to screen (as close to, or) at the AET in an extraction Study	*Per FDA, it is **mandatory** to <u>identify</u> and <u>quantify</u> all leachables above the AET (= 250 µg/L)*

CHROMATOGRAPHIC SCREENING FOR ORGANIC EXTRACTABLES

DISCOVER
ALL COMPOUNDS

ABOVE A TOX
THRESHOLD (AET)

IDENTIFY
ALL COMPOUNDS



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Discover all Extractable Compounds: Identification

- Why is Identification so important?

✓ **CORRECTLY** Linking a **Compound's Identity** to its **Toxicological Information**

✓ Identify **Bad Actors**?

✓ Important for **RRF correction** in semi-quantification (see later)

✓ Important to make a **correlation between extractables and leachables**

✓ Important to **select targets** for monitoring in **leachable studies**

- Method development & validation

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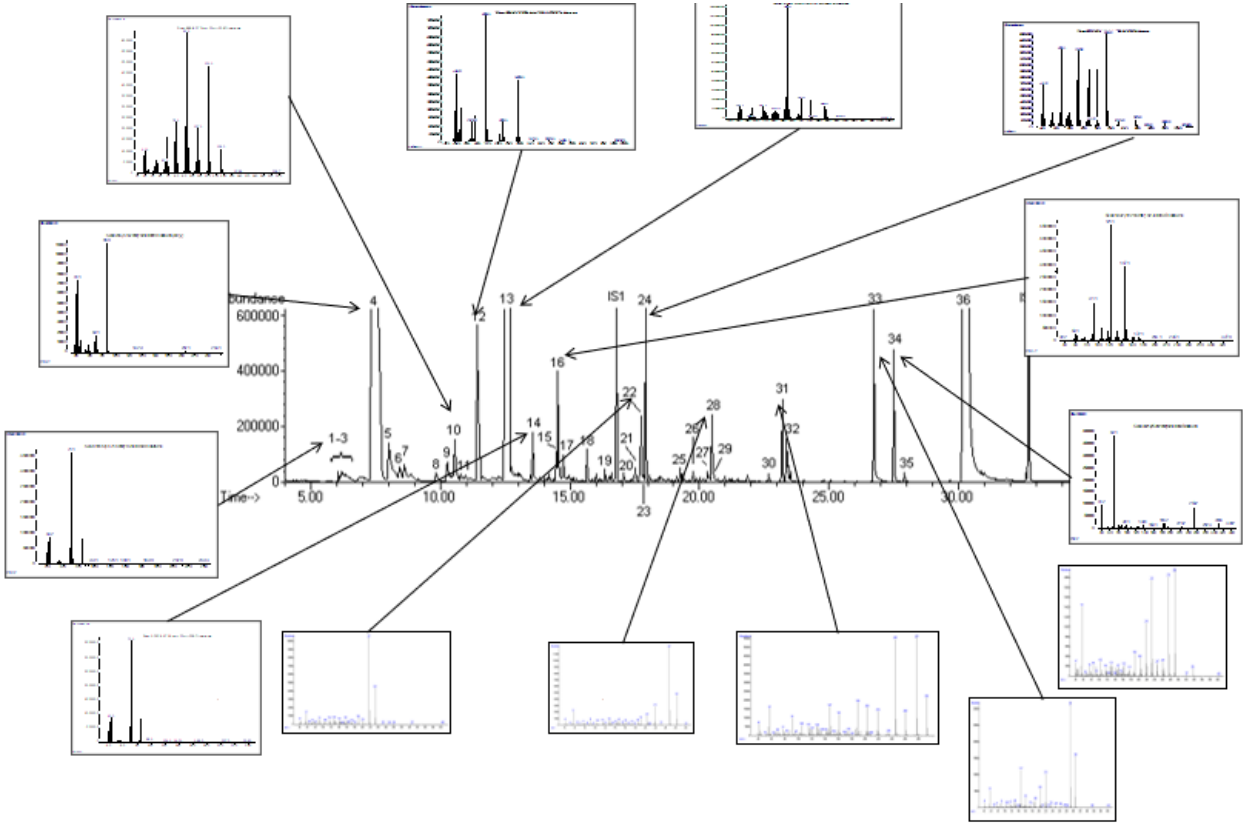
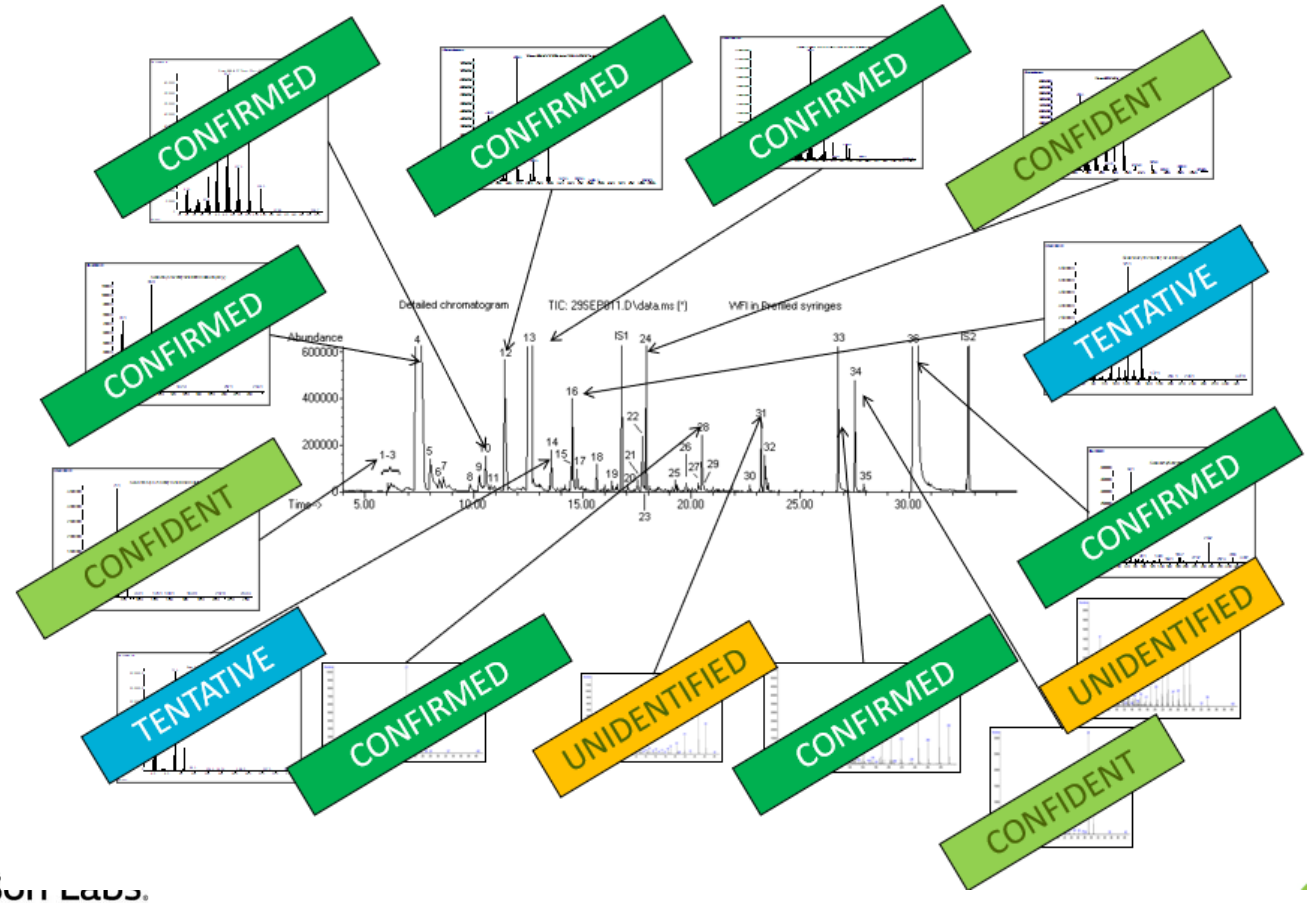
Discover all Extractable Compounds: Identification



Discover all Extractable Compounds: Identification



Discover all Extractable Compounds: Identification

CONFIRMED

- Authentic Standard Analysis (with CoA) confirms Mass Spectrum and Retention Time
- **CONFIRMED Class should be optimized** as Unequivocal Identifications are extremely important
- NELSON: the NELSON LABS Discovery and Screener Database

CONFIDENT

- Analytical Standard NOT available
- Excellent Mass Spectral Matching (MSM)with MS-library
- additional Expert Review & Verification

TENTATIVE

- Analytical Standard NOT available
- Lower fit with MS-library:
- Expert Review only reveals limited structural information, eg “Class” of compounds, Elemental Formula...

