

Extractables and Leachables

**November 2010, IPS – SGS Seminar
SGS Life Science Services**

SGS Life Science Services

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WHEN YOU NEED TO BE SURE



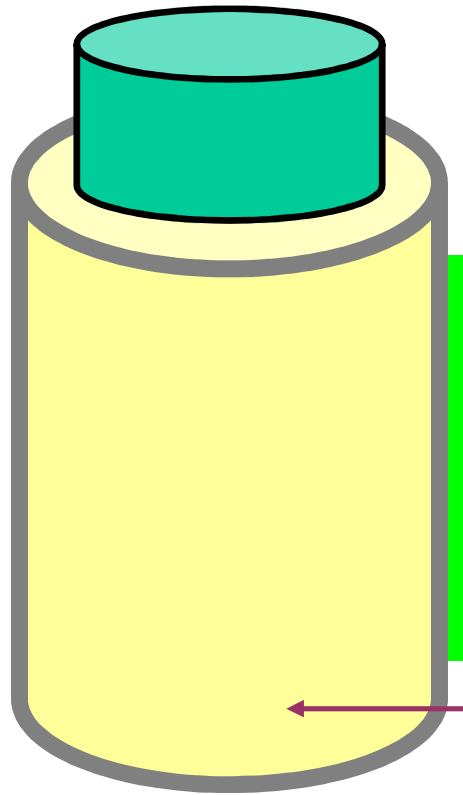
- **Agenda**
 - **Why?**
 - » Definitions
 - » Protection functionality
 - » Regulatory requirements
 - **When** do you need of comprehensive studies?
 - » Pack development
 - » Sources of extractables
 - » Classification of extractables
 - » Misconceptions
 - **How?** Global and tailored approaches
 - » Preparations
 - » Strategies for extractable studies
 - » Analytical tools
 - » Strategies for leachable studies
 - » Analytical Evaluation Threshold (AET)
 - » Special Cases
 - » Routine Testing

1. Why? Introduction: -Definitions

- **Extractable:** ... compounds that **can be extracted** from elastomeric, plastic components or coating of the container closure system when in presence of an appropriate solvent.
- **Extractable studies:** ...testing that specifically involves exposing a sample of the component to an appropriate solvent systems at **extreme conditions** in or to **maximize the amount of extractables** from the packaging in in the solvent.
- **Migration:** ...**release of substances (leachables)** from the plastic component into the content of the container under conditions which reproduce those of the intended use.

EMEA CVMP/205/04, CPMP/QWP/4359/03 (May 2005): Guideline on Plastic Immediate Packaging Materials (May 2005)

1. Why? Introduction: -Packaging material an effective protection?



O₂
(H₂O)

Material

LDPE

HDPE

Polystyrene

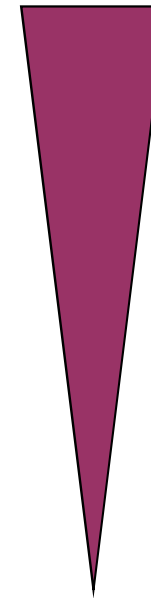
Polycarbonate

Polypropylene

PVC

PET

O₂ Permeability

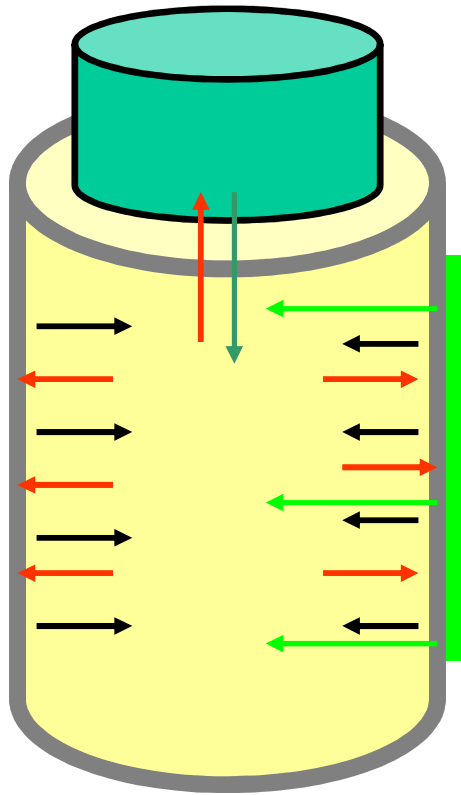


Reference:

Y. Wang, A.J. Easteal, and X.D.

Chen, Packag. Technol. Sci., 11 (1998) 169

1. Why? Introduction: - Extractable and Leachable -The theory



- FDA/EMEA guidelines make significant reference
- Pack/product interaction
- Label adhesive migration

But no guidance tells you exactly what to do or how to do it !

