Setting up extractables studies

Controlled extraction studies

Dr. Dries Cardoen

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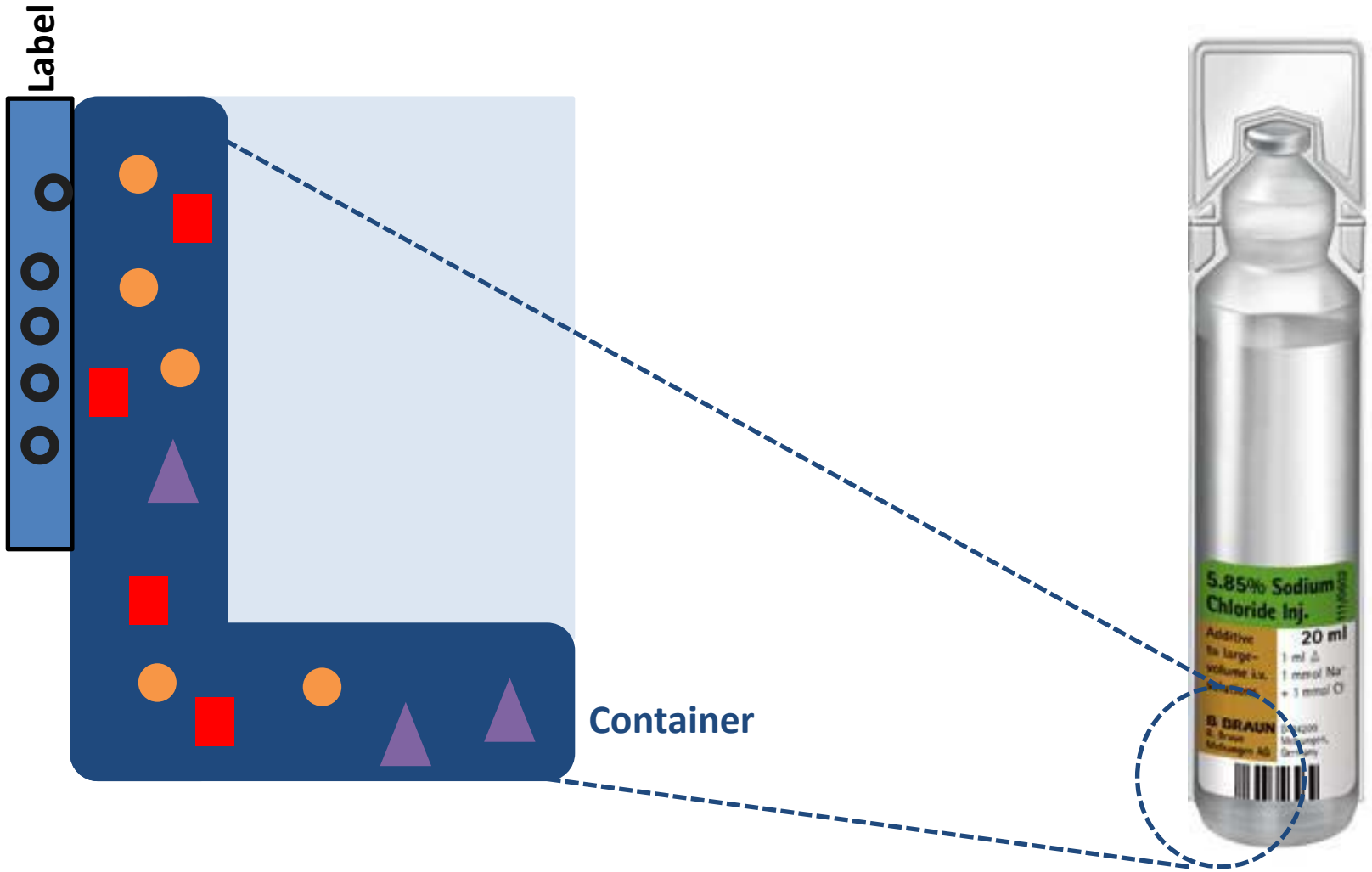
Extractables and Leachables



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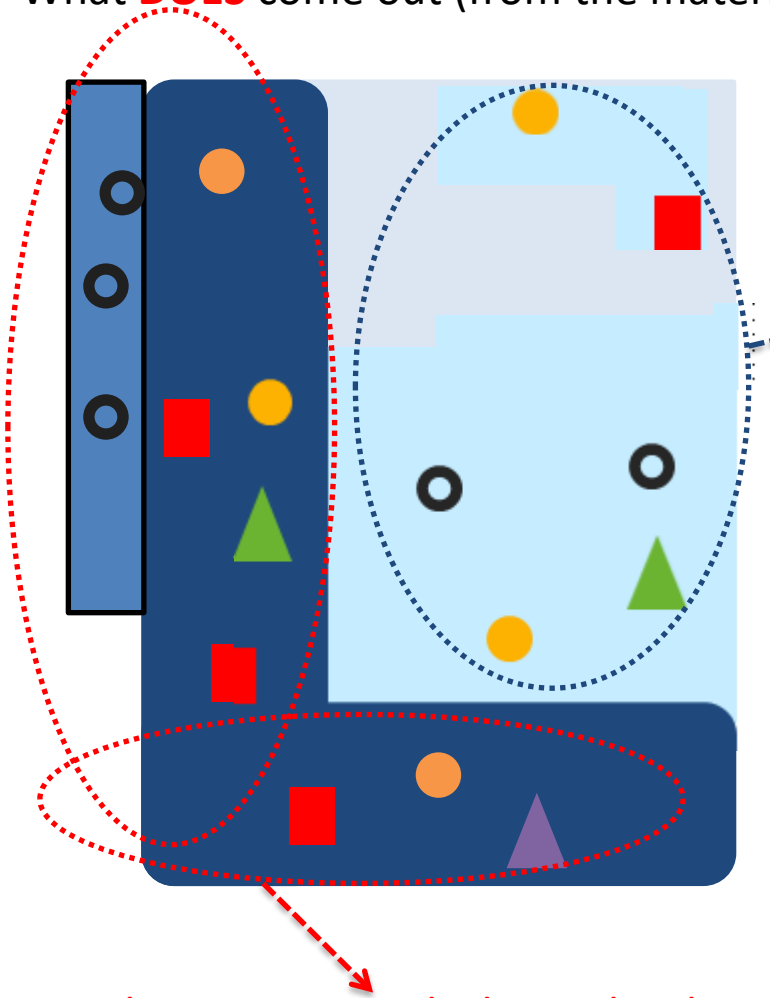
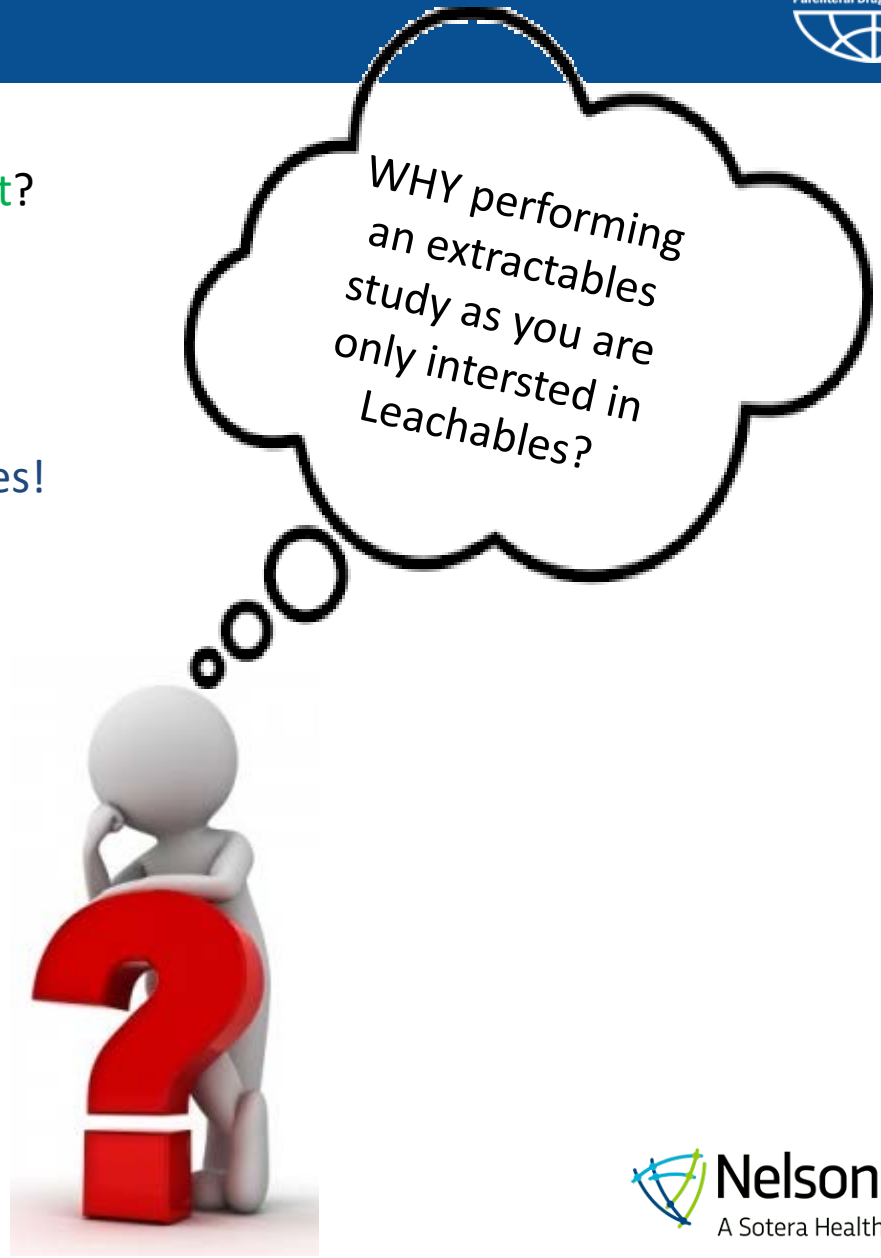
Extractables and Leachables

What **DOES** come out (from the material) in the drug product?