UNIDENTIFIED

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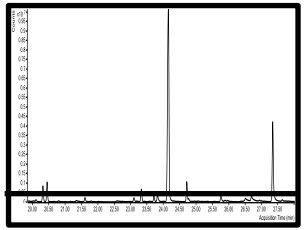
CHROMATOGRAPHIC SCREENING FOR ORGANIC EXTRACTABLES

DISCOVER ALL COMPOUNDS

ABOVE A TOX THRESHOLD (AET)

IDENTIFY ALL COMPOUNDS

(SEMI-)QUANTIFY ALL COMPOUNDS



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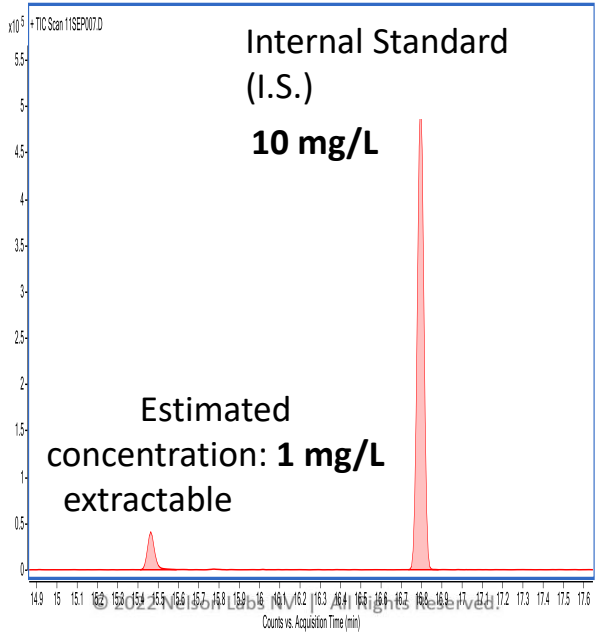
Discover all Extractable Compounds: Quantitation

Estimated Concentration

Assuming
$RF_{IS} = RF_{[EXT]}$

$$[Ext]_{Estimated} = \frac{Response_{Ext} \,.\, [I.S.]}{Response_{I.S.}}$$



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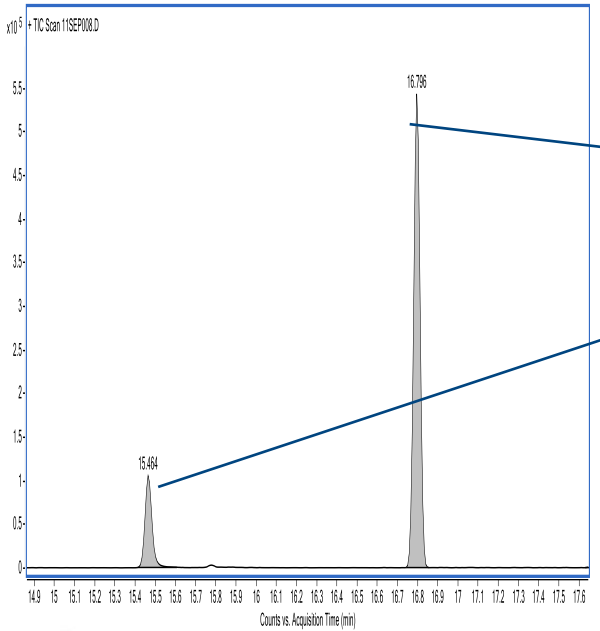
Discover all Extractable Compounds: Quantitation

