Connecting People, Science and Regulation

SETTING UP EXTRACTABLE / LEACHABLE STUDIES

PDA WORKSHOP
EXTRACTABLES – LEACHABLES
Brussels
13-14 March, 2014

Dr. Piet Christiaens

Content

1. The Chemical Assessment Triad
2. (Controlled) Extraction Studies
3. Simulation Studies
4. Leachable Studies

The Chemical Assessment Triad

A General strategy for the chemical aspects of the safety assessment of extractables and leachables in Pharmaceutical Drug Products

Dennis Jenke

PDA J Pharm Sci and Tech 2012, 66 168-183

Definitions E/L study

1. ***Donor phase*** : contact material

   E: **MAY BE** used to manufacture, store or deliver final drug product
   L: **IS** used to manufacture, store or deliver final drug product

2. ***Receiving phase***: contact solution

   E: extracting solvent
   L: Finished drug product

3. ***Migrant***: substance that migrates from the donor phase to the receiving phase as a result of contact between the two phases

   a)Active: e.g. solvation
   b)Passive: e.g. sorption

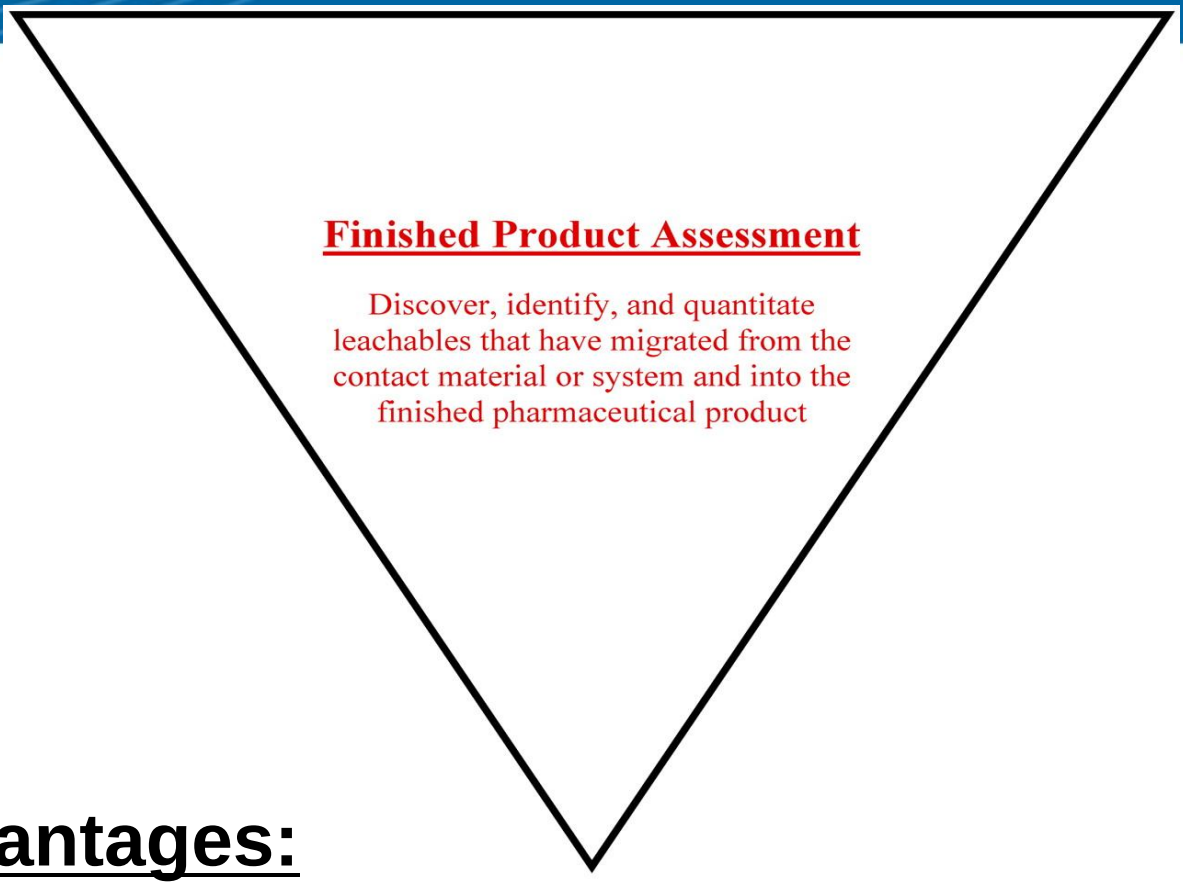
   Contact conditions:
   E: Laboratory conditions
   L: Actual use conditions

1. THE CHEMICAL ASSESSMENT TRIAD

- **Purpose**:
  - Which migrants will have a direct impact on patient safety?
  - Risk management
  - (Good) Quality by (good) Design
- **Necessary**: 1. Identification migrants
  2. Quantification migrants
  IN FINISHED DRUG PRODUCT

Chemical Assessment Triad
Efficient, effective and scientifically valid approach to develop safe packaging, manufacturing and delivery systems.

1. THE CHEMICAL ASSESSMENT TRIAD



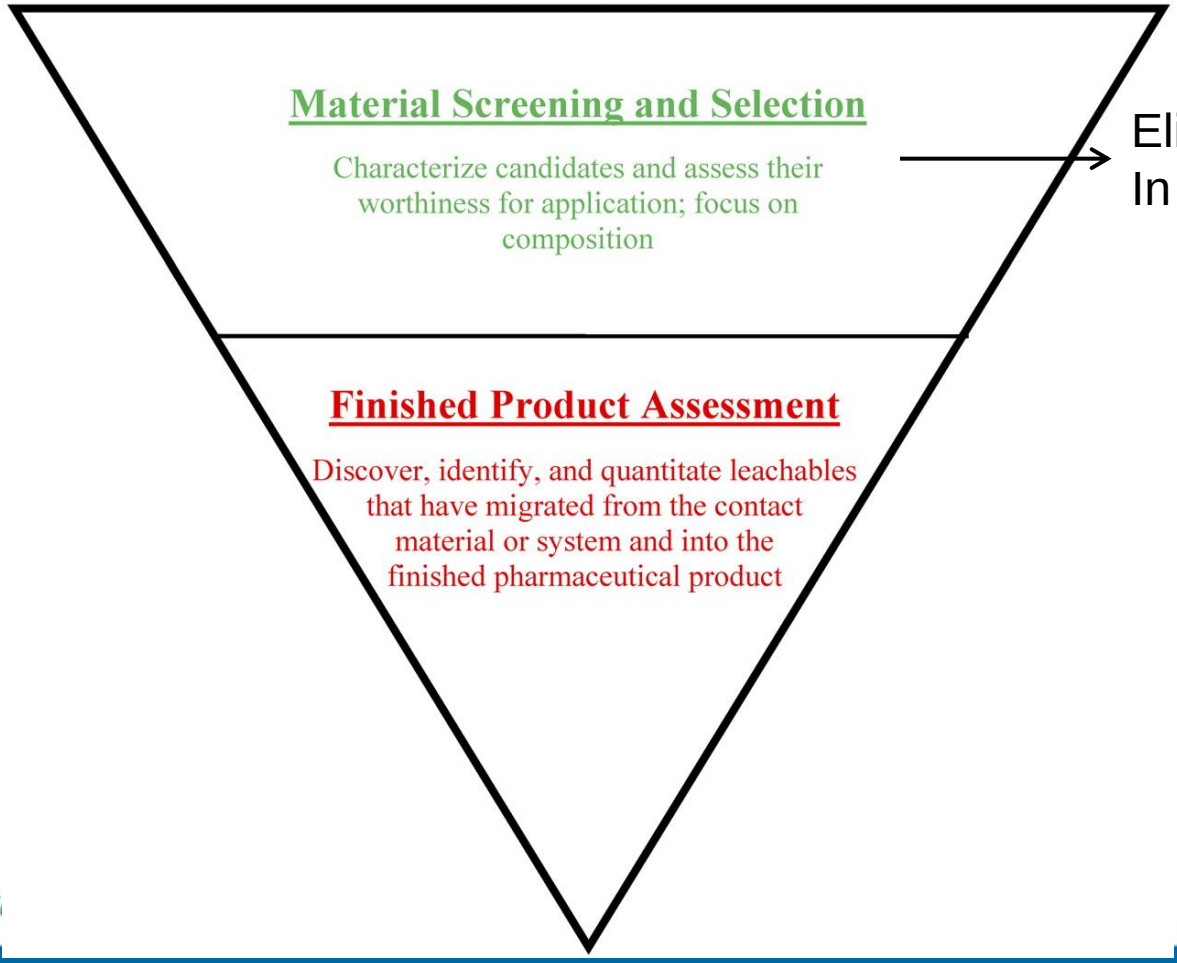
Disadvantages:

1. Performed in later stages of product development
2. Not consistent with QbD (Quality by Design)

⇨ Rarely applied

1. THE CHEMICAL ASSESSMENT TRIAD

- First step: Perform a screening of candidate materials
- Second step: migration / Leachable study



Eliminate bad actors
In beginning of proces

1. THE CHEMICAL ASSESSMENT TRIAD

- **Step 1: Material characterization**

  Early detection reduces risk on unfortunate outcome, BUT does not reflect actual use

- **Step 2: Migration study: in final drug product**

  What are all entities present in sample above certain concentration?

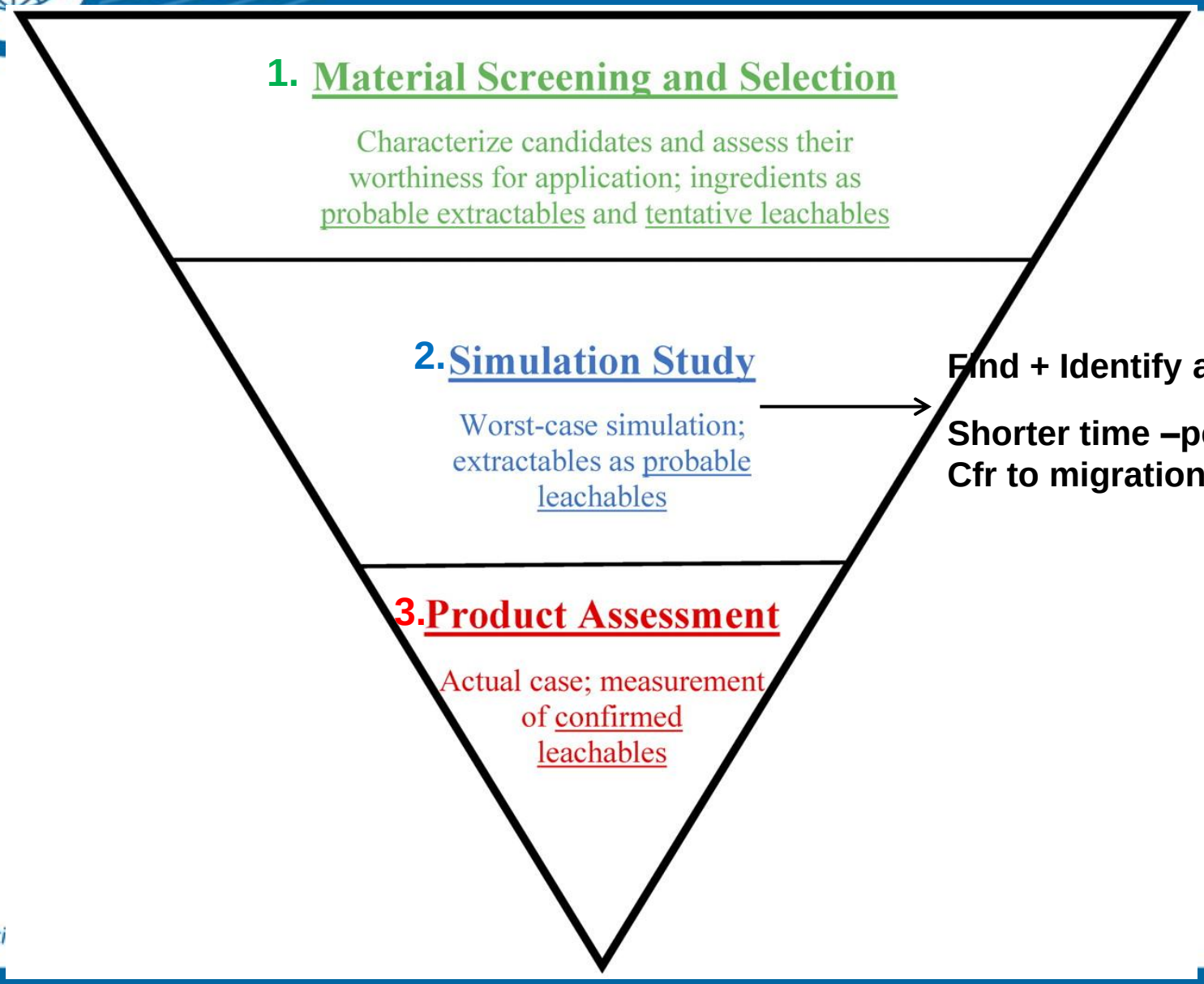
  Identification + Quantification in one step

  Problems: - complex matrices + low concentration of migrants
  - till end of shelf life
  - long time between step 1 and 2

⇨ Does the sample contain compound X above a certain conc.?