Leachables!

These compounds do **not** leach in the drug product



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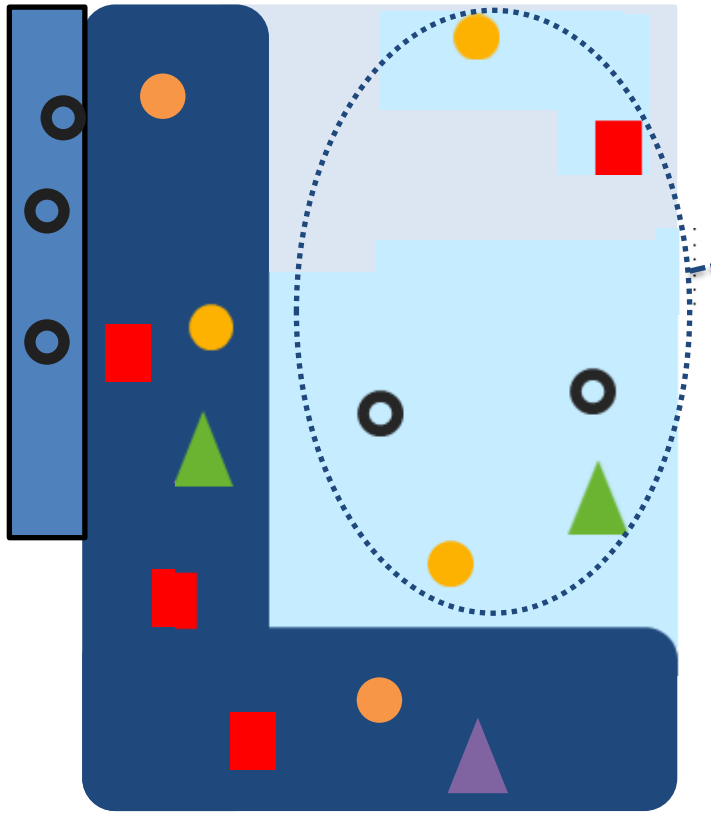
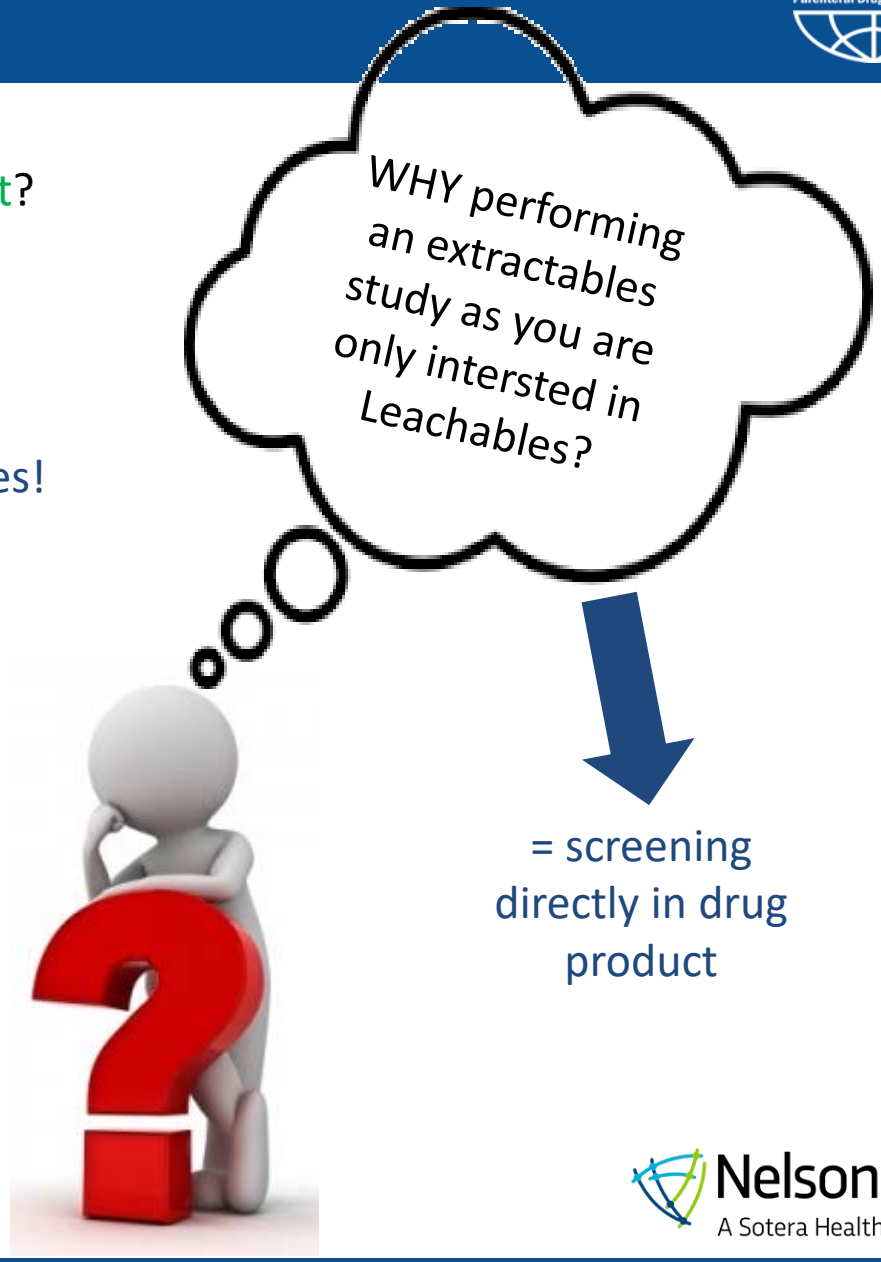


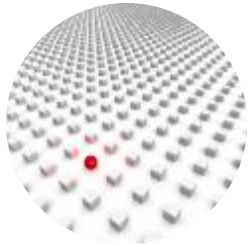
Leachables!



= screening directly in drug product

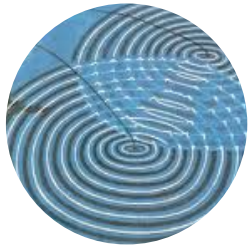
Extractables and Leachables

Drug product

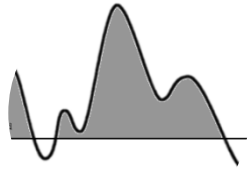


Screening

Compatible with drug product?



Interference?



Threshold?

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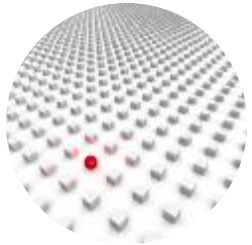
Extractables and Leachables

Drug product



Screening

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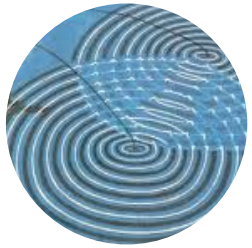

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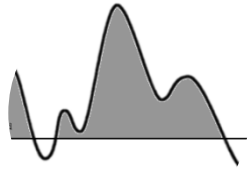

Threshold?

THE ANSWER: YOU NEED EXTRACTABLES DATA

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What is the PURPOSE of an extraction study?

- Material characterization of the packaging components
- "Impurities profiling" of the materials
  - Identify as many compounds as possible
  - Identify "bad actors" in the materials
- Early risk evaluation: potential *patient exposure* to chemical entities
- Allows to establish leachables – extractable *correlations*
- In certain cases (more applicable to OINDP): Facilitates extractable specifications of *acceptance criteria*.
- Identify compounds that may need to be monitored as leachable
  - Toxicity
  - Concentration in the materials
  - Risk for migration

Regulatory guidance

USP <1663> Monograph

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

This is an **INFORMAL** monograph

PQRI – Parenteral &Ophthalmic Drug Products

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

This is a **RECOMMENDATION**

REMARK: In Some Cases, Reference to the ISO 10993-12 (Medical Devices) can be Made to Determine the Extraction Conditions prior to Analysis.

Regulatory guidance

These two documents ar either **INFORMAL** or **RECOMMENDATIONS**

Allow flexibility in design

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

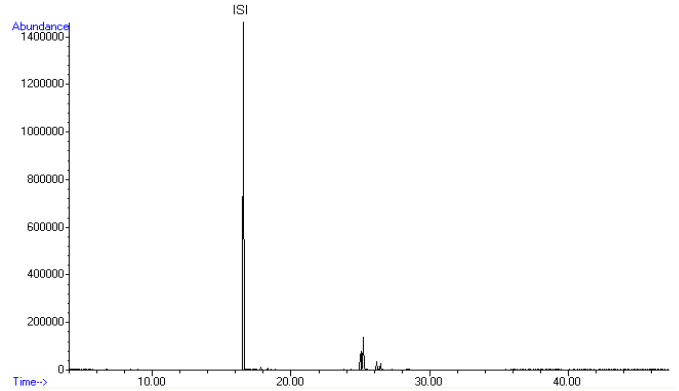
How to design the study for the envisioned intent? => **Tactics**

However, justification is needed!