Relative response factor (RRF) corrected quantification

Step 1: Determine the RRF Factor for the ext compound



Analysis of EXT Standard
[EXT] = 10 ppm and [I.S.] = 10 ppm

$[I.S.]_{known}$ = 10 mg/L

$Area_{[I.S.]}$ = 100

$[EXT]_{known}$ = 10 mg/L

$Area_{[EXT]}$ = 20

Relative Response Factor (RRF) EXT = 0,2

Chromatogram of EXT STANDARD

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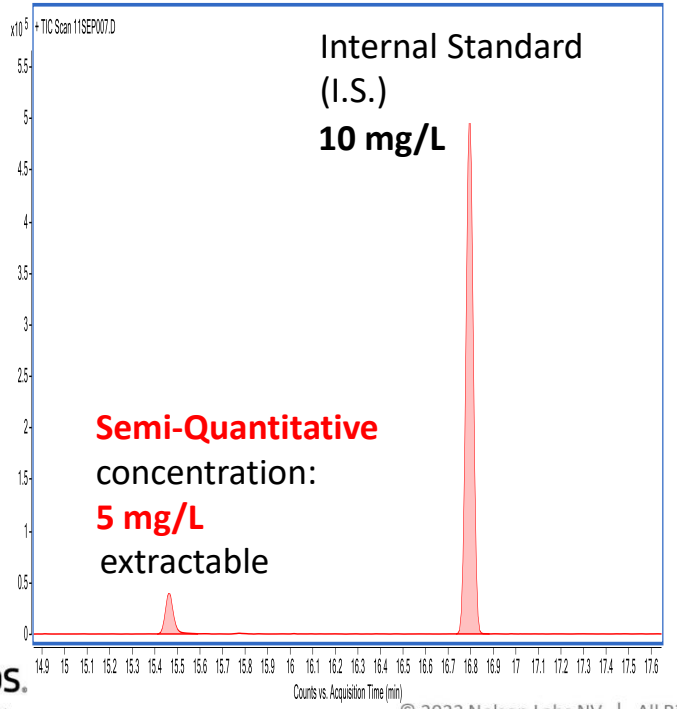
Discover all Extractable Compounds: Quantitation

Semi-Quantitative Concentration

Step 2: Using experimentally derived **RRF = 0.2**



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

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5. Packaged Drug Product Characterization and Qualification - Leachables

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Product Assessment (Leachables Study)

- **Test Article**: Packaging Drug Product
- **Purpose**: Determine the highest concentration achieved for each leachable over the drug product's shelf-life.
- **Test Strategy:** Test packaged drug product for targeted leachables (leachables which, as extractables, had the potential for adverse safety impacts).
- **Impact Assessment:** Complete impact assessment of targeted leachables, including toxicolgy for safety. Compare levels of target leachables with levels of extractables in simulation study (extractables/leachables correlation).
- **Value Proposition:** Drug product is tested, using quantitative/validated analytical methods, only for those substances which have the potential for an adverse impact. The purpose of the test is to establish concentration, not to establish identity.

Outcomes of the Product Assessment (Leachables Study)

- A **measured concentration** for the target leachable that is **more accurate** than the estimated concentration of the **extractable** study.
- **Real time leachables data** versus simulated time extractables data.
- **Trending of leachables** data over time.
- Bottom Line:

  A toxicological safety assessment performed on targeted leachables data is **likely** a **more accurate** projection of the **actual patient safety risk** than is an assessment performed on simulated extractables screening data.

USP<1664> – WHY?

Leachables studies are used to:

- **Establish correlations** between extractables & leachables (qualitative/quantitative)
- **Establish actual** DP **leachables profiles**, allowing a safety evaluation on the leachable compounds
- **Identify trends** in leachable accumulation levels in the drug product **over the shelf life**
- Facilitate the **change control** process (when necessary)
- Facilitate **investigations into the origin of identified leachables** that potentially may cause OOS for a marketed drug product
- ***Establish that the packaged drug product is safe and effective.***

USP<1664> – WHEN?

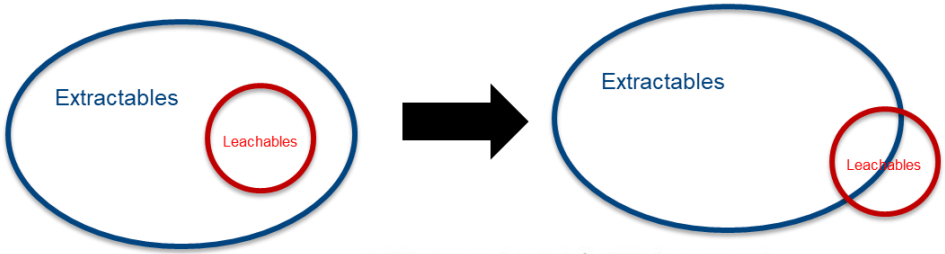
Formal leachables studies are especially relevant:

- With the **actual C/C-system that will be commercialized**
  - ✓ Final materials of construction (incl. color!)
  - ✓ Not with a prototype
  - ✓ Preferably on the same lots from the EXT study
- On the **product**, **manufactured under conditions that reflect actual commercial processes** of production
  - ✓ Fill & finishing
  - ✓ Sterilization
  - ✓ Distribution and storage
  - ✓ Clinical use
- During **late stage product development**
  - ✓ Simultaneous with the formal product stability assessment
  - ✓ Should be performed on the final drug product, not on simulations thereof
- On **registration batches** of the drug product during overall stability assessments
- **In clinical studies (phase III) for "high risk" dosage forms**
- After changes to the drug product, the packaging system or the manufacturing process (**change control**)

Leachables Screening: Why?

The main reason to screen drug products for unspecified leachables over shelf-life is to address "leachables" that are not first extractables.

- **Extractable Studies** are often performed on **freshly produced** components, **no** material **degradation yet**
- **Intrinsic Requirement per FDA**: *"Identify and Quantify all Leachables above SCT of 5µg/day"*
- Extractable Compounds **may change in structure if present in the DP**: (hydrolysis, oxidation, degradation…)
- **Reactive Leachables**: some leachables may be reactive with the API or other DP ingredients
- There are **doubts (generally unfounded) about the rigor and completeness** of the simulated **extractables study**.
- **Mis-named leachables** (packaging-drug product interaction degradation products or environmental contaminants) are not addressed in any other manner.



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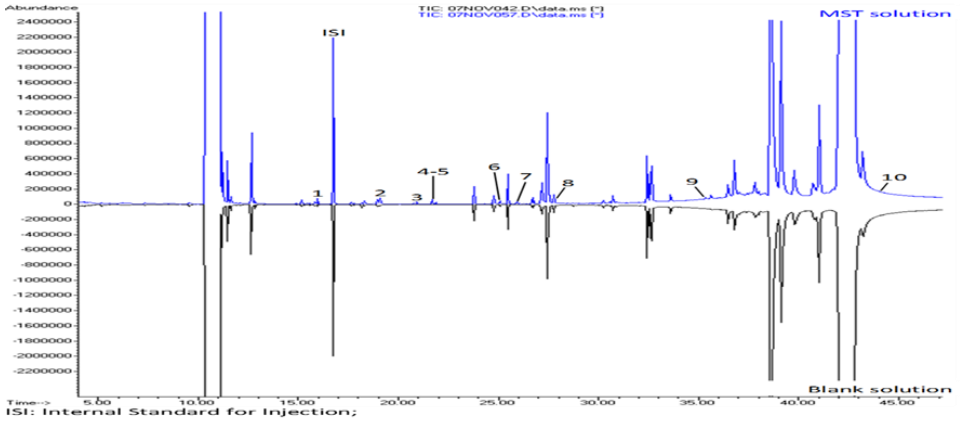
Selecting a BLANK Solution for a Leachable Study

When a drug product is tested chromatographically, a **veritable forest of peaks can be generated**:



in which case the analytical chemist is challenged to **distinguish peaks due to leachables from peaks dues to other sources**, such as:

- The drug product
- Excipients
- Impurities in the drug product and/or excipients,
- Degradation products

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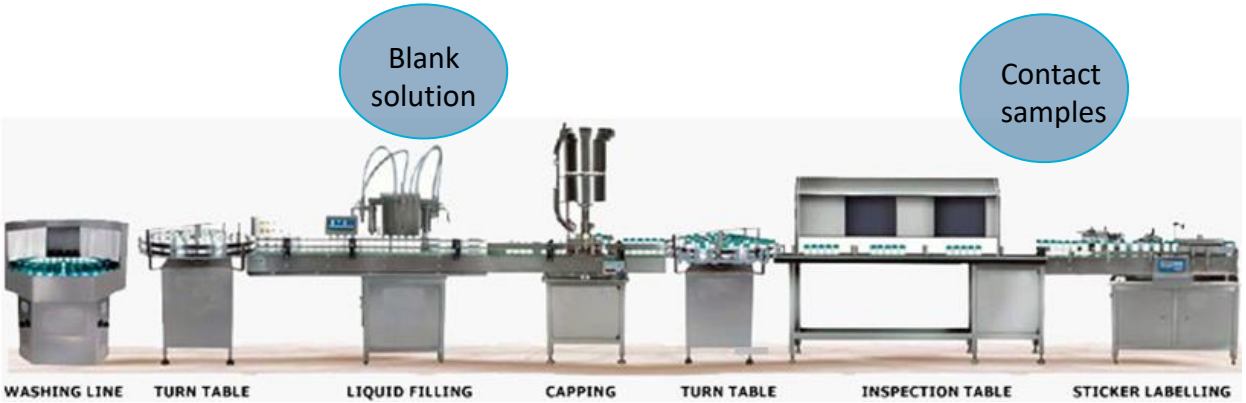
Selecting a BLANK Solution for a Leachable Study