Two steps: First identification, then quantification

1. THE CHEMICAL ASSESSMENT TRIAD



Find + Identify all leachables

Shorter time –period
Cfr to migration study

1. THE CHEMICAL ASSESSMENT TRIAD

- **<u>Purpose intermediate step</u>**

- Find + identify extractables which are probable leachables
- Establish which extractables must be targeted in a migration 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

- Triad: three distinct phases:

  consistent with regulatory expectations + best demonstrated practice recommendations

- BUT

1. THE CHEMICAL ASSESSMENT TRIAD

BUT no standard approach, e.g. packaging ↔ manufacturing

Packaging:

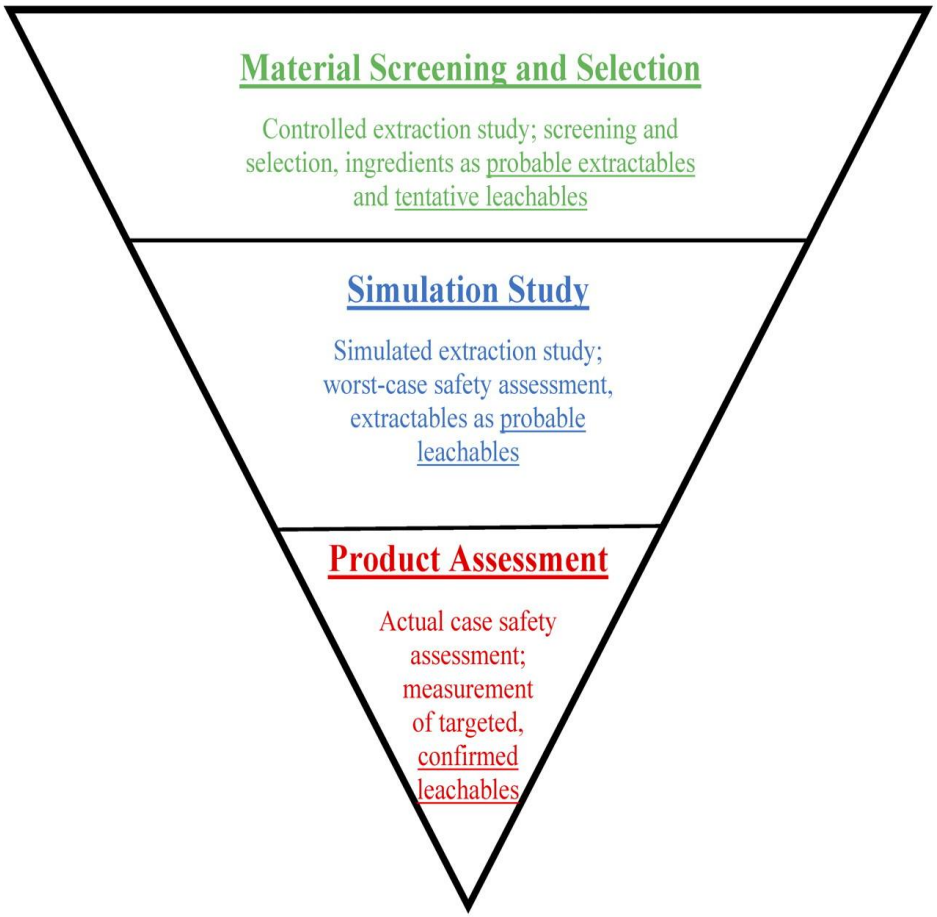
- Controlled extraction study:

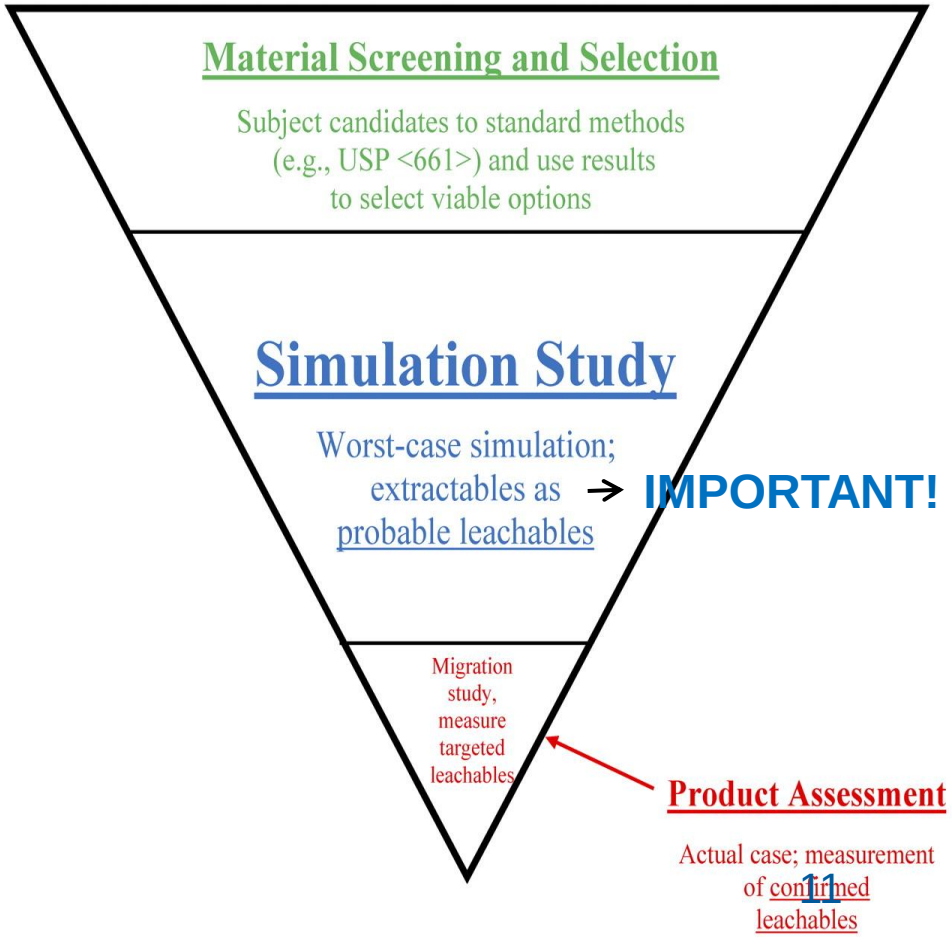
Characterize composition candidates

Manufacturing:

- Standard tests:

Potential to adversely affect safety



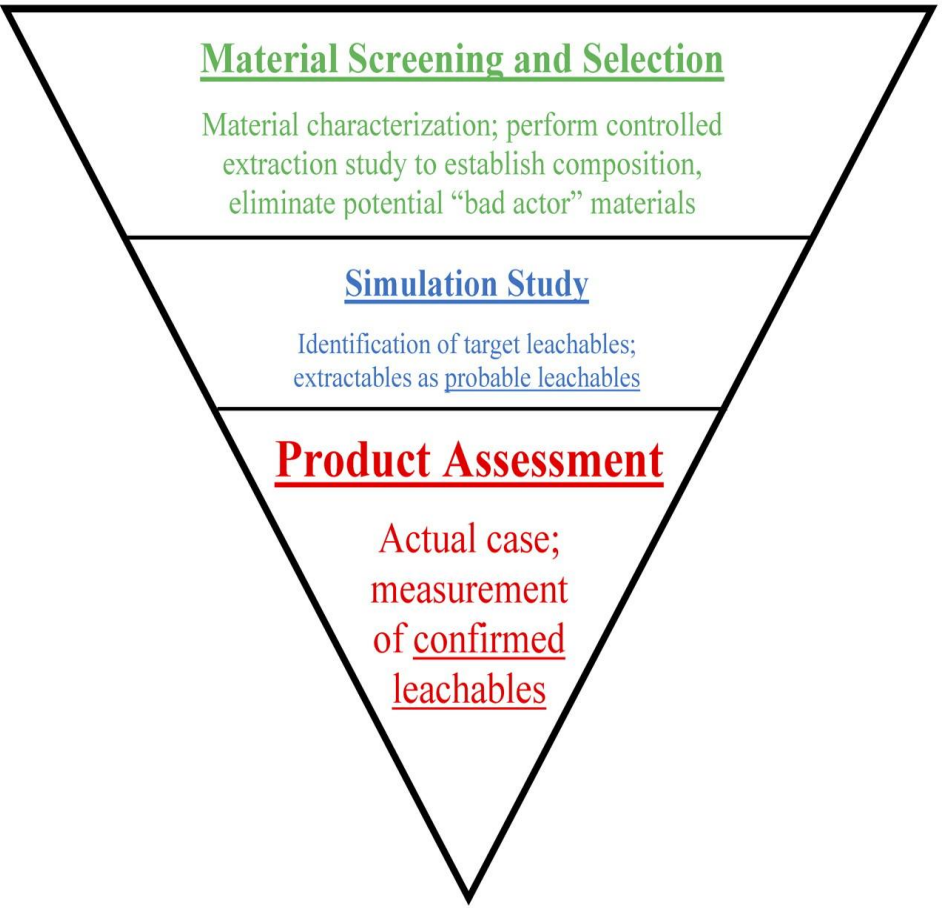


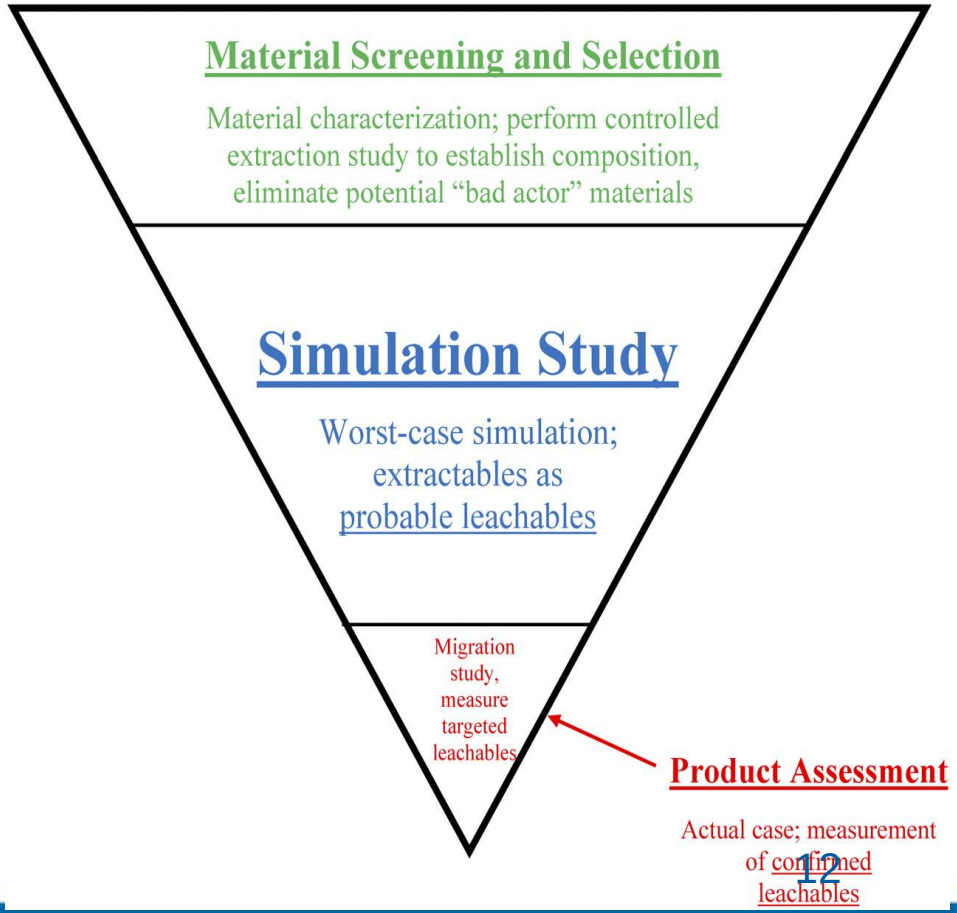
1. THE CHEMICAL ASSESSMENT TRIAD

- BUT no standard approach, e.g. simple ↔complex drug product

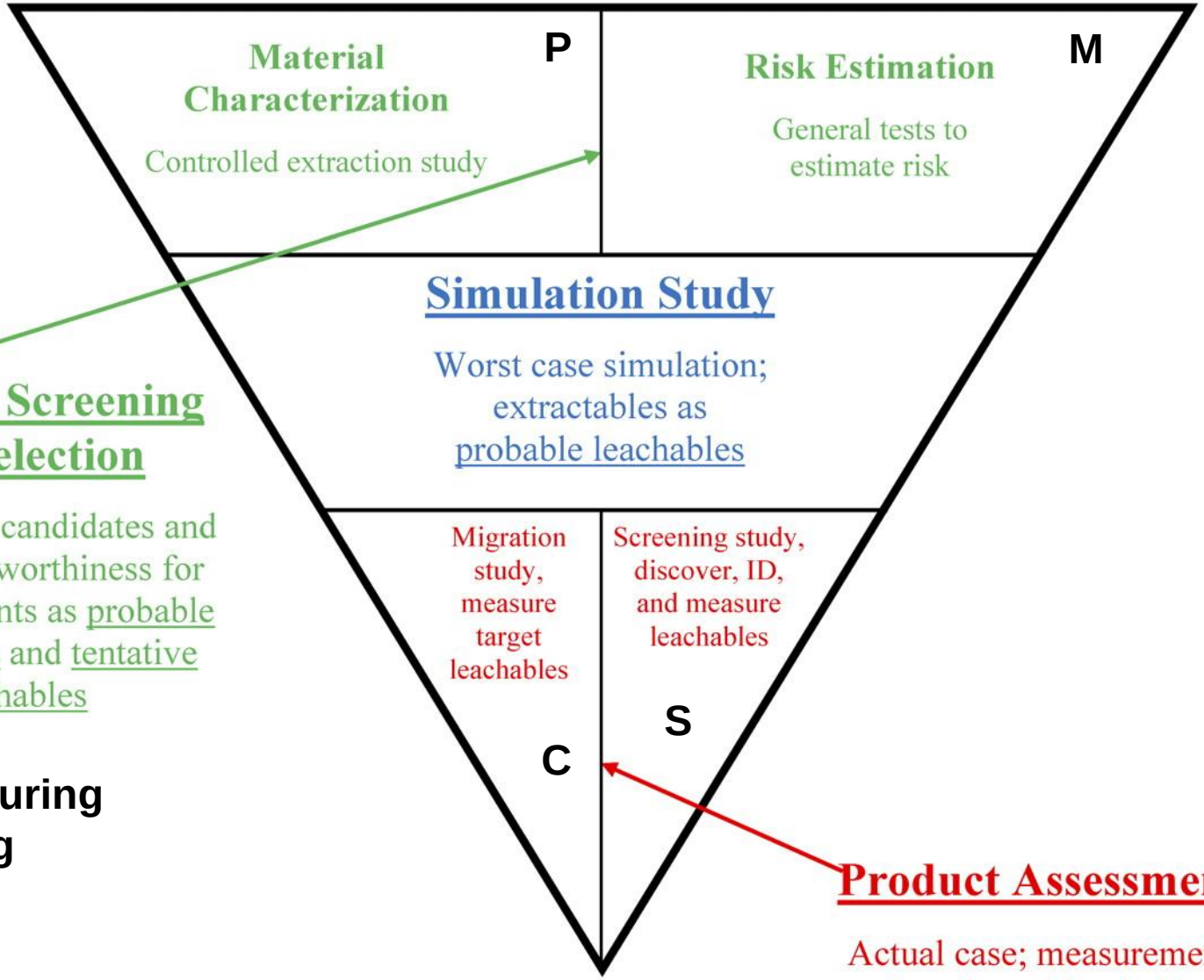
Simple drug:
- Simulation: early detection
- Migration: Important