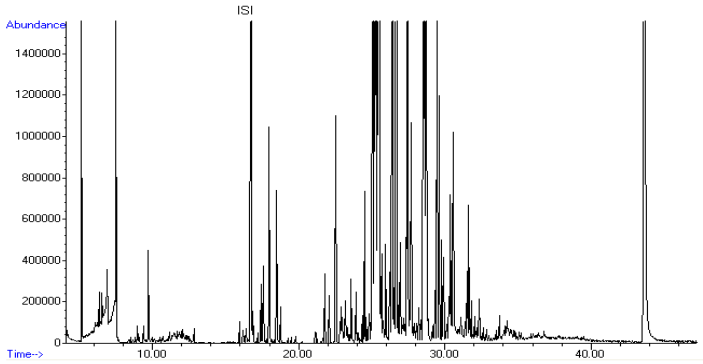
Both **identifying the necessity** for an extraction study, as well as **justifying the design**, is the responsibility of the holder of the NDA.

Depending upon the design of E-studies

1. **LOW Nr** of extractables



2. **HIGH Nr** of extractables



HOW CAN THIS BE HARMONIZED?

Useful documentation prior to E-study

GENERAL INFORMATION

Product Name, Product N° , Type, Manufacturer, Physical properties…

CERTIFICATES of compendial tests

USP<381>, USP <87>, USP<88>, EP 3.2.9, JP<49>, ISO 8871

INGREDIENTS OF RUBBER/PLASTIC

Very useful information, but this will not tell the complete E-story!!

EXTRACTABLES DATA FROM SUPPLIER

Highest Level of information ! *Check relevancy of technical and testing conditions!!*

DESIGN SPACE OF AN EXTRACTABLES STUDY

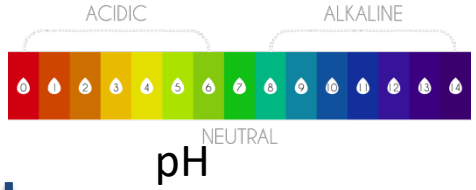
VARIABLES that may/will have an impact on the study design of an extractables study

- The **classification & specific requirements** per drug product
  - Table 1 in FDA C/C-Guidance (1999)
  - Decision tree in the EMA-Guideline (2005)
  - USP<1664>
- 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 **types of materials** used in te manufacture of the C/C
  - E.g. rubber versus polyolefin for BFS
- The **knowledge on 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?
- Packaging versus Manufacturing Equipment
  - **Dedicated session**

DESIGN SPACE OF AN EXTRACTABLES STUDY

Extraction Solvents

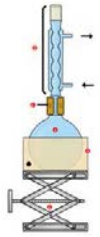
Polarity,...



Extraction conditions

Time & Temperature

autoclave



Reflux

Incubation (shaking)

Extraction ratio

Guidelines

PQRI ISO

Filling volume

SELECT WORST CASE CONDITIONS REPRESENTATIVE FOR FINAL APPLICATION

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Extraction Solvents

Perform E-study in Drug Product (Vehicle), suggested in:

FDA-Container/Closure Guidance (1999), (eg parenteral/Ophthalmic)

> If the extraction properties of the drug product vehicle may reasonably be expected to differ from that of water (e.g., due to high or low pH or due to a solubilizing excipient), then drug product should be used as the extracting medium.

EMEA-Guideline - immediate packaging (2005)

> stress conditions to increase the rate of extraction. The solvent used for extraction should have the same propensity to extract substances as the active substance/dosage form as appropriate. In the case of medicinal products the preferred solvent would be the medicinal product or placebo vehicle. The

USP<1663>

> qualitative and quantitative extractables profile. This is clearly stated in regulatory guidances and best practice recommendations (*1*, *4*, *5*). Therefore, the most logical *tactic* for this simulation study is to use the formulation itself as the extracting medium and in the absence of complicating factors, such an approach is recommended. However, in certain cases the use of the formulation as an extracting medium complicates extract characterization to such an extent that it is impractical. The various guidances and recommendations suggest that if the use of the drug product as the extracting solvent is not feasible, then the drug product vehicle, or placebo, could be used as an effective extracting medium. This recommendation is derived from the fact that the drug substance itself does not typically create the "leaching power" of a drug product but rather that it is the formulation's ingredients (drug product vehicle) that establish the drug product's ability to leach substances from a contacted material.

Extraction Solvents

ADVANTAGE: simulation of extractables behaviour in DP(V): same extraction propensity!

DISADVANTAGE: Risk of missing the presence of compounds

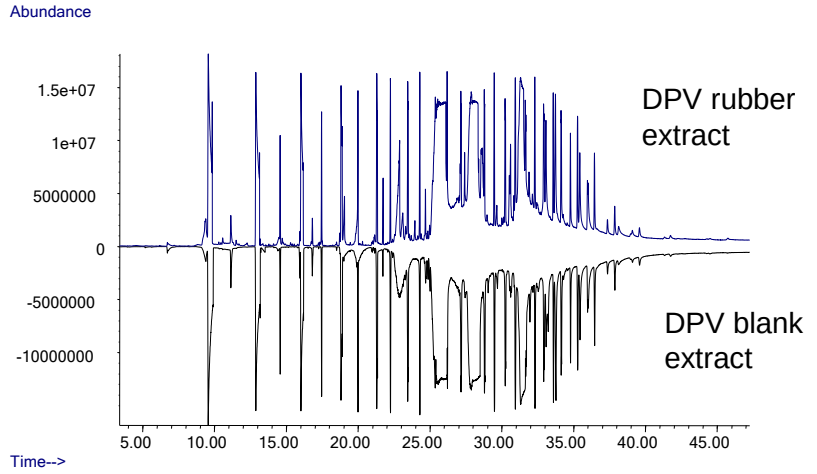
- *Matrix interference of DP(V)*

Risk of misinterpretation of analytical data

- *DP(V) Matrix degradant may be misinterpreted as extractable!*

Risk of underestimating the concentration of compounds

- *Extraction conditions – may potentially be too mild*
- *Difficult to select the right set of extraction conditions (e.g. Extraction time, temperature!)*



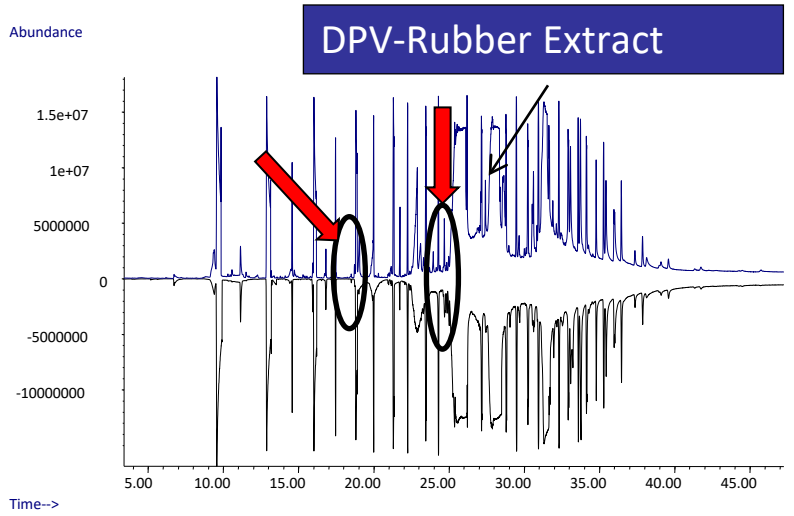
Extraction Solvents

Chemical Nature of the Extracting Medium (USP<1663>)

If: PURPOSE: simulating worst case EXT-profile

- *Look for Similar or Greater Extraction Propensity*
- *That gives Similar Qualitative and Quantitative EXT-profile*

- ***Use Drug Product Formulation***
  - *May be complex or impractical*
- ***DPV/Placebo can be an Alternative***
  - *REMARK: Extraction at High T with DP/DPV may lead to degradation (eg Polysorbate)*

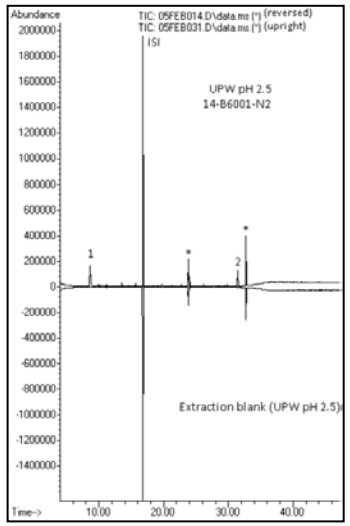


Extraction Solvents

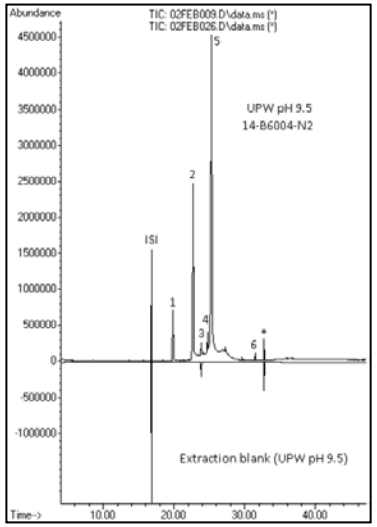
Example: *Extraction of a rubber component*

GC/MS Semi-Volatile Organic Compound "Profile"