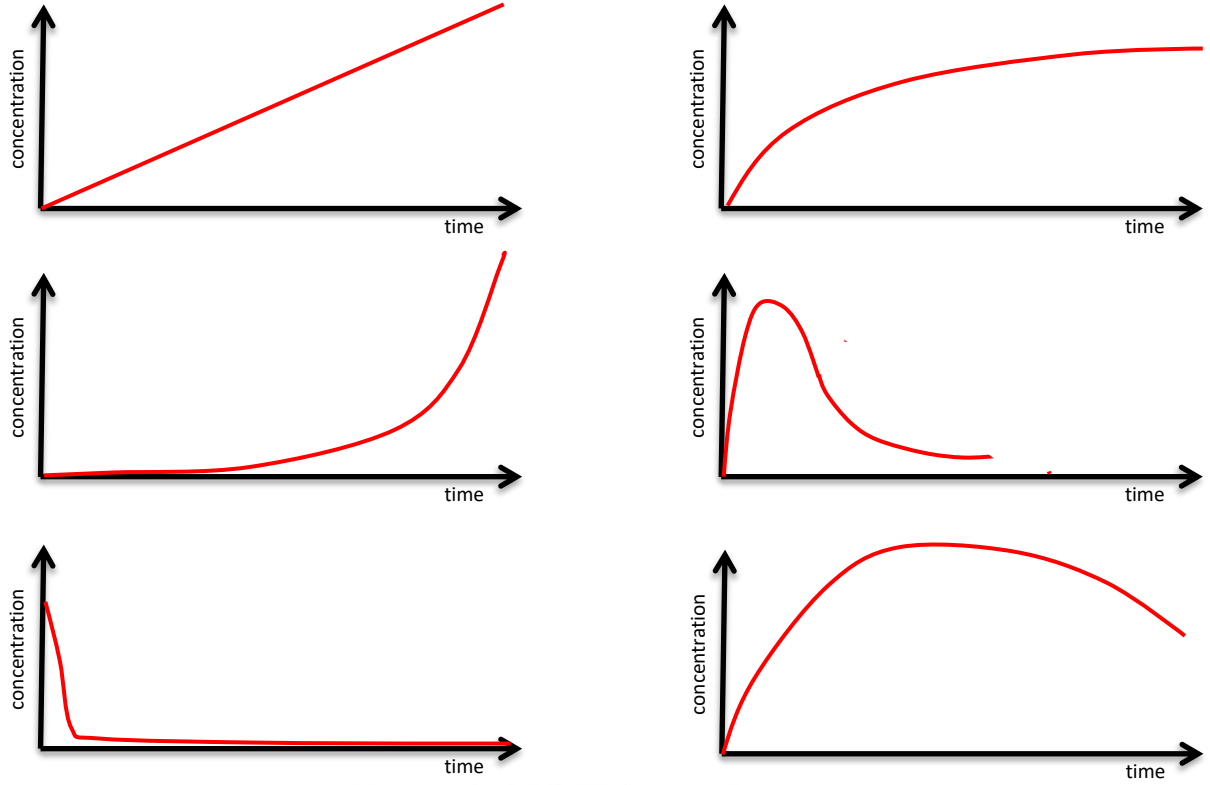
What is a good blank solution for leachables testing?