Complex drug:
- Simulation is important
- Limited Migration study





1. THE CHEMICAL ASSESSMENT TRIAD



Material Screening and Selection

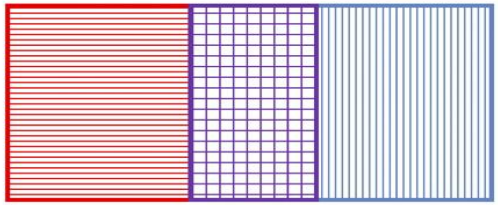
Characterize candidates and assess their worthiness for use, ingredients as probable extractables and tentative leachables

M= manufacturing
P= Packaging
S= Simple
C= Complex

1. THE CHEMICAL ASSESSMENT TRIAD

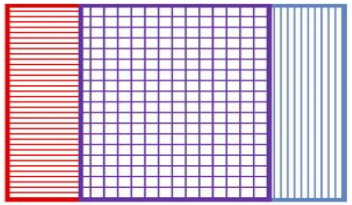
= Extractables = Leachables = Extractables that are also Leachables

Material Characterization: Ingredients as Probable Extractables and Tentative Leachables



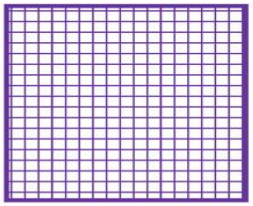
Filter out bad materials
No safety assessment

Simulation Study: Extractables as Probable Leachables



Greatest possible concentration
Worst case safety impact

Product Assessment: Extractables as Confirmed Leachables



Real case safety impact

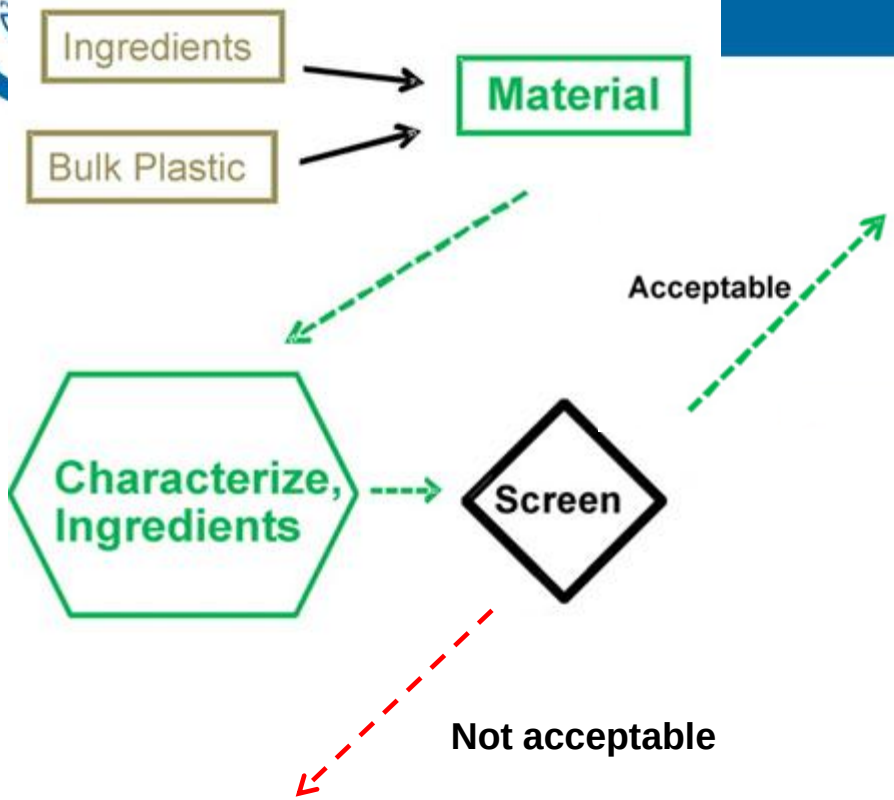
Threshold?

1. Material characterization: major compositional components
   - no safety assessment
   - 100 µg/g: typical ingredient concentration

2. Simulation study: worst-case safety risk assessment
   - AET = TTC or SCT: assume that compounds are carcinogenic
   - Result:
     > AET, but not carcinogenic: also above qualification threshold?
     > AET with toxicological risk:
     select as target compound for migration study
     < AET: probably also in migration study conc. < AET
   - Suggestion: only chemical + biological nature, not full identification
     Chemical: structural characterization (SAR)
     Biological: in vivo + in vitro tests for carcinogenicity

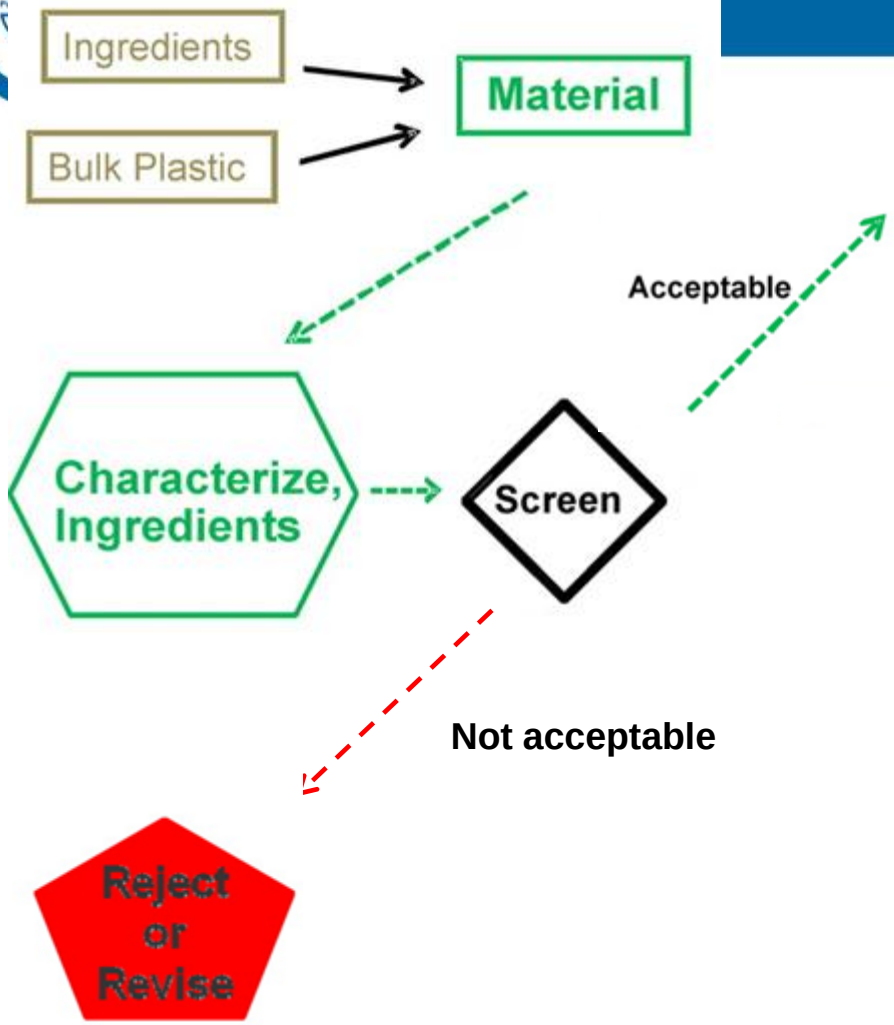
3. Migration study: focus on target compounds
   - ID is known: SCT and TTC are irrelevant, base on toxicological data
   - SCT or TTC only in case of insufficient toxicological data