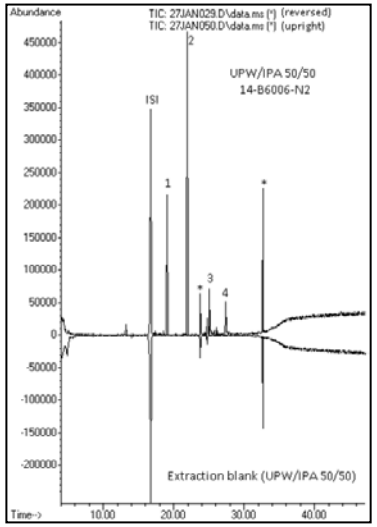
pH 2,5



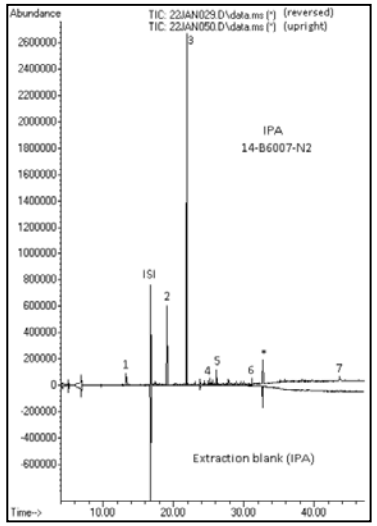
pH 9,5



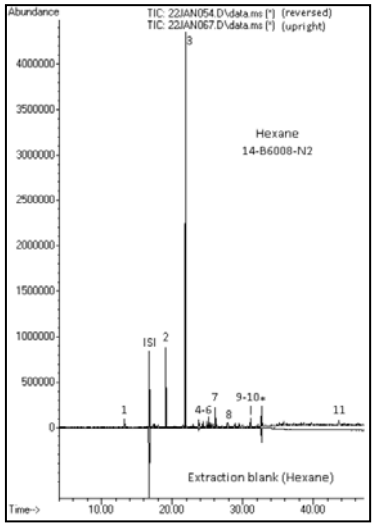
UPW/IPA 50/50



IPA



HEXANE



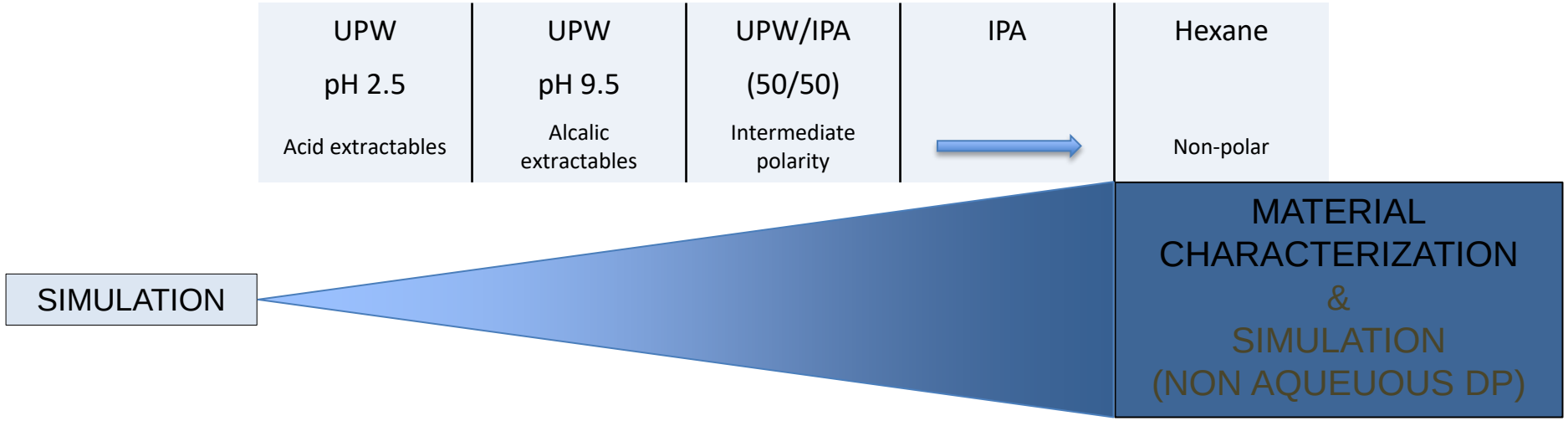
IS: Internal Standard for GC/MS

*: Internal Standard for LC/MS (not used in this GC/MS evaluation)

REMARK: Notice the Substantial "Visual" Difference in Extraction Profiles for the Different Extraction Solvents!

Extraction Solvents

PQRI P(O)DP best demonstrated practice **recommendations**



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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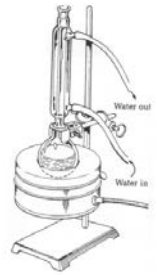
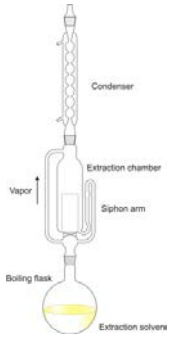
Extraction conditions

Mechanism of Extraction – Extraction Technique

Reflux or Soxhlet Extractions



- Similar Extraction yields
- Reflux has shown - in limited cases - to introduce artefacts in extraction profile
  - Degradation of extractables during Relfux could occur



- Soxhlet has more practical implications
  - Takes longer (24h) to have the same extraction yields as reflux (8h)
  - Safety implications in Lab (24h extraction)
  - Less practical for solvents with high boiling points
  - Less practical for aqueous extraction vehicles
  - Not to be used when *pH adjusted solvents* or *mixtures (e.g.IPA/UPW)* are used

Extraction conditions

Sonication

- **Less exhaustive** than reflux & soxhlet (PQRI)
- However, it may be **less detrimental to certain materials**
- Often used as the extraction technique for **labels**
  - Avoids desintegration of label, while extracting most relevant compounds
- Difficult to control (see USP<1663>)

Closed vessel

- Closed vessel avoids loss of **VOLATILE Organic Compounds**
- Typically ISO 10993-12 Conditions can be Used (e.g. 50° C, 72h)
- In general, a **24h SV-extraction** at a temperature of **10° C below boiling** point is **equivalent in yields** to an **8h reflux** extraction

Extraction conditions

Neat Headspace enrichment

- *Direct analysis of the material* using Headspace GC/MS
- Complete profile of **VOLATILE Organic Compounds**
- **Water soluble** Compounds are **better detected**
  (often a problem for Headspace GC on aqueous extracts)

"In Situ" extraction

- Container is filled with extraction solution, capped with closure and incubated.
- Allows **"one sided extraction"**
  - Coated rubbers
  - Sealing discs for cartridges
  - Multi-layer foils
- Better simulation, less exhaustive

Extraction conditions

Consideration for “In-Situ” Extractions:

- Static Extraction: Pharmaceutical Packaging

- Dynamic Conditions, often considered for Production Items
    - *Tubings*
    - *Filters*
    - *Pump systems (also for IV administrations)*

- Dynamic extraction is a better simulation if the contact between the components and the DP/DS is also dynamic,

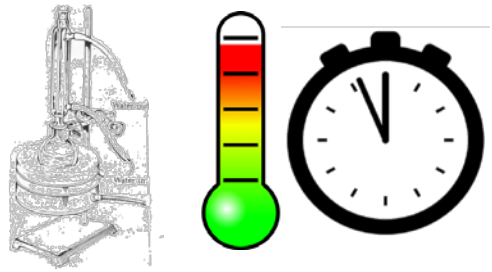
Extraction time and temperature

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



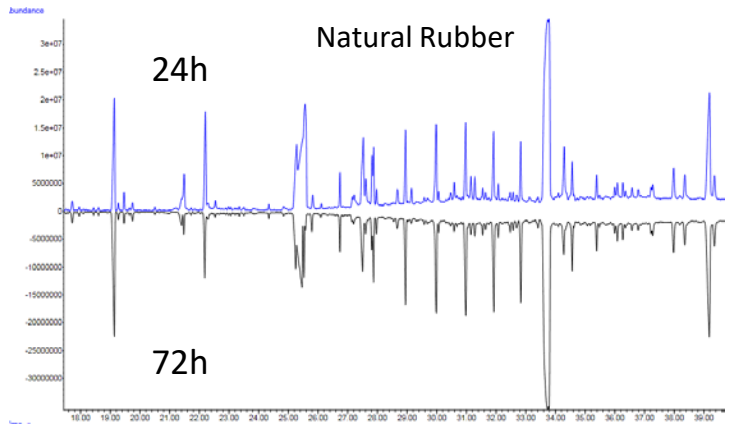
Extraction time and temperature

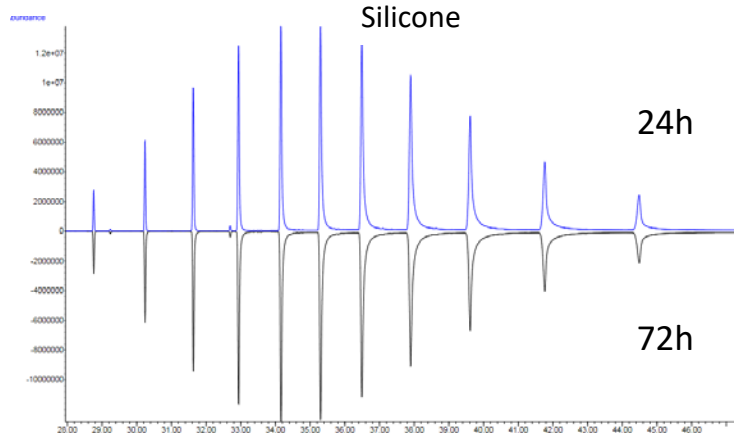
Typical temperature / time settings:

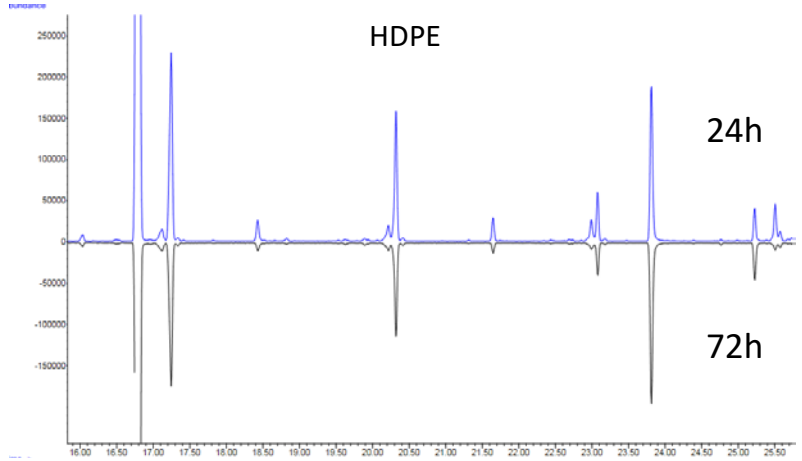
- Reflux with organic solvents:
  - Boiling temperature, 8 h
- Soxhlet with organic solvents:
  - Boiling temperature, 24 h
- Sonication:
  - Room temperature, ½ to 1h
- Sealed vessel and "*in situ*" extraction:
  - 50°C, 72 h (ISO 10993-12)
  - 24h below boiling point of extraction solvent = equivalent 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 time and temperature

Case study: impact of extraction time







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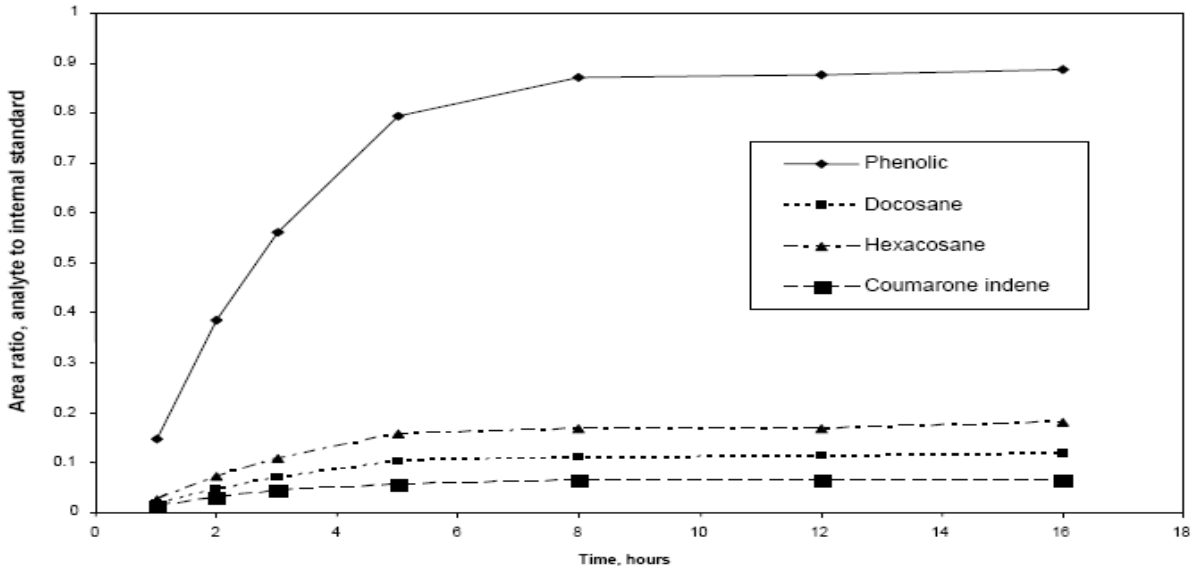
Extraction time and temperature

Asymptotic extraction profile - exhaustive extractions:



PQRI-Example:

- Test article: sulphur cured elastomer
- Extraction: DCM – soxhlet

CONCLUSION: Extraction conditions on the 'plateau'-regime (equilibrium)
= "MAXIMUM RISK"

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
  - E.g. 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, broadly accepted ratio is 1g/10mL
- For certain container closure systems (e.g. LVP), the final AET levels that may need to be considered may have an impact on the extraction ratio's!

  Example
  - For a 1 L bag (bag weighs 50g), Final AET in DP is at 1.5µg/L
  - This means that for the extraction study, 1.5µg/Bag(50g) or 30µg/g needs to be attained
  - With a ratio of 1bag in 1L, this AET cannot be attained
  - Higher material-to-solvent ratios will need to be considered

Analyses of the extracts

What **CAN** come out of the **material**?

PACKAGING/MATERIAL

Extraction Solvents

Extraction conditions

Extraction ratio

ANALYSES OF THE EXTRACTS

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Analyses of the extracts

Extracts

What is important?

Analyses of the extracts

Analyses of the extracts

A **broad identification** in “First Pass” extractable studies requires:

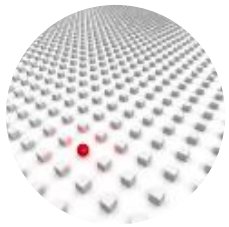
1. A compound specific detector: **Mass Spectrometry**

2. A **database** to allow Identification based upon Mass Spectra
   - Commercial Databases for GC/MS: NIST, WILEY
   - Customized Databases

Analyses of the extracts

Extract

Identification



Screening

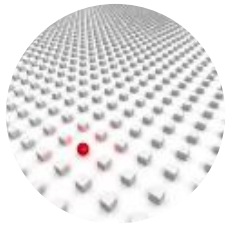
Trying to identify every single peak in a chromatogram

Targeted

Analyses of the extracts

Extract

Identification

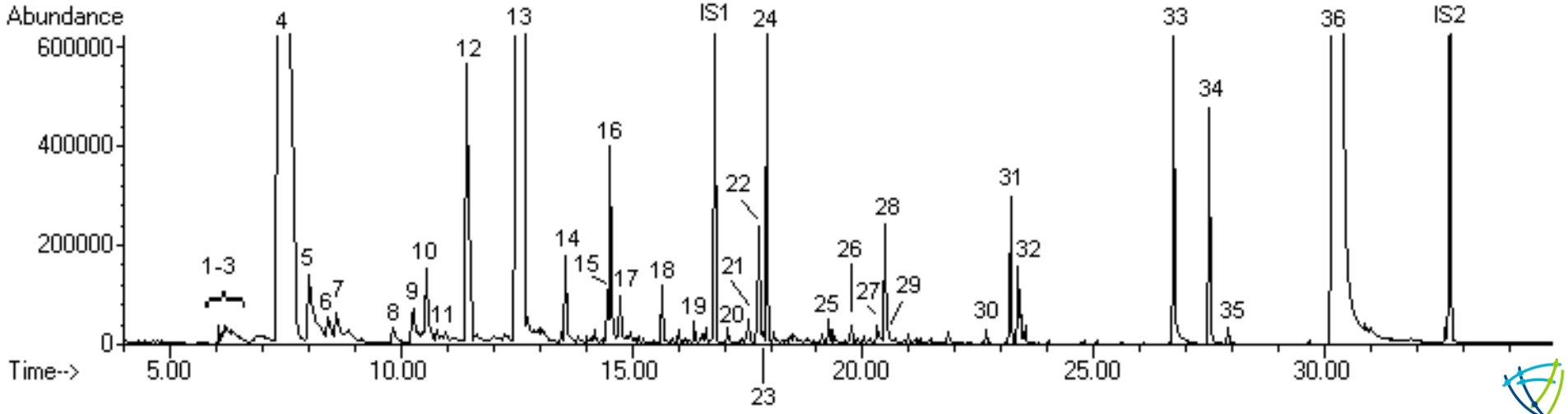


Screening

Trying to identify every single peak in a chromatogram

COMPOUND SCREENER DATABASE: HOW DOES IT WORK?

IDENTIFICATION



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COMPOUND SCREENER DATABASE: HOW DOES IT WORK?

IC Identified Compound (confirmed identification)

- Analytical Standard Available
- MS and RT confirmed: 100%

COMPOUND SCREENER DATABASE: HOW DOES IT WORK?

IC — Identified Compound (confirmed identification)

- Analytical Standard Available
- MS and RT confirmed: 100%

MPC — Most Probable Compound

- Analytical Standard NOT available
- Excellent fit with MS-library (>80%)

COMPOUND SCREENER DATABASE: HOW DOES IT WORK?

IC — Identified Compound (confirmed identification)

- Analytical Standard Available
- MS and RT confirmed: 100%

MPC — Most Probable Compound

- Analytical Standard NOT available
- Excellent fit with MS-library (>80%)

TIC — Tentitavely Identified Compound

- Analytical Standard NOT available
- Lower fit with MS-library: only limited structural information/ molecular formula

COMPOUND SCREENER DATABASE: HOW DOES IT WORK?

IC — Identified Compound (confirmed identification)

- Analytical Standard Available
- MS and RT confirmed: 100%

MPC — Most Probable Compound

- Analytical Standard NOT available
- Excellent fit with MS-library (>80%)

TIC — Tentitavely Identified Compound

- Analytical Standard NOT available
- Lower fit with MS-library: only limited structural information/ molecular formula

U — Unidentified

COMPOUND SCREENER DATABASE: HOW DOES IT WORK?