- A good blank solution is a **leachables free drug product**
- A good blank solution **is best from the same drug product batch** as the contact samples
- A good blank solution is **put on controlled storage** together with the contact samples



Leachables Profiling over Shelf-life

- Test your drug product ACROSS the shelf-life: Potential Leachable profiles
- **Per FDA: establish Trends across shelf life**



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Quantitative Methods?

How quantitative should the methods to measure the leachables be?

ICH Q2 R1 (part I, Chapter 1)

"The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose"

Possibilities:

- **Fully validated** method according to ICH Q2 R1 (Part II)
  - Complete (linear) method range
  - Known accuracy and precision
- **Limited validation** (less parameters of ICH Q2 R1 taken in account)
- **Limit test**
- **Method Suitability Test**

What should you choose?

It depends on

- Therapy (chronic vs acute)
- Drug product complexity
  - Chance on successful MST on complex drug matrices is rather low
- Required sensitivity
- Intended market (USA vs EU vs …)
- Company policy
- …

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Do's for Leachables Studies

- **Do** perform the leachables testing on **multiple lots** of the packaged drug product. Pay attention to the difference between multiple lots of the drug product and multiple lots of the packaging.
- **Do** test **multiple product units from each lot** at each test interval (if possible).
- **Do** use units of **differing disposition** (for example, upright versus inverted) if multiple dispositions are possible during storage/distribution.
- **Do** use **matrixing** (with justification) to address multiple product configurations (e.g., different packaging sizes or fill volumes).

6. Simulation Studies when Leachables Studies are not Possible

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Simulation Studies

- **Purpose** Find + identify extractables which are probable leachables
  - Establish which extractables must be targeted in a leachables study
    - Screening
    - Mimic circumstances of final drug product: acceleration, moderate exaggeration
    - Worst case: sufficient amounts to identify
    - Safety/ toxicological risk assessment to define target leachables
  - Replace or augment a leachables study when leachables cannot be screened down to the AET in the drug product.
- **Differences versus a leachables studies**
  - The drug product is replaced with a simulating solvent
  - The ageing conditions have been accelerated
  - The test article can be the complete packaging system or a partial packaging system

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Simulation Studies

Pros:

- Simulation studies are scientific rigorous (when properly designed and justified)
- Simulation studies are recognized and recommended in both USP <1664> and the PDP Recommendations
- Produces usable data when leachables cannot be measured

Con:

The regulatory acceptance of these studies (certainly in lieu of leachable studies) is limited.

Factors to Consider in Designing Simulation Studies

1. Extraction Solvent(s): same propensity to leach as the drug product.
2. Temperature/Duration: accelerated versus drug product shelf-life.
3. Stoichiometry: exaggerated surface area to solution volume ratio to increase extractables concentrations so that AET can be achieved.
4. Analysis: Screening with semi-quantitation

Simulation Study vs. Leachables Study

How to select the conditions of a simulation study?

1. **Exaggerated and accelerated conditions**
   - Exaggerated:
     - Composition of the simulant
     - Increased surface area
     - Underfilling (bags)
   - Accelerated: temperature of storage – accelerated ageing

2. **Study the complete packaging system, not only the individual parts**

3. **Or study some parts of the packaging system which are of particular interest**

   Example Novo Nordisk (Carsten Worsoe, PDA Pre-Filled Syringes Conference)
   ➔ exaggerated exposure: 10x increase of exposed surface area + accelerated ageing
   ➔ 3 months at 40 °C using the drug product

Remark: beware of solubility of the extractables in the extraction medium when “back extrapolating” to original ratios

When Material, Packaging System and Drug Product Qualification is Complete:

- Materials have been rationally selected on the basis of a preponderance of available safety-related information. The selection of safe materials increases the likelihood that extractables and leachables levels will ultimately be acceptable.
- Material data used for selection can also be used as the basis of change control.
- Extraction studies have been performed and extractables have been established to be likely safe via the toxicological safety assessment of the screening data.
- Extractables or leachables that have been established to be possibly unsafe if the patient is exposed to them either become target leachables for further assessment or the packaging system is rejected as being unsafe.
- These targeted leachables were measured in the drug product over shelf-life using robust, accurate and validated analytical methods.
- The drug product has been screened for “unexpected” leachables
- The true patient impact of these target leachables were toxicologically safety risk assessed.
- The packaged drug product is established to be either safe or unsafe based on the combined outcome of the screening and targeting assessments.

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Thanks

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