AL ASSESSMENT TRIAD

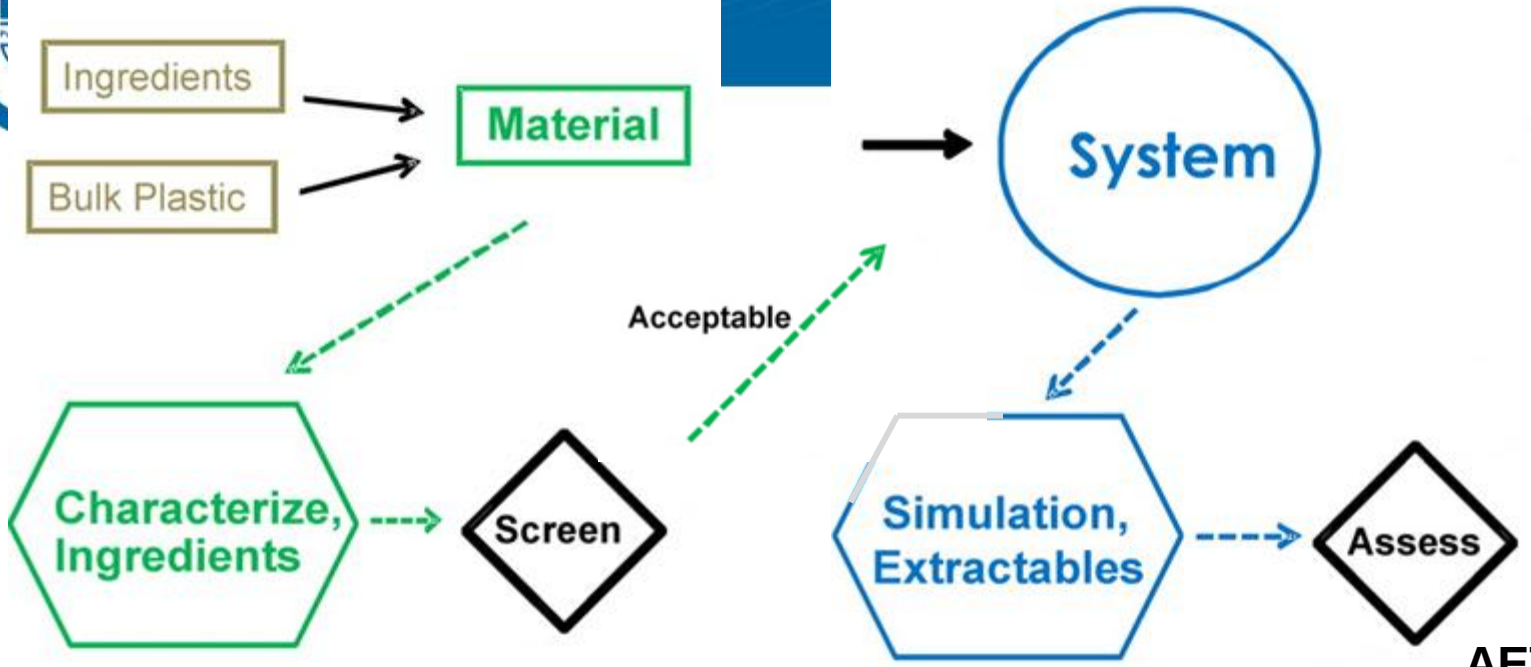


1. Material Characterization

AL ASSESSMENT TRIAD

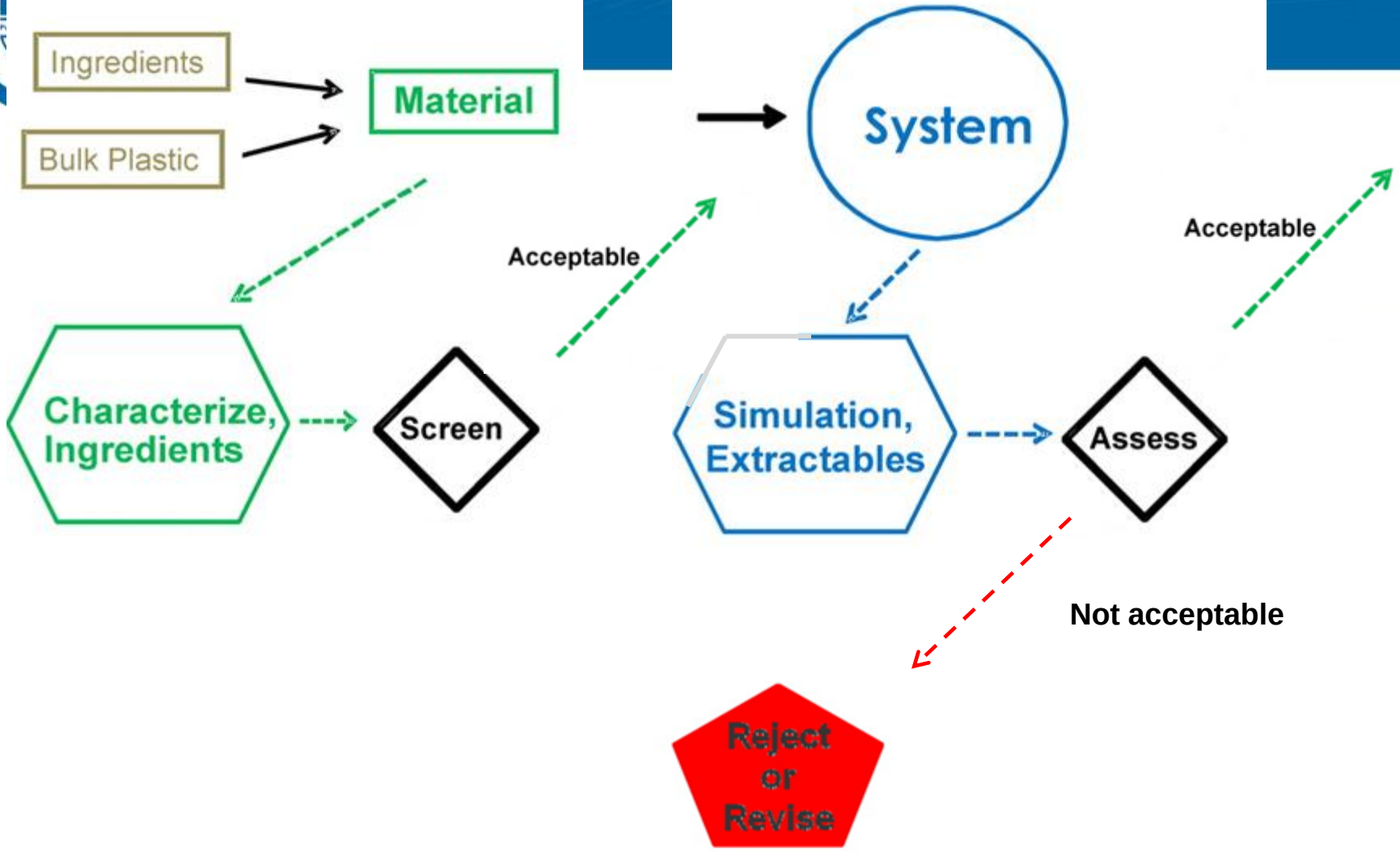


1. Material Characterization

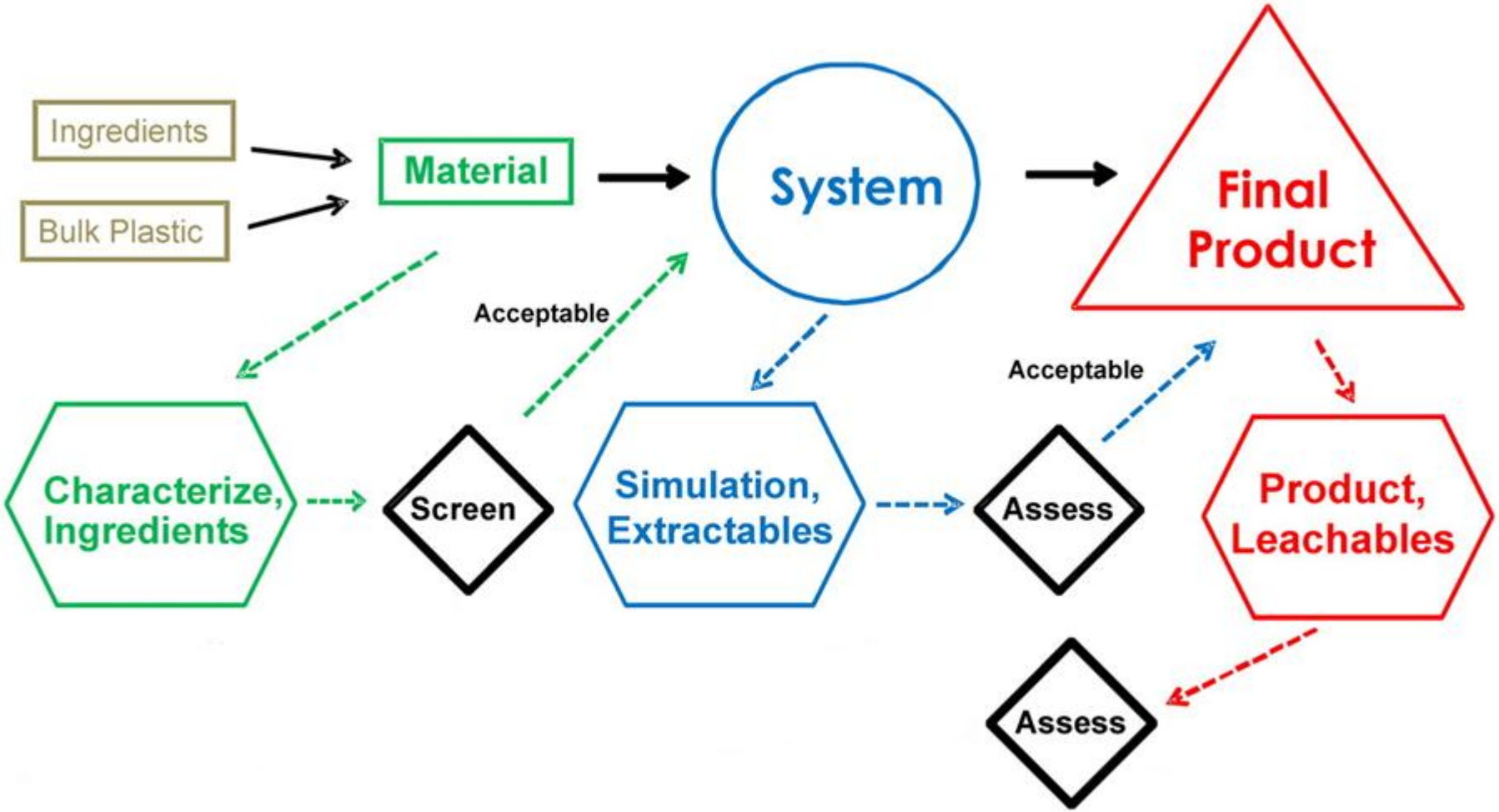


AET= TTC/SCT
Derek?

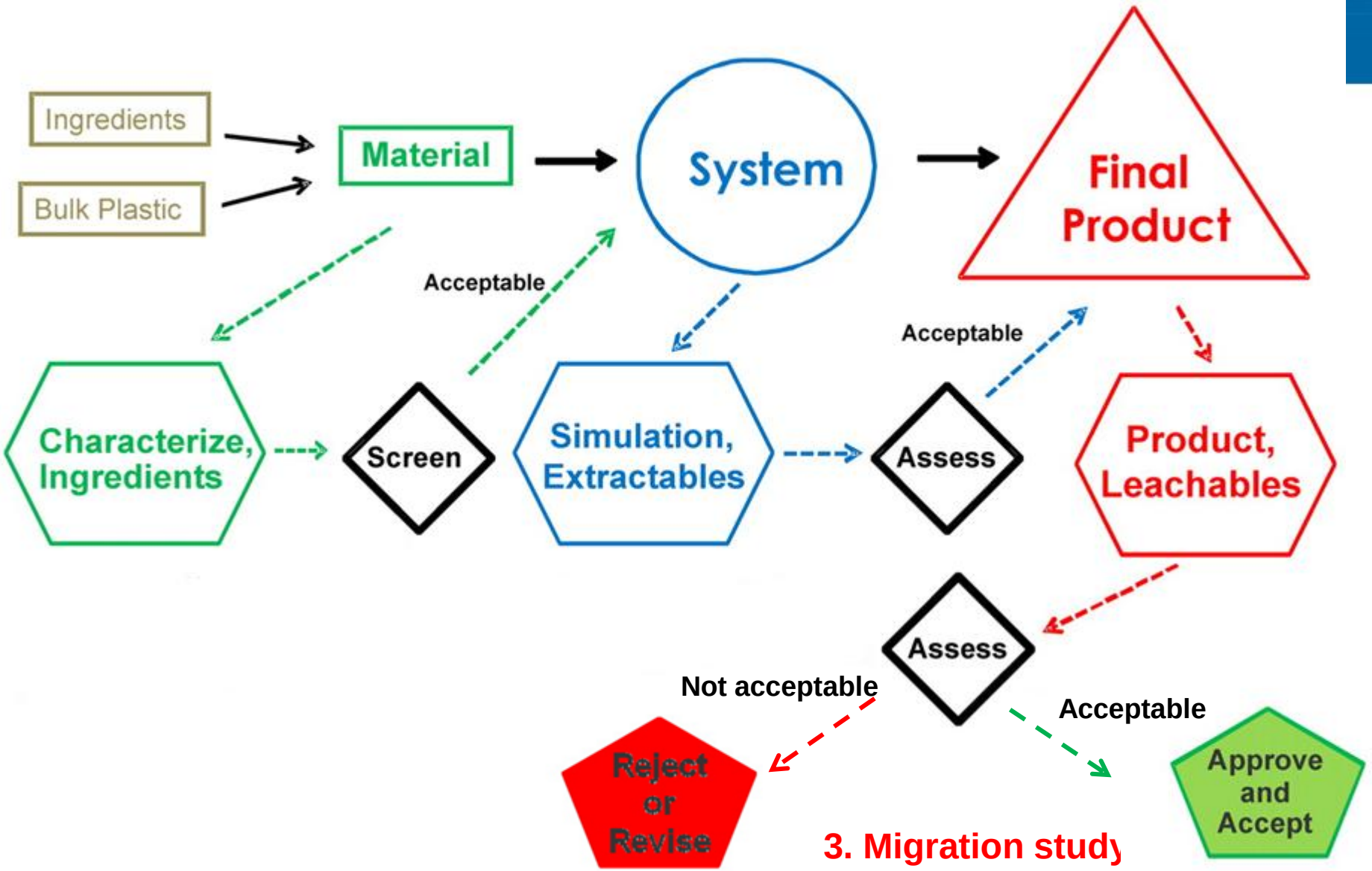
2. Simulation study



2. Simulation study

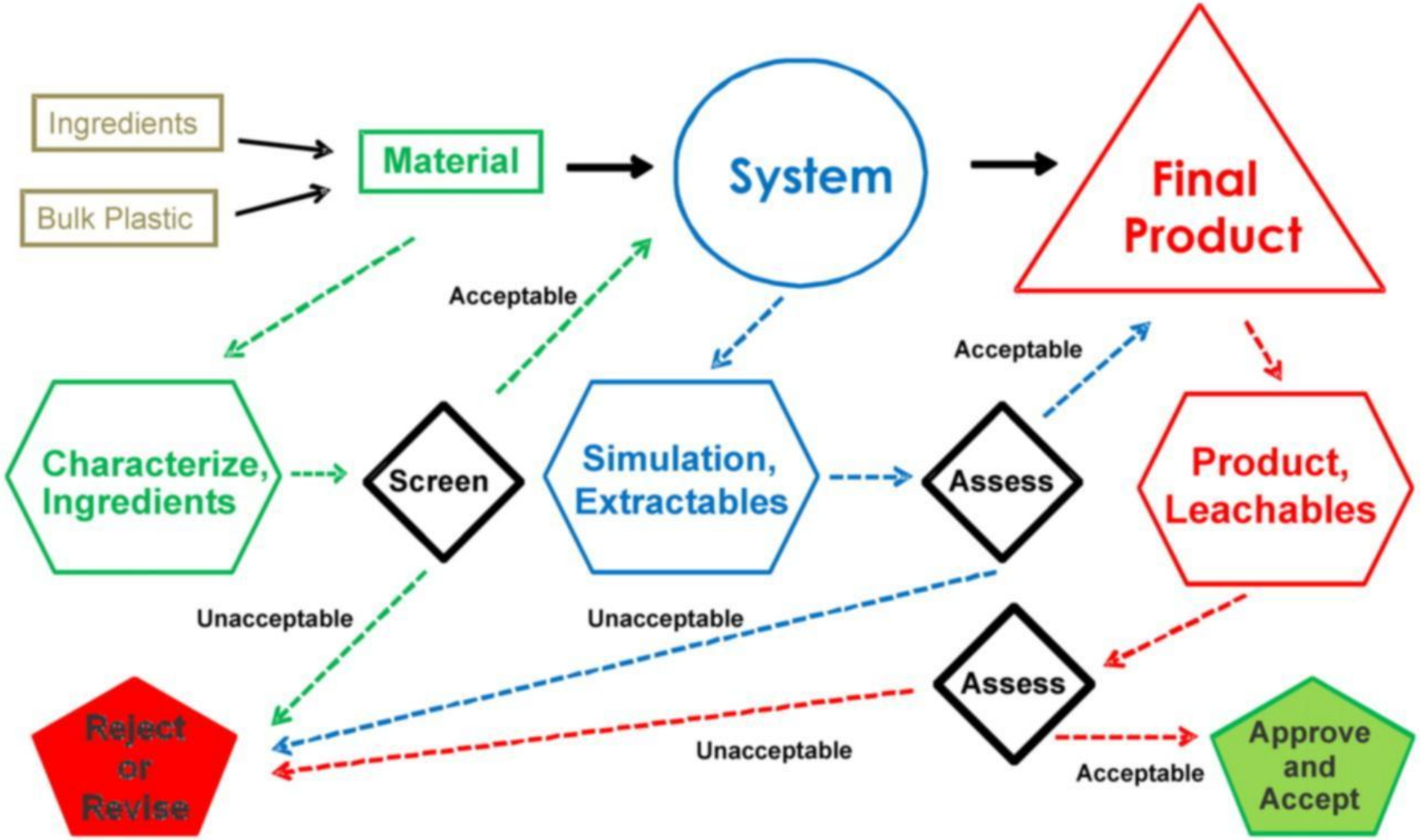


3. Migration study



3. Migration study

1. THE CHEMICAL ASSESSMENT TRIAD



Key for success: collaboration of Product developers, Analytical scientists, and toxicological experts

STEP1

Material Characterization via Controlled Extraction Studies

Note: a lot of valuable information on how to develop a scientific protocol for Parenteral / Ophthalmic DP can also be found in the following documents from the PQRI-PODP workgroup

PQRI
Product Quality Research Institute

Parenteral and Ophthalmic Drug Products (PODP) Leachables and Extractables Working Group

Issued and Effective
September, 2011

Study Protocol – Stage 2

Experimental Protocol for Simulation Study of Blow-Fill-Seal (BFS) PODP Container Closure Systems

PQRI
Product Quality Research Institute

Parenteral and Ophthalmic Drug Products Leachables and Extractables Working Group

Issued and Effective
September, 2011

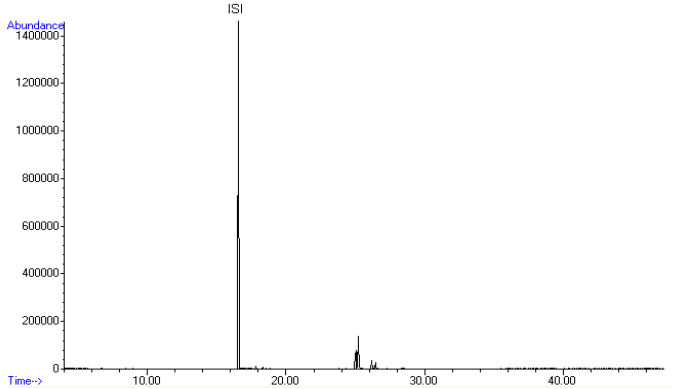
Study Protocol – Stage 1
Amendment #1

Experimental Protocol for Qualitative Controlled Extraction Studies on Material Test Articles Representative of Prefilled Syringe (PFS) and Small Volume Parenteral (SVP) Container Closure Systems

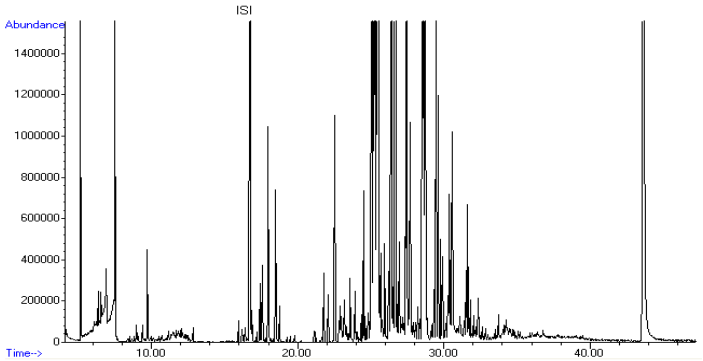
2. THE EXTRACTION STUDIES

DEPENDING UPON THE DESIGN OF E-STUDIES:

1. **LOW Nr** of extractables



2. **HIGH Nr** of extractables



HOW CAN THIS BE HARMONIZED?