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Nelson Labs proprietary DB

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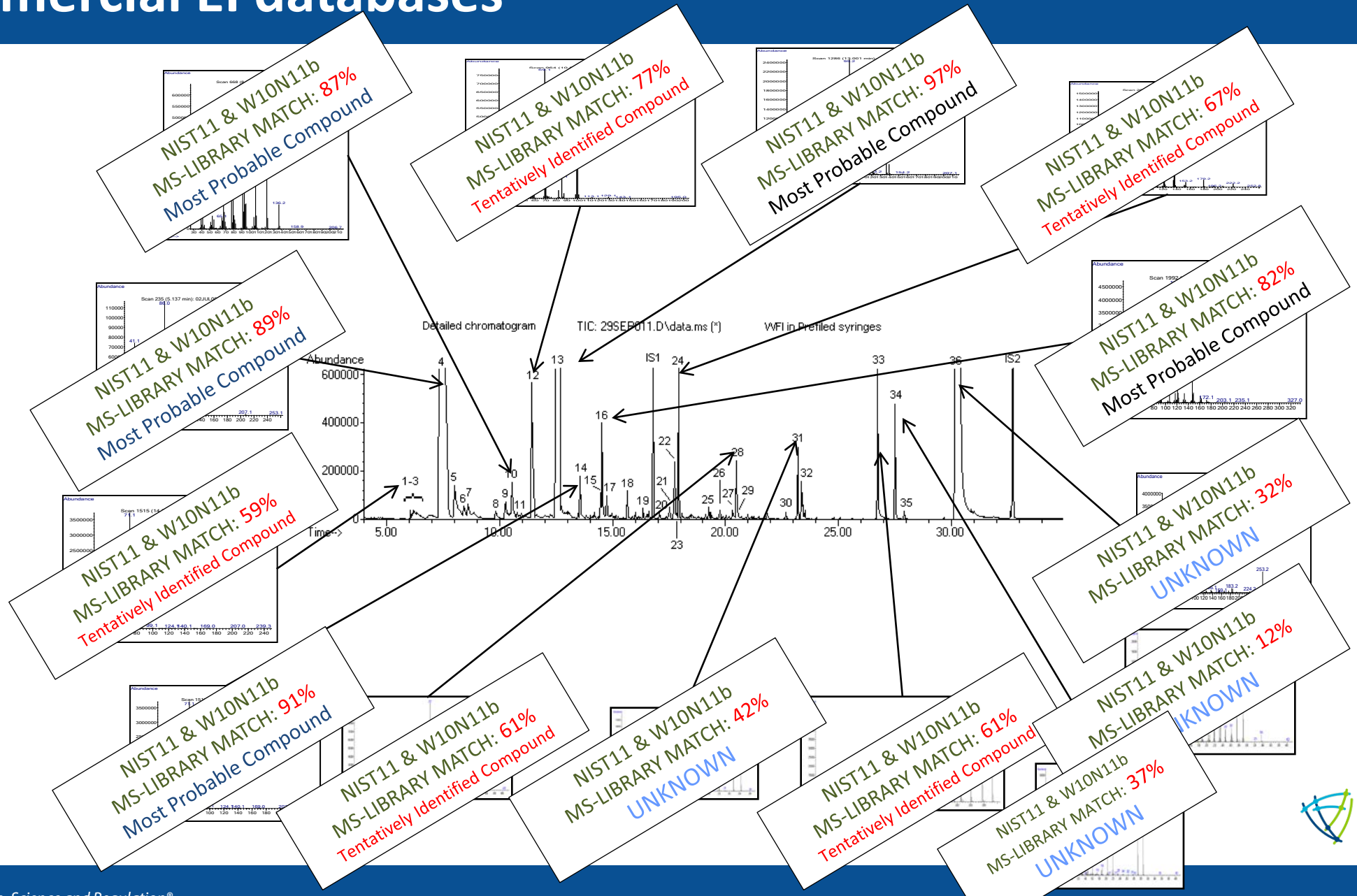
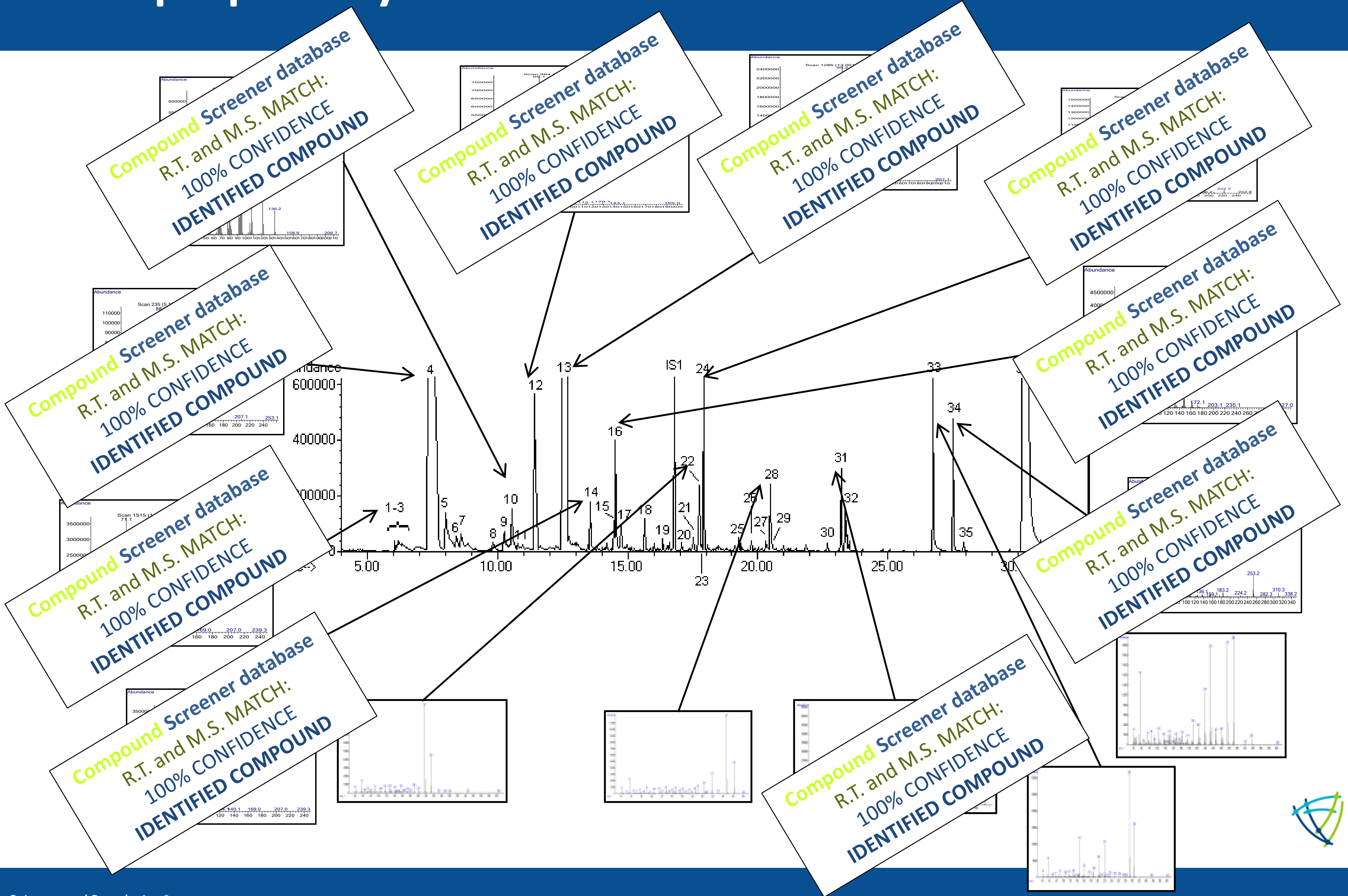
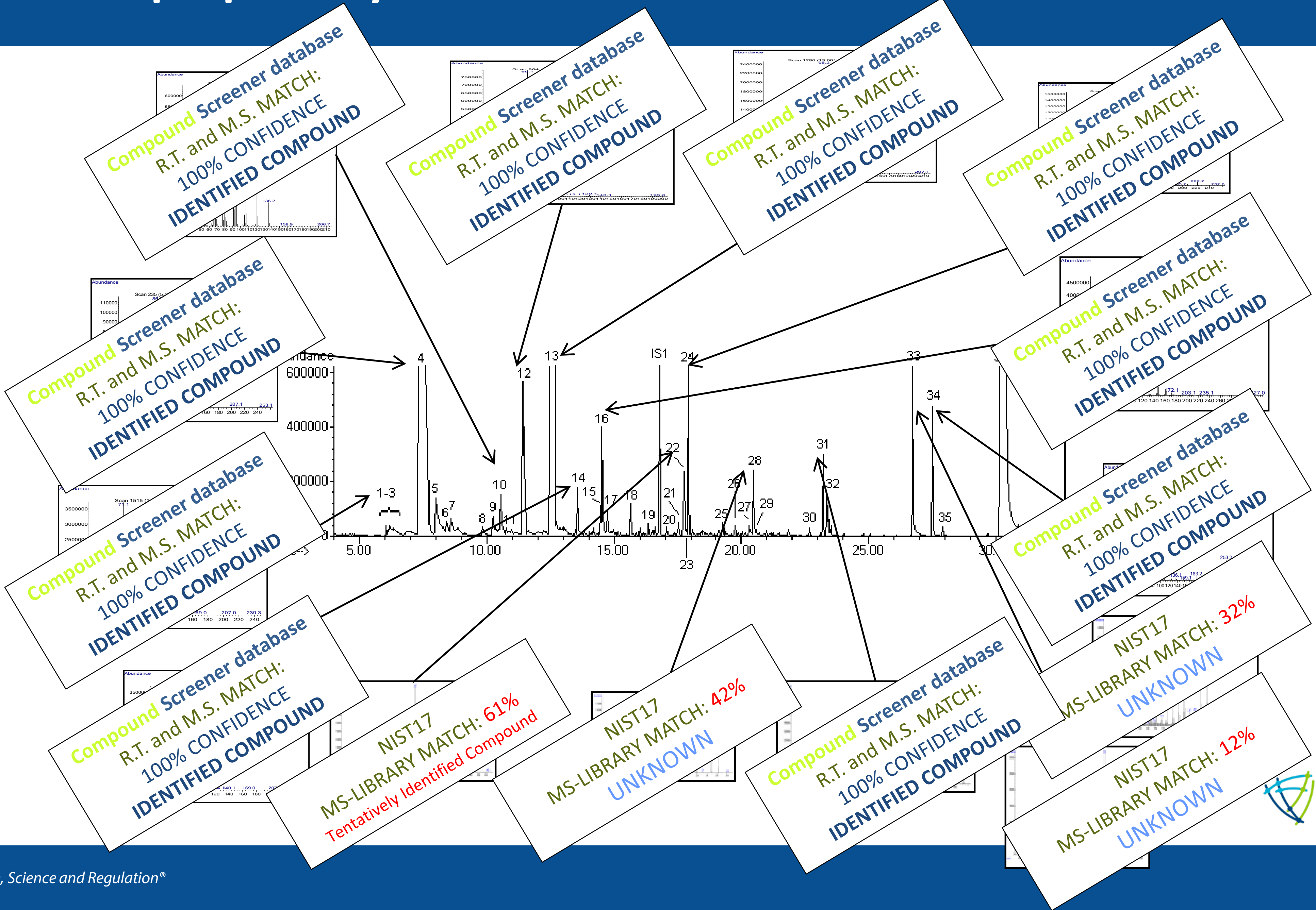
Commercial EI databases