2. THE EXTRACTION STUDIES

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
- Allows to Compare the Supplier Information with Actual Data
- Allows a QbD Approach
- Use of Extraction solutions which are "Compatible" with Screening techniques: CLEAN SOLVENTS
- Identify Compounds that may need to be Monitored as Leachable
  - Toxicity
  - Concentration in the Materials
  - Risk for Migration
- Not as a Final Step in the Safety Assessment!

2. THE EXTRACTION STUDIES

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

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!!

2. THE EXTRACTION STUDIES

VARIABLES that may/will have an impact on the Study Design of an Extractable 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 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?
- Primary Packaging versus Manufacturing Equipment

2. THE EXTRACTION STUDIES

IF PROVIDED <u>INFORMATION IS NOT AVAILABLE/SUFFICIENT</u>:

SET-UP AN EXTRACTABLE STUDY

1. **DESIGN** YOUR E-STUDY, SO THAT IDEALLY:

"LEACHABLES ARE A SUBSET OF EXTRACTABLES"

2. **DO NOT ALLOW SURPRISES IN YOUR LEACHABLE / STABILITY STUDIES!!!**

E-study: Take worst case conditions compared to "real use"

2. THE EXTRACTION STUDIES

Parameters To be Considered for an Extraction Study

- ✓ Extraction Solvents
- ✓ Extraction Techniques
- ✓ Extraction Conditions (Temperature, time)
- ✓ Extraction Ratio's
- ✓ Analytical Techniques
  - – Screening Techniques
  - – Targeted analysis for specific compounds

Extraction Solvents

What do you want to learn from an Extraction Study?

Determine the "Impurities Profile" of a material

Exhaustive Extraction Solvents

PQRI: Isopropanol
Hexane
Dichloromethane

BPSA: EtOH

Aqueous Extractions at different pH

Allows to determine the *"TOTAL POOL"* of Material Impurities

Risk Assessment of Total Conc. of Material Impurities

- More Complete
- More Challenging

Incorporate a level of "Simulation" already in the Extraction Study

Exaggerated Extraction Solvents

PQRI: WFI pH 2.5
WFI pH 9.5
IPA/UPW 50/50

BPSA: UPW

BPOG: 0.5N NaOH
0.1M Phosphoric Acid
WFI (neutral)
5 M NaCl
EtOH/WFI 50/50
1% Tween

Risk Assessment is

- More Realistic wrt final Use
- Does not really assess "Total Pool"

Extraction Solvents

What do you want to learn from an Extraction Study?

✓There is no Guidance, “written in stone” on which solvents to take

✓Preferably, combine:

(at least) 1 Exhaustive Extraction Solvent

preferably 2 Exhaustive Solvents

- POLAR Organic Solvent

- NON-POLAR Organic Solvent

(at least) 1 Exaggerated Solvent

✓This allows:

A profound safety assessment of the complete “Impurities Profile” of the material, while taking into account the actual composition of the DP already.

2. THE EXTRACTION STUDIES

THE CRITICALITY OF USING THE **DRUG PRODUCT (VEHICLE) (DP(V))** AS A SOLVENT

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.

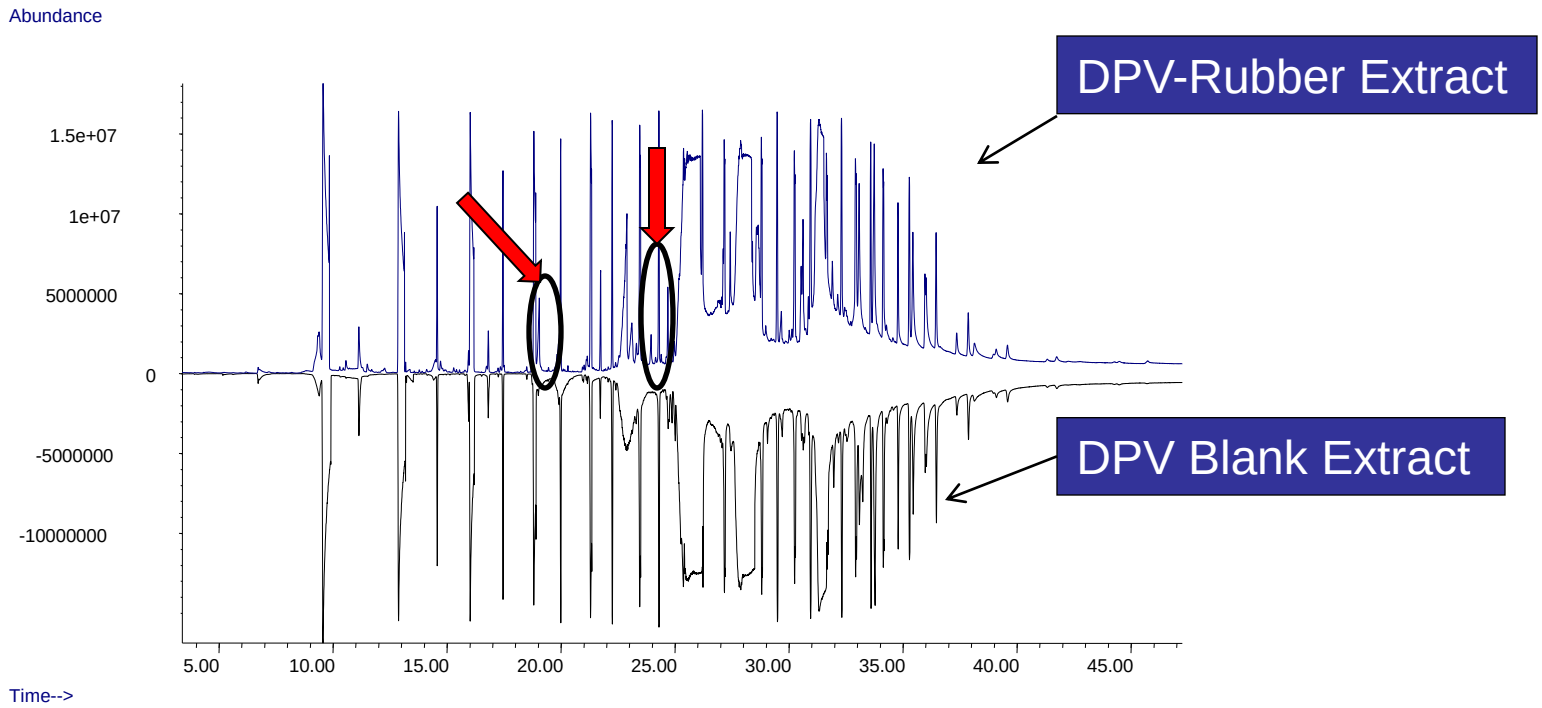
EMEA-Guideline - immediate packaging (2005)

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

2. THE EXTRACTION STUDIES

THE CRITICALITY OF USING THE **DP(V)** AS A SOLVENT

- Complex DPV: <u>COMPLEX INTERPRETATION OF E-STUDIES!!</u>



2. THE EXTRACTION STUDIES

THE CRITICALITY OF SELECTING **DP(V)** AS SOLVENT

Similar advantages/disadvantages as for WFI:

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

DISADVANTAGE: Risk of missing the presence of compounds

- *Matrix interference of DP(V) (see previous slide)*

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 to mild*
- *Difficult to select the right set of extraction conditions (e.g. extraction time, temperature!)*

EXAMPLE for DP(V) – does 8 hour reflux mimic a 3 year shelf life?

2. THE EXTRACTION STUDIES

THE CRITICALITY OF SELECTING **DP(V)** AS SOLVENT

ADVISE when selecting DP(V) as extraction solution:

1. Combine it with organic model solvent (e.g. IPA, DCM, Hexane)
   - *Minimize the risk of missing the presence of extractables*
2. If necessary: Use validated methods, developed for extraction study with DP(V) as solvent
   - *Eliminate matrix interference from DP(V) matrix*
   - *Assess DP(V) matrix degradation during extractable study*
3. Consider the right set of extraction conditions, relevant for the DP(V) contact
   - *Extraction time*
   - *Temperature*
   - *Better to consider a "simulation study" or screening leachable study set-up*

2. THE EXTRACTION STUDIES

Extraction Technique

Preferred: *Use of "old", low cost extraction techniques which can be implemented in every lab*

Exhaustive extractions: Reflux or Soxhlet

- Similar Extraction yields
- Reflux has shown - in limited cases - to introduce artefacts in extraction profile
- 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 Technique

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

Closed Vessel

- Amount of material is extracted with Extraction Solution
- Closed vessel avoids loss of **VOLATILE Organic Compounds**
- Typically ISO 10993-12 Conditions are used (e.g. 50°C, 72h)

Extraction Technique

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.
- Typically ISO 10993-12 Conditions are used (e.g. 50°C, 72h)
- Allows "One Sided Extraction"
  - Coated Rubbers
  - Sealing Discs for Cartridges
  - Multi-Layer Foils
- Better Simulation, Less Exhaustive

Extraction Technique

"Static" versus "Dynamic" Extraction

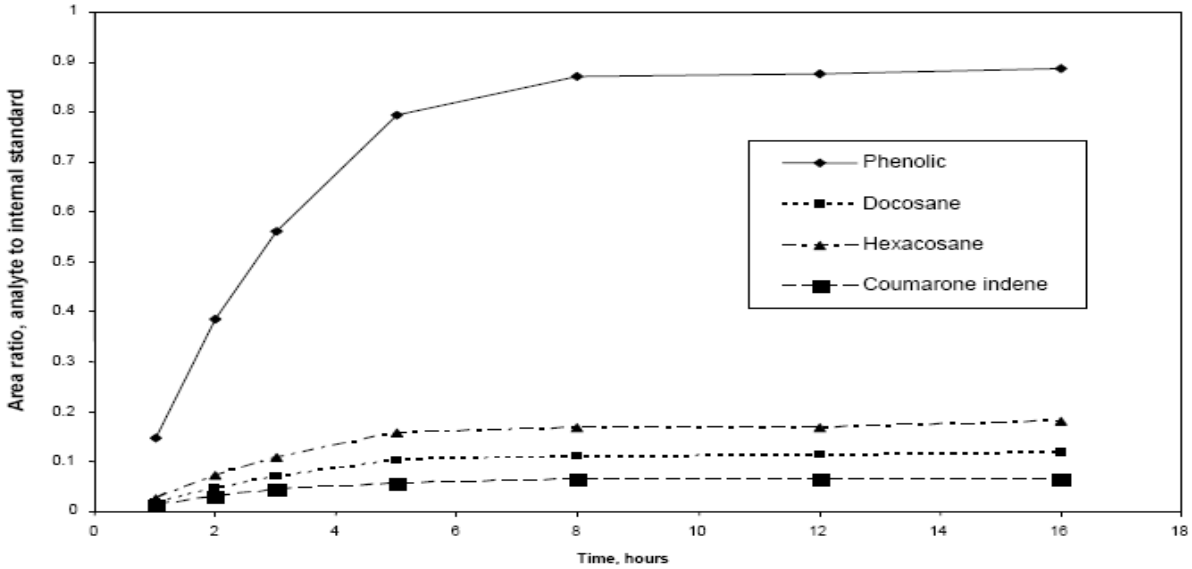
- Consideration for "In-Situ" Extractions.
- Dynamic Conditions, often considered for Production Items
  - Tubings
  - Filters
  - Pump Systems (also for IV administrations)
- Better Simulation

Extraction Conditions - Temperature / Time

- For Reflux with Organic Solvents, typically:
  - Boiling Temperature, 8 h
- For Soxhlet with Organic Solvents, typically:
  - Boiling Temperature, 24 h
- For Sonication, typically:
  - Room temperature, ½ to 1h
- For Closed Vessel and “In Situ” Extraction, typically:
  - 50°C, 72 h (ISO 10993-12)
  - However, no documentation about the completeness of extraction
- For Headspace Enrichment:
  - 40 minutes, Temperature is selected based upon the type of material (from 70°C for LDPE to 150° for Rubbers/Elastomeric Material)
- For Dynamic Extractions:
  - Extraction Conditions are determined based upon the conditions of use

2. THE EXTRACTION STUDIES

Asymptotic Extraction Profile:



PQRI-Example: Test Article: Sulphur Cured Elastomer

Extraction: DCM – Soxhlet

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

Extraction Ratio's

- 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

Analytical Techniques used to Characterize Extracts

- **PURPOSE**: Identify As many compounds as possible
- "SCREENING" Mode (see next slide)
- Broad Screening for Known & Unknown Compounds
- More Taylored Analyses for specific "known" Compounds, present in specific materials
  - Derivatisation GC/MS
  - S8 for (certain) rubbers
  - TMPTMA (HPLC) for adhesives
  - Acrylic Acid
  - Formaldehyde
  - ...

2. THE EXTRACTION STUDIES

FRESHEN UP ANALYTICAL KNOWLEDGE – TECHNIQUES USED IN EXT STUDY

Anions	Fluoride, Acetate, Formate, Chloride Nitrite, Bromide, Nitrate, Sulphate, Phosphate	Ion Chromatography
Metals/Cations	Ag, Al, Ba, Ca, Cd, Co, Cr, Cu, Fe, In, K, Mg, Mn, Na, Ni, Pb, Si, Sr, Tl, Zn...	ICP-OES or ICP-MS
Volatile Organic Compounds (VOCs)	Monomers, solvents, polymer treatment residues, smaller polymer breakdown products	Headspace GC/MS **SCREENING** (semi-quantitative)
Semi-Volatile Organic Compounds (SVOCs)	Lubricants, Plasticizers, anti-oxidants, polymer degradation products	GC/MS **SCREENING** (semi-quantitative)
Non-Volatile Organic Compounds (NVOCs)	Polymer additives: anti-oxidants, nucleating agents, UV-stabilizers, fatty acids, waxes, Polymer Degradation Products	LC-UV UPLC-HRAM **SCREENING**
Sulfur **Silicone Oil**	Cross Linking Lubrification	HPLC-UV GF-AAS

Other Techniques & Methods used in Extractable Studies

NVR: Non-Volatile Residue (BPSA – Single Use Systems)

FTIR: Characterization of NVR (BPSA – Single Use Systems)

TOC: Total Organic Content (BPSA – Single Use Systems)

pH: Release of Acidic Alkalinic compounds in Aqueous Extracts

Conductivity: Release of Salts in Aqueous Extractrs

...

- *These Techniques and Methods only allow a limited identification (FTIR) or no Identification at all.*
- *TOC reconsiliation with Chromatographic Methods may be considered, but is always a Challenge.*

Safety Evaluation of Extractable Results:

Learning from the PQRI PODP Threshold Approach

INITIAL PQRI EFFORTS: ESTABLISH SAFETY THRESHOLDS FOR OINDPs – 2006

- Toxicologists: acquired data through extenensive literature and database searches and analyses
- Chemists: acquired data by conducting extractions studies and placebo LEA studies
- Assess data and reach consensus
- Develop L & E Recommendations Document
  Submitted to FDA in 2006 for consideration in support of Regulatory Submission
- Recommendations widely used in Industry
  Not a policy/regulatory document

In 2008, PQRI started a similar approach for Parenteral & Ophthalmic DP. Expected to be finalized in 2014.

Information, from presentation D. Paskiet, CPhI Pharma Extractables & Leachables, November 29,2012, Hyderabad.

2. THE EXTRACTION STUDIES

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

The SCT is not a Control Threshold, it is not a TTC

2. THE EXTRACTION STUDIES

AET: ANALYTICAL EVALUATION THRESHOLD

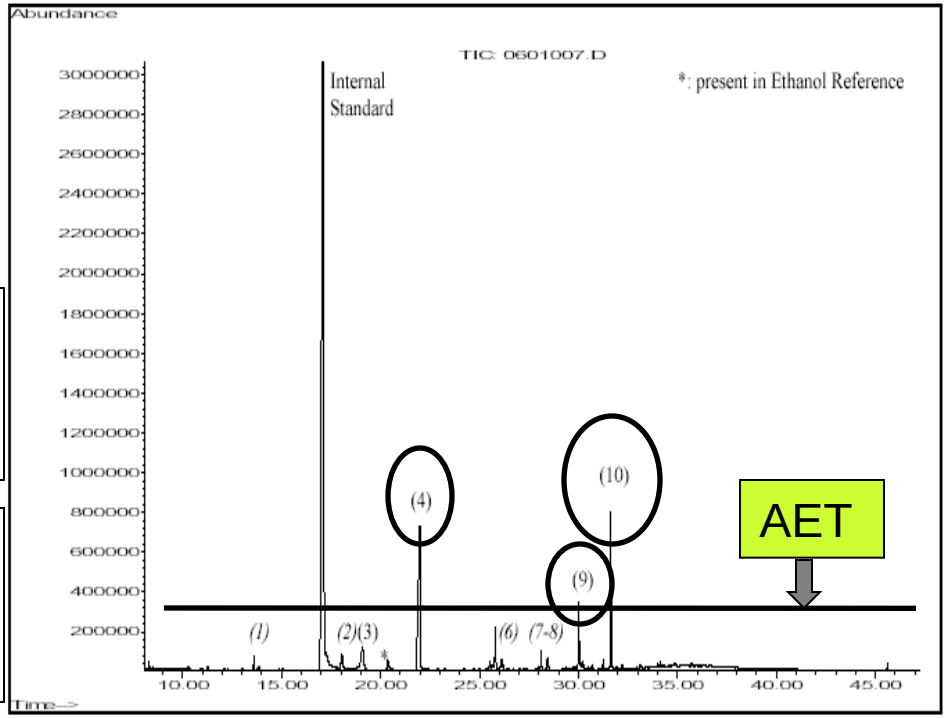
Translate SCT

into Analytical Thresholds

for Extractable Studies

Taking into account:

- *Total N° of doses / packaging*
- *Max. N° of doses administered / day*



2. THE EXTRACTION STUDIES

PQRI: SUGGESTED THRESHOLDS FOR **PARENTERAL** & OPHTHALMIC APPLICATIONS – current status

	Class I	Class II	Class III
Threshold Level (µg/day)	150 (to be confirmed)	5	1.5 - tbd

Class I: class of compounds which are **no** sensitizers, irritants, genotoxicants or carcinogens.
Class II: class of compounds which are known or expected to have sensitizing or irritating properties, but do not have any indications of genotoxicity or carcinogenicity.
Class III: class of compounds which are known or expected to be genotoxic or carcinogenic.

2. THE EXTRACTION STUDIES

THRESHOLD APPROACH CAN BE USED AT 2 DIFFERENT LEVELS

1. Safety Evaluation on results of an **Extraction Study**
2. Assisting in a Safety Evaluation on the results of a **Leachable Study**

2. THE EXTRACTION STUDIES

THRESHOLD APPROACH FOR EXTRACTION STUDIES

1. Facilitates the safety qualification of the (parts) of a Primary Packaging

2. Threshold approach could assist in a better determination of the steps to be taken in a subsequent leachable study

   - Selected Target Compounds for Quantitative LEA Study (i.e. Targets for validation)
   - Additional efforts in identification of compounds
   - In some cases, additional efforts in a safety evaluation of compound/part of a CCS
   - Expected concentration range to validate
   - ...

2. THE EXTRACTION STUDIES

THRESHOLD APPROACH FOR LEACHABLE STUDIES

Could assist in reducing efforts in safety evaluation of Leachables

- Leachables, detected below their respective threshold may not need further individual safety evaluation
- Only Leachables, detected at a level above their respective threshold, will need a more in depth chemical and risk assessment

2. THE EXTRACTION STUDIES

AET: **A**NALYTICAL **E**VALUATION **T**HRESHOLD

Example:

PFS Contains 1 dose

Maximum Daily Intake: 1 dose

Evaluation of Polymer Barrel (weight: 2 g)

Extraction ratio: 1 Barrel is extracted per 5 mL of Isopropanol
(exhaustive extraction)

EXTRACTABLES:

Threshold Class I: 150 µg/day: final AET level: 75 µg/Barrel

Threshold Class II: 5 µg/day: final AET level: 2.5 µg/Barrel

Threshold Class III: 1,5 µg/day: final AET level: 0,75 µg/Barrel

AET: ANALYTICAL EVALUATION THRESHOLD

Formula used (see PQRI recommendations):

$$\text{Est. AET} = \frac{\text{Threshold}}{\text{dose/day}} \cdot \frac{\text{total dose}}{\text{PFS}}$$

$$\text{Class I: Est. AET} = \frac{150\ \mu\text{g / day}}{1\text{dose / day}} \cdot \frac{1\text{dose}}{\text{Barrel}} = 150\ \mu\text{g / rubber}$$

$$\text{Final AET} = 75\ \mu\text{g / Barrel}$$

50% uncertainty for screening methods

2. THE EXTRACTION STUDIES

Further Calculations will give the following AET levels for the respective Classes:

	Threshold (µg/day)	Final AET (µg/barrel)	Final AET (mg/Kg)	Final AET (mg/L)
Class I	150	75	37	15
ClassII	5	2,5	1,2	0,5
Class III	1,5	0,75	0,37	0,15

Barrel weight: 2g

Extr. Ratio: 1barrel/5 mL

2. THE EXTRACTION STUDIES

Typical Results for an Exhaustive Extraction on a Polymer Barrel

	EXT result mg/L extract	EXT result mg/Kg Barrel	EXT result µg/Barrel
COMPOUND #1	0,1	0,25	0,5
COMPOUND #2	0,2	0,5	1
COMPOUND #3	1,25	3,13	6,3
COMPOUND #4	2	5	10
COMPOUND #5	0,4	1,0	2,0
COMPOUND #6	0,25	0,63	1,3
COMPOUND #7	13	32,5	65
COMPOUND #8	0,1	0,25	0.5
COMPOUND #9	27	67,5	135
COMPOUND #10	0,4	1	2
COMPOUND #11	0,1	0,25	0,5
COMPOUND #12	5,5	13,8	27,5
COMPOUND #13	32,5	81,3	163
COMPOUND #14	1,2	3	6
COMPOUND #15	0,35	0,88	1,8

2. THE EXTRACTION STUDIES

EXAMPLE OF GC/MS RESULTS FOR EXTRACTABLE STUDY

	EXT result mg/L	Class	Threshold for Class (µg/day)	AET for Class (mg/L)
COMPOUND #1	0,10	Class I	75	15
COMPOUND #2	0,20	Class I	75	15
COMPOUND #3	**1,25**	**Class III**	**0,75**	**0,15**
COMPOUND #4	2,00	Class I	75	15
COMPOUND #5	0,40	Class II	2,5	0,5
COMPOUND #6	0,25	Class I	75	15
COMPOUND #7	**13,00**	**Class II**	**2,5**	**0,5**
COMPOUND #8	0,10	Class III	0,75	0,15
COMPOUND #9	**27,00**	**Class I**	**75**	**15**
COMPOUND #10	0,40	Class II	2,5	0,5
COMPOUND #11	0,10	Class III	0,75	0,15
COMPOUND #12	5,50	Clas I	75	15
COMPOUND #13	**32,50**	**Class III**	**0,75**	**0,15**
COMPOUND #14	1,20	Class I	75	15
COMPOUND #15	0,35	Class II	2,5	0,5

Conclusion of the Threshold Evaluation:

- Exhaustive Extraction Results indicate that – if all would come out – these compounds would be detected as leachable above their respective threshold level

- Were Compounds 3, 7, 9 and 13 identified?
  In some cases, furthe attention to additional identification needs to be given

- Analytical methods for compounds 3, 7, 9 and 13 will need to be validated for the subsequent leachable study

- The validation range will be different for the 4 compounds as a result of:
  - The concentration level of the compound, found in the rubber
  - The different classess for the respective compounds:
  - The validation range should always include the AET level for the respective compound, as a minimum

- Presence of other compounds may be monitored (semi-quantitatively) in Leachable Study, using screening methodology

STEP 2

SIMULATION STUDY

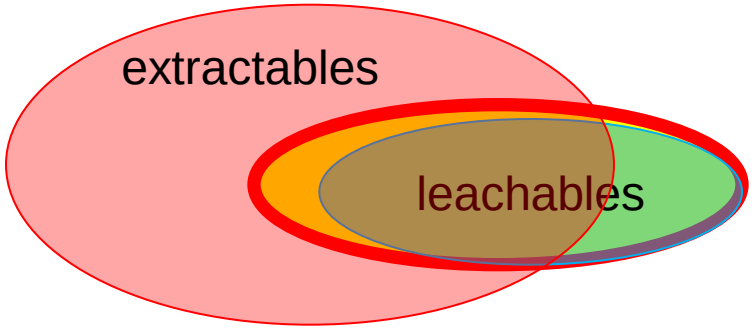
3. THE SIMULATION STUDIES

» Purpose of Simulation Study

- Find + identify extractables which are **probable leachables**
- Establish which extractables must be targeted in a migration 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

3. THE SIMULATION STUDIES

CLOSING THE GAP!!



Additional Study Design: SIMULATION STUDY

What SIMULANTS can be considered?

1. **Aqueous based solutions with organic solvent added** to mimic the extraction propensity of the actual DP
   - XX% Ethanol in UPW
   - XX% Isopropanol in UPW

2. The **Drug Product Vehicle**
   - When the DPV is not substantially different from the DP

3. The **Drug Product** itself (see “Closing the Gap” presentation)
   - “Screening Leachable Study”

3. THE SIMULATION STUDIES

Conditions of a Simulation Study:

1. Exaggerated & Accelerated Conditions:

   Exaggerated: Composition of the Simulant

   Increased Surface area

   Underfilling (e.g. 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: Exposed Surface Area of Plungers 10x compared to reality

Accelerated: 3 Months at 40℃

Using the DP

Only for visualisation – rubber plunger surface area to solution >> 10

3. THE SIMULATION STUDIES

Using a **SIMULANT** For SIMULATION Studies

Advantage

- Good solution if you have multiple DP using 1 C/C system
- Account for Unexpected Leachables
- Simulant allows to “screen”
- Allows to narrow down efforts in FORMAL Leachable Study
- Typically, not an end point in the E/L assessment. If considered as an end point, more documentation needs to be provided

Disadvantage

- Not Account for Reactive Leachables
- High Documentation Requirements
- Regulatoy Acceptance

Using a **DRUG PRODUCT** For SIMULATION Studies

Advantage

- Account for Unexpected Leachables
- Account for Reactive Leachables
- Allows to Predict Leachables very accurately
- Allows to narrow down efforts in FORMAL Leachable Study
- In some cases, it can be an end point

Disadvantage

- You ONLY have documentation of *“End of Shelf Life”* under accelerated conditions
- Not All DP can be used to “screen” for leachables

Regulatory Acceptance of SIMULATION Study

Think as a Regulator!

"Can you Prove that the Extraction Propensity of the Simulant is "worst case" compared to the Drug Product?"

e.g. 20% EtOH in UPW: More Documentation is needed

Simulant = DP: Yes

"Can you prove that there is no interaction between the leachables and the composing ingredients of a DP?"

e.g. 20% EtOH in UPW: No, needs to be studied

Simulant = DP: Yes

Regulatory Acceptance of SIMULATION Study

Can a SIMULATION study be considered as an alternative to a FORMAL LEACHABLE Study?