Nelson Labs proprietary screener database: HOW DOES IT WORK?



Nelson Labs proprietary screener database: HOW DOES IT WORK?



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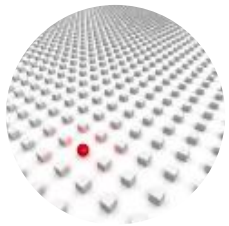
Analyses of the extracts

Extract

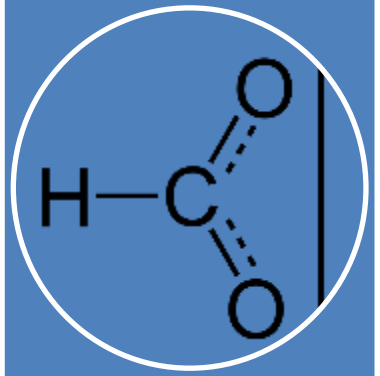
Identification



Screening

Complementary techniques

Analyses of the extracts

VOC	SVOC	NVOC		
HS-GC/MS **Screening**	GC/MS **Screening**	UPLC/MS **Screening**	ICP/OES ICP/MS	IC GF-AAS LC/UV ...

EXTRACTABLES PROFILE:Potentially Leaching Compounds of Concern

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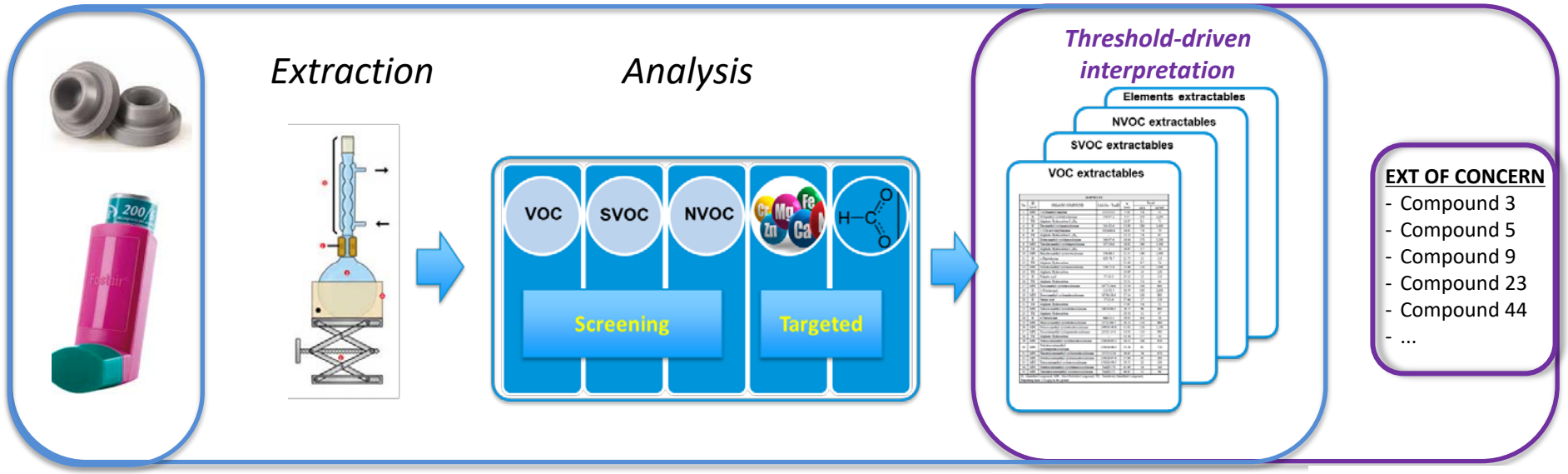
Summary - Bridging E&L

TYPICAL EXTRACTABLES STUDY



Packaging (test material)

Comprehensive EXT data set

Target compounds for LEA study

Applying <u>threshold approach</u> filters out "Extractables of Concern"

- Safety evaluation on results of an extractables study
- Critical information for leachables study

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The threshold approach – organic compounds

SAFETY CONCERN THRESHOLD (SCT)

*"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 (Product Quality Research Institute)

- SCT in function of toxicological endpoints
- Additional cancer risk of 1 in 1.000.000 over life-time exposure (0.15 µg/day)
- SCT dependent on the **administration route** of the final product:
  - OINDPs (Orally Inhaled and Nasal Drug Products)
  - PDPs: Parenteral Drug Products
  - ODPs: Ophthalmic Drug Products
  - Oral and Topical/Transdermal products

The threshold approach – organic compounds

SAFETY CONCERN THRESHOLD (SCT)

Orally Inhaled and Nasal Drug Products (OINDPs):

- **PQRI "Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled Drug Products" (SEP 2006).**

Compound class details	Suggested threshold level
Qualifcation Threshold (QT): Threshold below which a given leachable is not considered for safety qualification unless the leachable presents structure-activity relationship (SAR) concerns	5 µg/day
Safety Concern Threshold (SCT): Threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and noncarcinogenic toxic effects	0.15 µg/day

The threshold approach – organic compounds

SAFETY CONCERN THRESHOLD (SCT)

Parenteral Drug Products (PDPs): ***(to be published)***

- Presentation Dennis Jenke " The PODP Best Demonstrated Practice Recommendations – Chemistry and Toxicology, April 2016, Venice, PDA-Europe Extractables and Leachables Workshop."

Tox endpoint	General tox.	Sensitizer & irritant	Carcinogen
Class	Class I	Class II	Class III
Threshold level (µg/day)	*50?*	5	1.5 (PDP-SCT)

Ophthalmic Drug Products (ODPs): ***(to be published)***

concentration based threshold levels

Oral and Topical/transdermal products:

no threshold level available yet

The threshold approach – organic compounds

THRESHOLD OF TOXICOLOGICAL CONCERN (TTC)

"Threshold of Toxicological Concern (TTC) concept was developed to define an acceptable intake for any unstudied chemical that poses a negligible risk of carcinogenicity or other toxic effects"

ICH M7 guideline

- TTC in function of therapy duration
- Evaluation of genotoxic impurities
- Additional cancer risk of 1 in 100.000 over life-time exposure

Duration of treatment	≤ 1 month	> 1-12 months	> 1-10 years	> 10 years
Daily intake (µg/day)	120	20	10	1.5

PERMITTED DAILY EXPOSURE (PDE)

ICH Q3D guideline

- Lists PDE in function of administration route
- Limited list of elements (e.g. typical glass elements or rubber elements are no included)

Element	Class[2]	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

The threshold approach – AET

ANALYTICAL EVALUATION THRESHOLD (AET)

➔ Translating the SCT into Analytical Thresholds for Extractables studies

OINDPs:

$$\text{AET} = \frac{0.15\ \mu g/\text{day}}{\text{maximum administered volume/day}}$$

PDPs:

$$\text{AET} = \frac{1.5\ \mu g/\text{day}}{\text{maximum administered volume/day}}$$

➔ Screening methods are semi-quantitative: correction factor of 50%

$$\text{Final AET} = \frac{\text{AET}}{2}$$

Cornerstone of all E&L testing:
Compounds detected below the (Final) AET should not be considered for toxicological assessment

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FIT Screening evaluation (v2.0)

Fast Initial Toxicity (FIT) screening evaluation?