Using a Simulant like 20% EtOH/UPW:

- *A Lot of evidence will need to be provided to prove the Predictive Character of a Simulation Study.*
- *Secondary Leachables – Reaction products of leachables with DP – are not covered*
- *CONCLUSION: Risky!*
- *The approach can be taken if a DP is Extremely Complex in its composition and no trace analysis is possible. However, the failed attempts should be documented to help justify the alternative approach*

Using a the DRUG PRODUCT as a Simulant:

- *Some evidence will need to be provided to prove the Predictive Character of a Simulation Study, compared to a FORMAL LEACHABLE Study*
- *REMARK: a Screening approach does NOT work for ALL Drug Products*
- *Secondary Leachables – Reaction products of leachables with DP – are covered*
- *However: only the end point is tested, no across the whole shelf life...*
- *CONCLUSION: More Likely to be Accepted, but this cannot be generalized.*

CONCLUSION:

A Simulation Study

- Can help you to predict the “Probable” leachables
  - Narrow Down the long list of Extractables
  - Look at Unexpected leachables
  - Reactive Leachables
- Assist on reducing the efforts in “FORMAL” Leachable Study
- Considering a Simulation study as an End Point in E/L Qualification:
  - For Simulants: Be Careful!
  - For DP (Screening Leachable Study): yes in certain cases

STEP 3

MIGRATION / LEACHABLE STUDY

4. THE MIGRATION / LEACHABLE STUDIES

- TRYING TO ASSESS THE LEACHING BEHAVIOUR
- ASSESS POTENTIAL TOXIC CONSEQUENCES = **SAFETY**
- ASSESS IMPACT ON **DRUG PRODUCT QUALITY**
- FOCUS ON QUANTIFICATION OF **"TARGET" COMPOUNDS**

  KNOWN POLYMER ADDITIVES USED
  VALIDATION PACKAGE OF CONTAINER SUPPLIERS
  EXTRACTABLES STUDY INFORMATION

- **"SIMULATED USE"** CONDITIONS

  STORAGE TIME / TEMPERATURE / HUMIDITY
  CONDITIONS: SIMILAR TO STABILITY STUDIES
  PHARMACEUTICAL FORMULATION AS CONTACT SOLUTION

- **VALIDATED METHODS** (ICH Q2(R1))

4. THE MIGRATION / LEACHABLE STUDIES

Typically, a **Leachable Study** is **looking at all DIFFERENTIAL peaks** in a **Comparative Assessment** between:

- *DP, aged in inert container (Aged Blank DP) (no contact with Packaging)*
- *The DP, aged in the Packaging System (Primary & Secondary Packaging)*

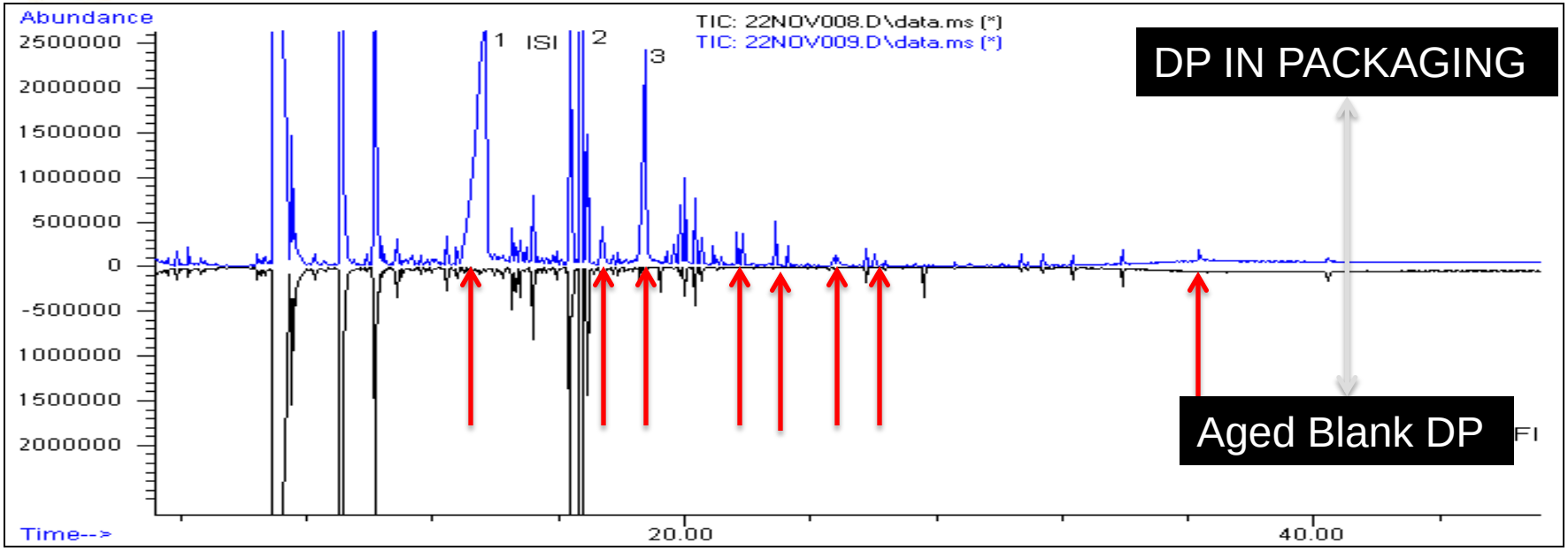
DP IN PACKAGING

Aged Blank DP

Every Compound that is present in the DP, aged in the Packaging System But NOT in the DP, aged in inert container

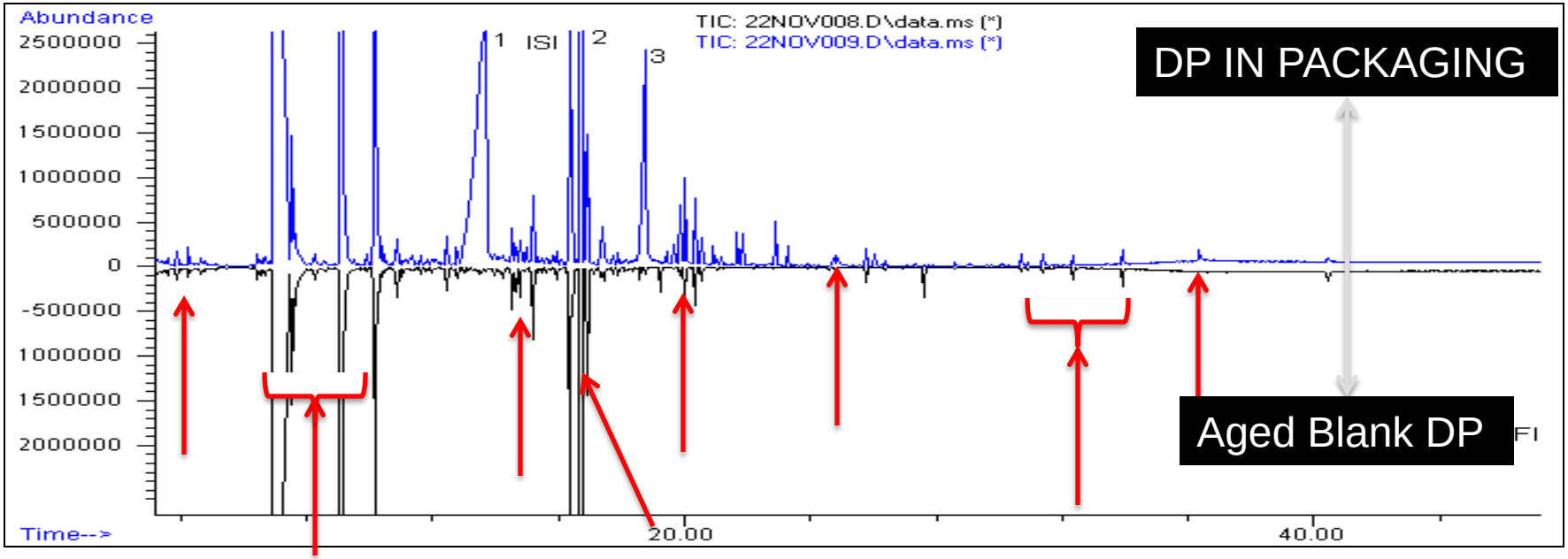
CONSIDERED AS LEACHABLE

4. THE MIGRATION / LEACHABLE STUDIES



Differential peaks can be attributed to the interaction of the DP with the Packaging

4. THE MIGRATION / LEACHABLE STUDIES

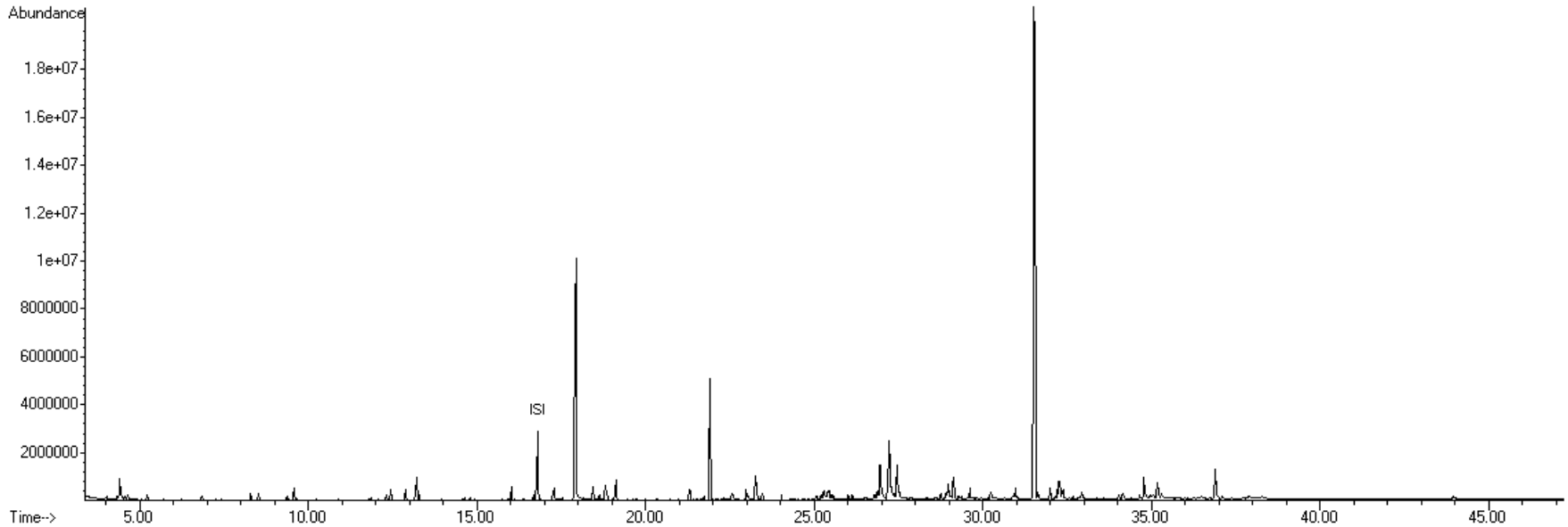


In addition to LEACHABLES from Primary Packaging, what else can be seen (Present in both conditions?)

- *API, API degradants (expected & unexpected)*
- *Impurities from API (a.o. Genotoxic Impurities, residues from synthesis of API)*
- *DP ingredients + degradants*
- *Impurities from Ingredients (excipients, adjuvants, buffers,...)*
- *Leachables from processing materials (storage bags, filters, tubing materials...)*
- *Leachables from Intermediate Storage*
- *Secondary Leachables (reactive leachables)*
- *Leachables from the secondary packaging (label, ink, adhesive, overwrap, cardboard boxes…)*
- *in certain cases: batch cross contamination (traces)...*

4. THE MIGRATION / LEACHABLE STUDIES

Leachable without Blank Reference = IMPURITIES PROFILING



75 Organic Impurities = More than only Leachables!

4. THE MIGRATION / LEACHABLE STUDIES

Leachable without Blank Reference = IMPURITIES PROFILING

n°	Ident. Level	SEMI-VOLATILE COMPOUND	CAS-No. or Spectrum		Retention Time (min)	Test result (µg/L)
4	IC	2-Octanone	Leachable		9.38	25
5	IC	Octamethylcyclotetrasiloxane / $(C_2H_6SiO)_4$			9.58	45
6	IC	Nonanal			11.87	17
8	IC	3,6-Dimethyl-1,4-dioxane-2,5-dione			12.46	53
9	IC	Decamethylcyclopentasiloxane / $(C_2H_6SiO)_5$			12.89	29
10	IC	3,6-Dimethyl-1,4-dioxane-2,5-dione			13.23	90
11	IC	$C_{13}H_{24}$ Rubber Oligomer	Leachable		13.30	22
12	TIC	$C_{13}H_{26}$ Rubber Oligomer	Leachable		14.65	19
13	IC	1,3-Di-tert-butylbenzene			14.82	17
14	IC	Dodecamethylcyclohexa-siloxane / $(C_2H_6SiO)_6$			16.04	56
15	TIC	Aliphatic*, $C_{14}H_{26}$			16.69	12
17	IC	Chloro-aliphatic*, $C_{13}H_{23}Cl$;	Leachable		17.54	18
19	IC	BHT-OH			18.46	53
20	IC	Bromo-aliphatic*, $C_{13}H_{23}Br$;	Leachable		18.63	24
21	MPC	Tetradecamethylcyclohepta-siloxane $(C_2H_6SiO)_7$			18.82	69

4. THE MIGRATION / LEACHABLE STUDIES

Leachable without Blank Reference = IMPURITIES PROFILING

n°	Ident. Level	SEMI-VOLATILE COMPOUND	Leachable		Retention Time (min)	Test result (µg/L)
22	IC	Bromo-aliphatic*, $C_{13}H_{23}Br$;	Leachable		18.87	29
23	IC	BHT	Leachable		19.13	57
24	MPC	Hexadecamethylcycloocta-siloxane / $(C_2H_6SiO)_8$			21.31	34
25	IC	Heptadecane	Leachable		21.73	16
26	IC	Aliphatic*, $C_{21}H_{40}$ Rubber Oligomer	Leachable		21.92	390
31	MPC	Octadecamethylcyclonona-siloxane / $(C_2H_6SiO)_9$			23.47	23
32	IC	Diisobutyl phthalate			24.04	11
34	IC	n-Hexadecanoic acid	Leachable		25.08	14
35	IC	Dibutyl phthalate			25.20	20
37	MPC	Eicosamethylcyclodecasiloxane $(C_2H_6SiO)_{10}$			25.40	26
38	IC	Bromo-aliphatic*, $C_{21}H_{39}Br$;	Leachable		25.44	49
42	TIC	Aliphatic*; main masses: 57, 97, 99, 83, 43	Leachable?		26.14	24
45	TIC	Aliphatic*; main masses: 97, 57, 45, 107, 55	Leachable?		26.87	74
46	TIC	Aliphatic*; main masses: 97, 57, 45, 107, 80	Leachable?		26.95	177
47	IC	Oleic acid	Leachable		27.22	324
49	MPC	Tetraicosamethylcyclododeca-siloxane $(C_2H_6SiO)_{12}$			28.76	17

4. THE MIGRATION / LEACHABLE STUDIES

Leachable without Blank Reference = IMPURITIES PROFILING

n°	Ident. Level	SEMI-VOLATILE COMPOUND	Leachable		Retention Time (min)	Test result (µg/L)
53	IC	Oleamide			29.61	42
54	MPC	Hexaicosamethylcyclotrideca-siloxane $(C_2H_6SiO)_{13}$			30.23	17
57	IC	DEHP			31.52	2200
58	MPC	Octaicosamethylcyclotetradeca-siloxane / $(C_2H_6SiO)_{14}$			31.62	24
66	MPC	Triacontamethylcyclopentadeca-siloxane / $(C_2H_6SiO)_{15}$			32.93	37
67	IC	Squalene			34.02	14
68	MPC	Dotriacontamethylcyclohexa-decasiloxane $(C_2H_6SiO)_{16}$			34.15	27
72	MPC	$(C_2H_6SiO)_{17}$			35.29	12
74	MPC	$(C_2H_6SiO)_{19}$			37.89	19
75	IC	Irgafos 168 oxidized			43.95	28

CONCLUSION: Leachables are only a part of the total impurities profile of a DP!