Derek Nexus software (Lhasa Ltd):

- Compounds submitted to a rule based Structure Activity Relationship (SAR) assessment
- Several 'toxicological end points', 'likelyhood levels' and 'negative predictions' are used

Endpoints included		
Carcinogenicity	Cerebral oedema	Respiratory sensitization
Photocarcinogenicity	Chloracne	Occupational asthma
Chromosome damage *in vitro*	Cumulative effect on white cell count and immunology	Skin sensitization
Chromosome damage *in vivo*	Cyanide-type effects	photoallergenicity
photo-induced chromosome damage *in vitro*	High acute toxicity	Thyroid toxicity
Genotoxicity *in vitro*	Methaemoglobinaemia	Rapid prototype: bradycardia
Genotoxicity *in vivo*	Neurotoxicity	Rapid prototype: nephrotoxicity
Photogenotoxicity *in vitro*	Ocular toxicity	Rapid prototype: hepatoxicity
Photogenotoxicity *in vivo*	Oestrogenicity	Rapid prototype: kidney disorders
Hepatotoxicity	Peroxisome proliferation	Rapid prototype: mitochondrial dysfunction
hERG channel inhibition *in vitro*	Phospholipidosis	Rapid prototype: bladder disorders
Irritation (of the eye)	Phototoxicity	Rapid prototype: blood in urine
Irritation (of the gastrointestinal tract)	Pulmonary toxicity	Rapid prototype: thyroid toxicity
Irritation (of the respiratory tract)	Nephrotoxicity	Rapid prototype: splenotoxicity
Irritation (of the skin)	Uncoupler of oxidative phosphorylation	Rapid prototype: bone marrow toxicity
Lachrymation	Mutagenicity *in vitro*	Rapid prototype: adrenal gland toxicity
Alpha-2-mu-Globulin nephropathy	Mutagenicity *in vivo*	Rapid prototype: cardiotoxicity
Anaphylaxis	Photomutagenicity	Rapid prototype: chromosome damage *in vitro*
Cholinesterase inhibition	Developmental toxicity	Rapid prototype: testicular toxicity
Bladder urothelial hyperplasia	Teratogenicity	–
Cardiotoxicity	Testicular toxicity	–

Likelihood	Explanation
Certain	**= Endpoint is considered for classification**
Probable	
Plausible (baseline)	
Equivocal	
Doubted	The weight of evidence opposes the proposition.
Improbable	There is at least one strong argument that the proposition is false and there are no arguments that it is true.
Impossible	There is proof that the proposition is false.
Open	There is no evidence that supports or opposes the proposition.
Contradicted	There is proof that the proposition is both true and false.

Prediction	Explanation
Inactive prediction	The query structure does not match any structural alert for bacterial *in vitro* mutagenicity in Derek. Additionally, the query structure does not contain any unclassified or misclassified features.
Inactive prediction with misclassified features	Features of the query structure were found in the Lhasa Ames test reference set and have been observed in mutagens that do not match bacterial *in vitro* mutagenicity structural alerts in Derek. The relationship between these features and mutagenic activity may be coincidental or contributory.
Inactive prediction with unclassified features	The query structure contains features that were not found in the Lhasa Ames test reference set and do not match any structural alerts for bacterial *in vitro* mutagenicity in Derek.

FIT Screening evaluation (v2.0)

Example of a Derek assessment for 'compound X'

Toxicological endpoint

Likelyhood level

Derek predictions (Reasoning summary and alerts found):

- alpha-2-mu-Globulin nephropathy in bacterium is IMPOSSIBLE
- alpha-2-mu-Globulin nephropathy in human is IMPOSSIBLE
- alpha-2-mu-Globulin nephropathy in mammal is DOUBTED
- Carcinogenicity in bacterium is IMPOSSIBLE; Glycidyl ether, amine, ester or amide
- Carcinogenicity in human is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Carcinogenicity in mammal is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Chromosome damage in vitro in bacterium is IMPOSSIBLE; Glycidyl ether, amine, ester or amide
- Chromosome damage in vitro in human is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Chromosome damage in vitro in mammal is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Developmental toxicity in bacterium is IMPOSSIBLE; Epoxide
- Developmental toxicity in human is PLAUSIBLE; Epoxide
- Developmental toxicity in mammal is PLAUSIBLE; Epoxide
- Irritation (of the eye) in bacterium is IMPOSSIBLE; Epoxide
- Irritation (of the eye) in human is PLAUSIBLE; Epoxide
- Irritation (of the eye) in mammal is PLAUSIBLE; Epoxide
- Irritation (of the skin) in bacterium is IMPOSSIBLE; Epoxide
- Irritation (of the skin) in human is PLAUSIBLE; Epoxide
- Irritation (of the skin) in mammal is PLAUSIBLE; Epoxide
- Mutagenicity in vitro in bacterium is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Nephrotoxicity in bacterium is IMPOSSIBLE; 1,2-Ethyleneglycol or derivative
- Nephrotoxicity in human is EQUIVOCAL; 1,2-Ethyleneglycol or derivative
- Nephrotoxicity in mammal is EQUIVOCAL; 1,2-Ethyleneglycol or derivative
- Skin sensitisation in bacterium is IMPOSSIBLE; Glycidyl ether, amine, ester or amide
- Skin sensitisation in human is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Skin sensitisation in mammal is PLAUSIBLE; Glycidyl ether, amine, ester or amide

FIT Screening evaluation (v2.0)

Compounds are divided in classes based on their Derek assessment:

- OINDPs
  - PQRI (Product Quality Research Institute) document: Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products, September 2006.

COMPOUND CLASS	COMPOUND CLASS DETAILS	SUGGESTED THRESHOLD LEVEL
Class I	**No DEREK Alert**: for following toxicological endpoints or **DEREK Alert** with a likelihood of „doubted", „improbable" or „impossible": Carcinogenicity – Genotoxicity – Mutagenicity – Chromosome damage - Irritation – Sensitization – Teratogenicity – Lachrymation – Chloracne - Photoallergenicity	5 µg/day (Qualification Threshold = QT)
Class II	**DEREK Alert**: Irritation – Sensitization – Teratogenicity – Lachrymation – Chloracne – Photoallergenicity	0.15 µg/day (Safety Concern Threshold = SCT)
Class III	**DEREK Alert**: for following toxicological endpoints with a likelihood of „equivocal" or higher: Carcinogenicity – Genotoxicity – Mutagenicity – Chromosome damage	

- PDPs
  - Presentation Dennis Jenke: "The PODP Best Demonstrated Practice Recommendations – Chemistry and Toxicology, April 2016, Venice, PDA-Europe Extractables and Leachables Workshop.

COMPOUND CLASS	COMPOUND CLASS DETAILS	SUGGESTED THRESHOLD LEVEL
Class I	**No DEREK alerts** are generated for the following toxicological end points: Sensitization – Irritation – Genotoxicity – Mutagenicity – Carcinogenicity – Teratogenicity	50 µg/day
Class II	**DEREK Alert**: Irritation – Sensitization – Teratogenicity – Lachrymation – Chloracne – Photoallergenicity	5 µg/day
Class III	**DEREK Alert**: Carcinogenicity – Genotoxicity – Mutagenicity – Chromosome damage	1.5 µg/day

FIT Screening evaluation (v2.0)

Example of a FIT screening result for 'compound X' in a parenteral application

Compound X	Structure

[ToxID] $C_{39}H_{46}O_8$ 642.79

FIT Screening Evaluation:

Cramer Classification: Class III
Derek predictions (Reasoning summary and alerts found):

- alpha-2-mu-Globulin nephropathy in bacterium is IMPOSSIBLE
- alpha-2-mu-Globulin nephropathy in human is IMPOSSIBLE
- alpha-2-mu-Globulin nephropathy in mammal is DOUBTED
- Carcinogenicity in bacterium is IMPOSSIBLE; Glycidyl ether, amine, ester or amide
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- Irritation (of the eye) in human is PLAUSIBLE; Epoxide
- Irritation (of the eye) in mammal is PLAUSIBLE; Epoxide
- Irritation (of the skin) in bacterium is IMPOSSIBLE; Epoxide
- Irritation (of the skin) in human is PLAUSIBLE; Epoxide
- Irritation (of the skin) in mammal is PLAUSIBLE; Epoxide
- Mutagenicity in vitro in bacterium is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Nephrotoxicity in bacterium is IMPOSSIBLE; 1,2-Ethyleneglycol or derivative
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- Nephrotoxicity in mammal is EQUIVOCAL; 1,2-Ethyleneglycol or derivative
- Skin sensitisation in bacterium is IMPOSSIBLE; Glycidyl ether, amine, ester or amide
- Skin sensitisation in human is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Skin sensitisation in mammal is PLAUSIBLE; Glycidyl ether, amine, ester or amide

FIT Screening Classification: Class III
Suggested Threshold level: 1.5 µg/day

Summary - Bridging E&L

ID	Class	Threshold for Class (µg/day)	Final AET for Class (µg/L)	Extractables study Result (µg/L)
COMPOUND #1	Class I	50	12500	> 100
COMPOUND #2	Class I	50	12500	> 200
COMPOUND #3	Class III	1.5	375	< 1300
COMPOUND #4	Class I	50	12500	> 2000
COMPOUND #5	Class II	5	1250	> 400
COMPOUND #6	Class I	50	12500	> 250
COMPOUND #7	Class II	5	1250	< 13000
COMPOUND #8	Class III	1.5	375	> 100
COMPOUND #9	Class I	50	12500	< 47000
COMPOUND #10	Class II	5	1250	> 400
COMPOUND #11	Class III	1.5	375	> 100
COMPOUND #12	Class I	50	12500	> 5500
COMPOUND #13	Class III	1.5	375	< 33000
COMPOUND #14	Class I	50	12500	> 1200
COMPOUND #15	Class II	5	1250	< 3500

1. Extractables study:
   - Compounds + concentration
2. FIT screening evalution:
   - Subdivide compound in classes with corresponding threshold
3. Convert threshold to final AET:
   - using max. daily dose and extraction ratio
4. Evaluate EXT results vs. Final AET per compound

5. Targets requiring further following up during leachables study

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Questions?

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