Impurities Profiling: also discribed in the **ICH Q3A**, under:
5.REPORTING IMPURITY CONTENT OF BATCHES

... The applicant should ensure that complete impurity profiles (e.g. Chromatograms) of individual batches are available, if requested...

Remark: Impurities Profiling for Elemental Impurities (ICH Q3D) is being implemented at this moment
Discrepancy between approach for inorganic and organic impurities...

CHALLENGES IN LEACHABLE STUDIES

LEACHABLE STUDIES ≡ STABILITY STUDIES

HOWEVER, THE **FOCUS** IS ON

1. *TRACE ANALYSES, LOW LEVELS*
2. *OF PACKAGING IMPURITIES*
3. *IN (OFTEN) COMPLEX MATRICES*
4. *USING OPTIMIZED METHODS*
   (HPLC-UV is not sufficient)

"...LEACHABLE STUDIES ARE OFTEN LIKE LOOKING FOR A NEEDLE IN A HAYSTACK..."

CHALLENGES IN LEACHABLE STUDIES

Guidelines (FDA, EMA) require to develop analytical methods that verify the presence of impurities at very low levels:

PQRI

Safety Concern Threshold (SCT) of 0.15 µg/day (OINDP) or 1.5 µg/day (PODP)

ICH

Genotoxic Impurities: TTC: 1.5 µg/day

This requires Analytical Methods which often need to go << 1 ppm in the Drug Product!

Typical MQL are between 0.01 mg/L and 0.1 mg/L...

CHALLENGES IN LEACHABLE STUDIES

METHOD DEVELOPMENT & VALIDATION: CHALLENGING BECAUSE OF THE

1. COMPLEXITY OF THE DRUG PRODUCT

2. REQUIRED LOW QUANTIFICATION LIMITS

CHALLENGES IN LEACHABLE STUDIES

METHOD DEVELOPMENT & VALIDATION: COMPLEXITY OF THE DRUG PRODUCT!

API – small molecules	0.01% - 10%
API – Biopharma (Strains, Proteins, MAb, Albumin...)	0.001% - 30%
Organic/Inorganic Buffers	0.01% - 1%
Tween 20 – Tween 80	0.001% - 5%
Sorbitol, Glucose	0.1 – 10%
PEG-400	0.1 – 1%
Preservatives	
Desinfectants	

METHODS SHOULD BE **"SUFFICIENTLY QUANTITATIVE"**

- Type of Drug Product – Route of Administration (From Inhalation to Oral)
- Primary Packaging versus Single Use Bioprocessing Equipment
- Administration Regimen ("*Daily, Chronic*" versus "*Once in a Lifetime*")
- Complexity of Drug Product Composition
  - ✓ *Can a Screening Methodology with Method Suitability Test be applied?*
  - ✓ *Analytical Interference: does a New Method need to be developed, specific for this DP?*
- Company Strategy for Compliance

"METHOD SUITABILITY TEST"

- Analytical Method used: Screening Method (also used for Extractables Testing)
- Spiking of Target Compounds
- Spiking at relevant Levels (e.g. AET level)
- Only verifying if Screening Methodology works at relevant levels
- Can be considered as a "LIMIT TEST"
- Lower Cost, compared to Full Validation

4. THE MIGRATION / LEACHABLE STUDIES

"METHOD SUITABILITY TEST", Not suitable for:

- Inhalation DP (MDI), LVP and certain General Parenteral Applications
- DP which require a *Daily and/or Chronic Administration*
- Complex of Drug Products in their Composition
  - ✓ Screening Methodology with Method Suitability Test may not work
  - ✓ Potential Analytical Interference for certain DP

Validated Methods (ICH Q2(R1))

• Specificity - Identification	
• Range	
• Linearity of Method	r > 0.990
• Extraction Yields (when applicable)	
• Detection Limit	Application
• Quantification Limit	Specific
• Accuracy in low, mid and high range	100 ± 25%
• Precision in low, mid and high range	< 25%

Other: Intermediate Precision, Robustness...

For Validation of Analytical Methods for Trace Analysis other specifications apply than for API validation

CHALLENGES IN LEACHABLE STUDIES

DIVERSITY OF STABILITY CONDITIONS TO BE CONSIDERED:

SIMILAR TO WHAT NEEDS TO BE OFFERED FOR STABILITY STUDIES!!

4. THE MIGRATION / LEACHABLE STUDIES

STABILITY CONDITIONS –CLIMATIC ZONES

General case	**25±2°C/ 60±5%RH**
	30±2°C/ 65±5%RH
	40±2°C/ 75±5%RH
DS intended for storage in refrigerator	5±3°C
	25±2°C/ 60±5%RH
DS intended for storage in freezer	-20±5°C
DP in semi-permeable containers	25±2°C/ 40±5%RH
	30±2°C/ 35±5%RH
	30±2°C/ 65±5%RH
	40±2°C/ 25±5%RH
Ultralow temperature for biotech products	-80°C

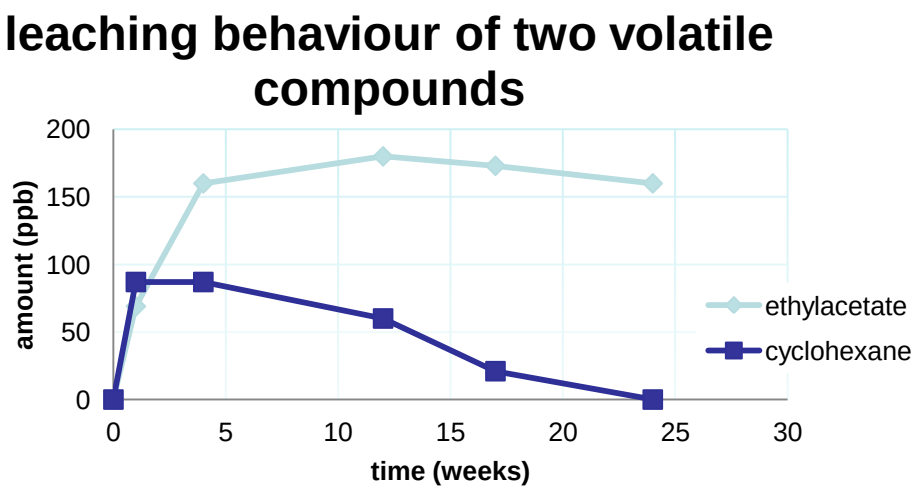
4. THE MIGRATION / LEACHABLE STUDIES

Case study LEA: 100 mL flexible multi-layer bag incl. Drug solution ageing at 25°C for 6 months

VOC (Volatile Organic Compounds) monitoring Ethylacetate and Cyclohexane

Conclusion: Ethylacetate: asymptotic behaviour

Cyclohexane: dissapears: worst case concentration is NOT ALWAYS AT THE END OF SHELF LIFE!!



CONCLUSION: LEACHABLES SHOULD BE STUDIED ACROSS THE SHELF LIFE OF A DRUG PRODUCT

Example Setup of the Study
Analytical Program for Leachable study of a Pre-Filled Syringe

Type of Solution	Storage Time (Months)				
	0	3	6	12	24
Pharmaceutical Matrix in Pre-filled Syringes (Test Item) at 5 ± 3 °C	×	×	×	×	×
Pharmaceutical Matrix in Inert Containers (Blank) at 5 ± 3 °C	×	×	×	×	×
Pharmaceutical Matrix in Pre-filled Syringes (Test Item) at 25 ± 3 °C	-	×	×	-	-
Pharmaceutical Matrix in Inert Containers (Blank) at 25 ± 3 °C	-	×	×	-	-
× = sampling time point					

4. THE MIGRATION / LEACHABLE STUDIES

Example Setup of the Study

Analytical Program for Leachable study of a Pre-Filled Syringe

TARGET COMPOUNDS	ANALYTICAL METHOD
VALIDATED METHOD	Headspace GC/MS
Volatile Organic Compounds (VOC) SCREENING	
VALIDATED METHOD	**GC/QQQ** GC/MS
Semi-Volatile Organic Compounds (SVOC) SCREENING	
VALIDATED METHOD	**LC/QQQ** UPLC/HRAM
Non-Volatile Organic Compounds (NVOC) SCREENING	
Element Analysis	ICP
Anions: fluoride, chloride, and bromide	IC
Sulfur (S_8)	LC/UV

Analytical Techniques used for LEACHABLE

Similar Techniques as for Extraction Testing, only Quantitative:

- Headspace GC/MS
- GC/MS
- LC/MS
- ICP
- IC
- Other specific Methods for Specific Leachables...

If Possible – in addition to validated methods – always perform SCREENING also (see “Closing the Gap” Presentation):

- Account for Unexpected Leachables
- Reactive Leachables
- In General: look for Leachables, not reported as Extractables

Analytical Techniques used for LEACHABLE

Specific Techiques for Monitoring Leachables at low levels:

- GC-QQQ
- LC-QQQ
  - Low Matrix Interference
  - Less extensive Sample Preparation
  - More “Robust” Methods

4. THE MIGRATION / LEACHABLE STUDIES

Singlicate versus **Triplicate** testing

- There are no strict Guidelines/Guidances for this wrt Leachable testing
- In US – or - for US Submissions: there is more a preference to perform Triplicate Testing
- In EU, more singlicate testing is performed

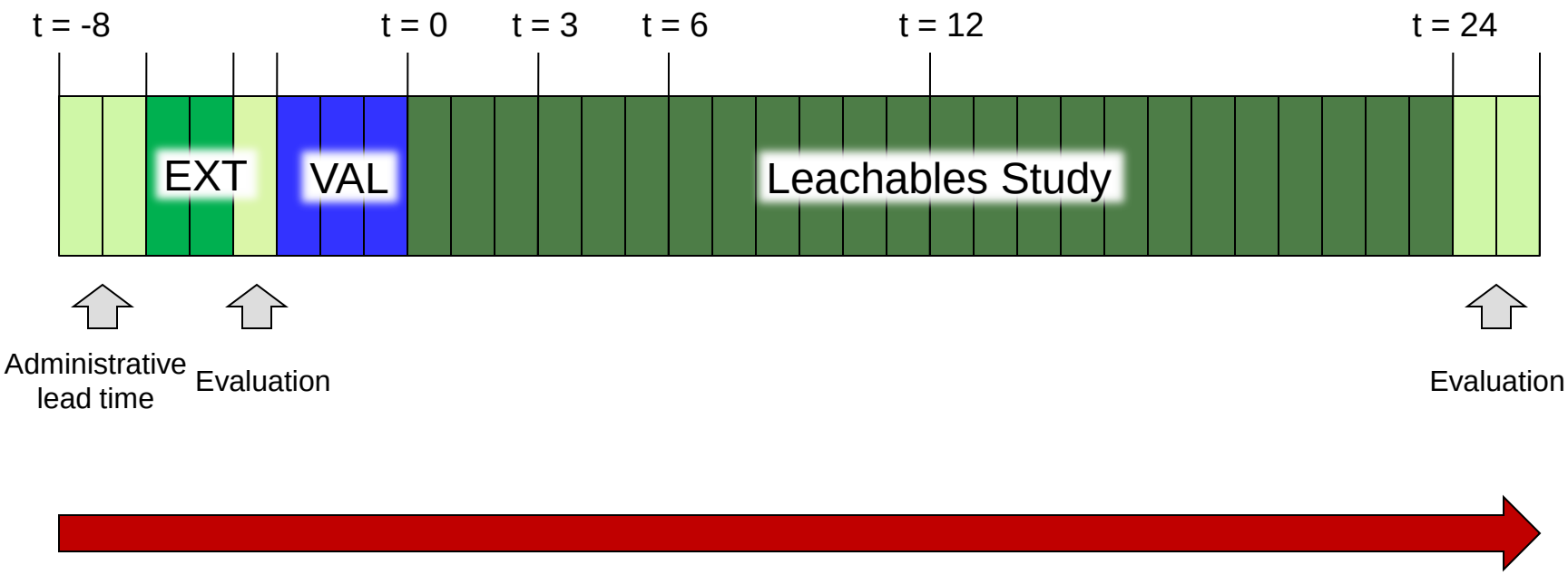
4. THE MIGRATION / LEACHABLE STUDIES

What if the DP is so Complex & Challenging in its Formulation that a normal Analytical Approach cannot be taken?

- Try to prove and document the analytical difficulties
- Narrow down the Analytics
  - *Very targeted, specific compound detection*
  - *No Screening possible*
- Consider a Simulation Study
  - *Justify a Simulation Study by proving the difficulties in the regular Leachable Study Approach*

4. THE MIGRATION / LEACHABLE STUDIES

Schedule for a 24 months Leachables Study



Total = 34 months

Thank you!