1. Why? Regulatory requirements

– Different efforts for different products

Degree of concern associates with the route of administration	Likelihood of packaging component-dosage form interaction		
	High	Medium	Low
Highest	Inhalation Aerosols and Solutions; Injections and Injectable Suspensions	Sterile powders and powders for injection and inhalation	
High	Ophthalmic Solutions and Suspensions, transdermal Ointments and Patches, Nasel Aerosol and Sprays		
Low	Topical Solutions and Suspensions, topical and liguial aerosol, oral solutions and suspensions	Topical powders Oral powders	Oral powders and oral capsuals

Reference: FDA Guidance for Industry, Container Systems.... (1999)

2. When do you need comprehensive studies?

- New Product design, selecting materials
- Change of packaging material or component of package
- Change of formulation
- Change of composition of packaging material
- Change of manufacturing process of packaging material
- Before start do your risk assessment

2. When do you need comprehensive studies? – Development, Phase I / Phase II Clinical Supply

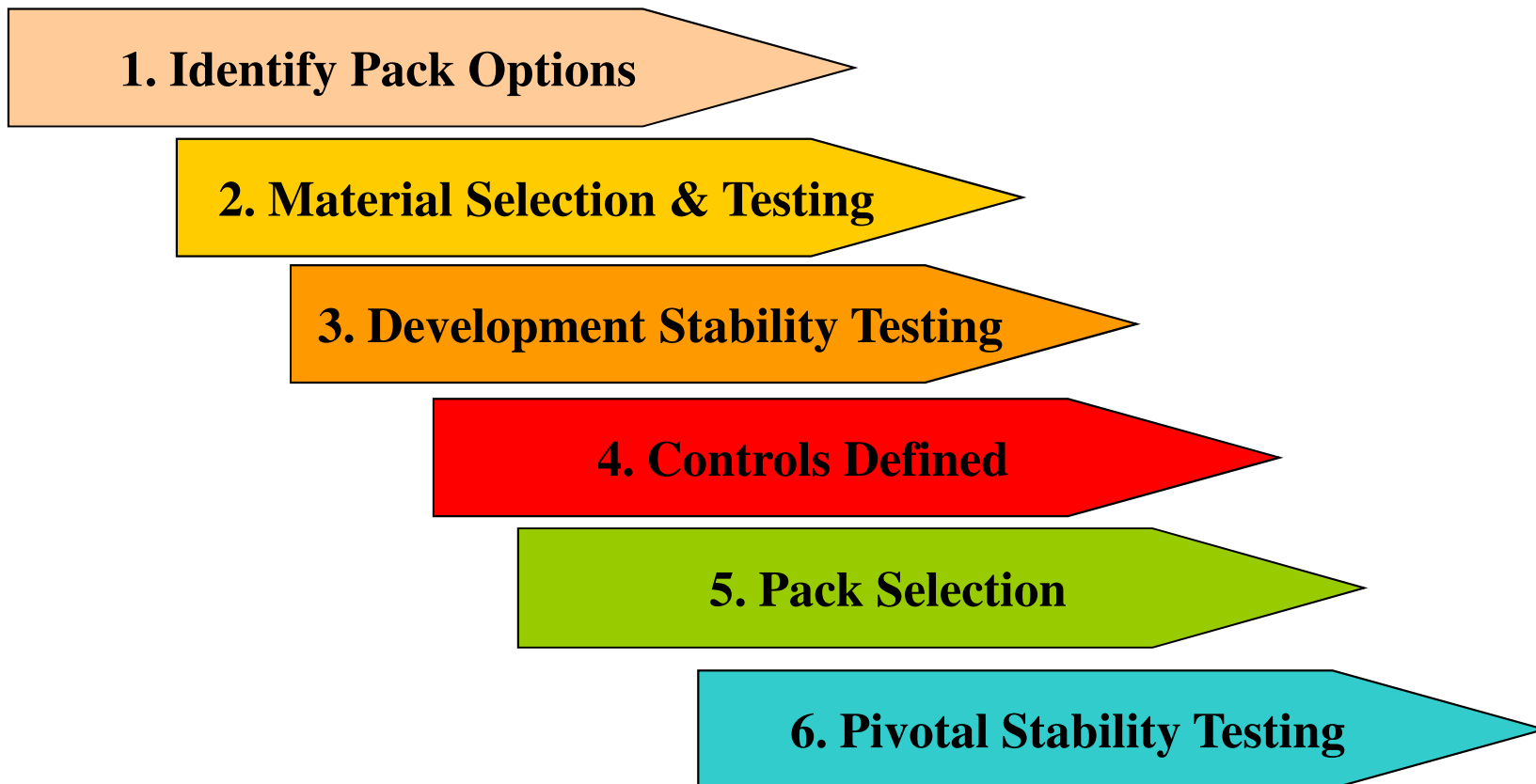
Selection of packs for clinical supply

■ Generally use:

- Limited range of standard packs, e.g. glass or HDPE bottles for solid forms
 - Inert packs, e.g. flouoresin laminated inert injection stoppers
- ☞ Packs and materials should be chosen to ensure pharmacopoeia and regulatory compliance is well understood
- ☞ Material performance is well characterised or known
- ☞ Pack selection is supported by stability testing for each product

3. When do you need comprehensive studies? – Phase II – III, Commercial Pack Development

- Objective
 - Identification, development and testing of commercial pack options
- Approach:



2. When do you need comprehensive studies? - Phase II – III, Commercial Pack Development

2. Material Selection & Testing

- Chemical characterisation, e.g., extractables and leachables studies, especially for parenteral, ophthalmic and inhalation products
- Toxicological assessment of extractables and leachables conducted

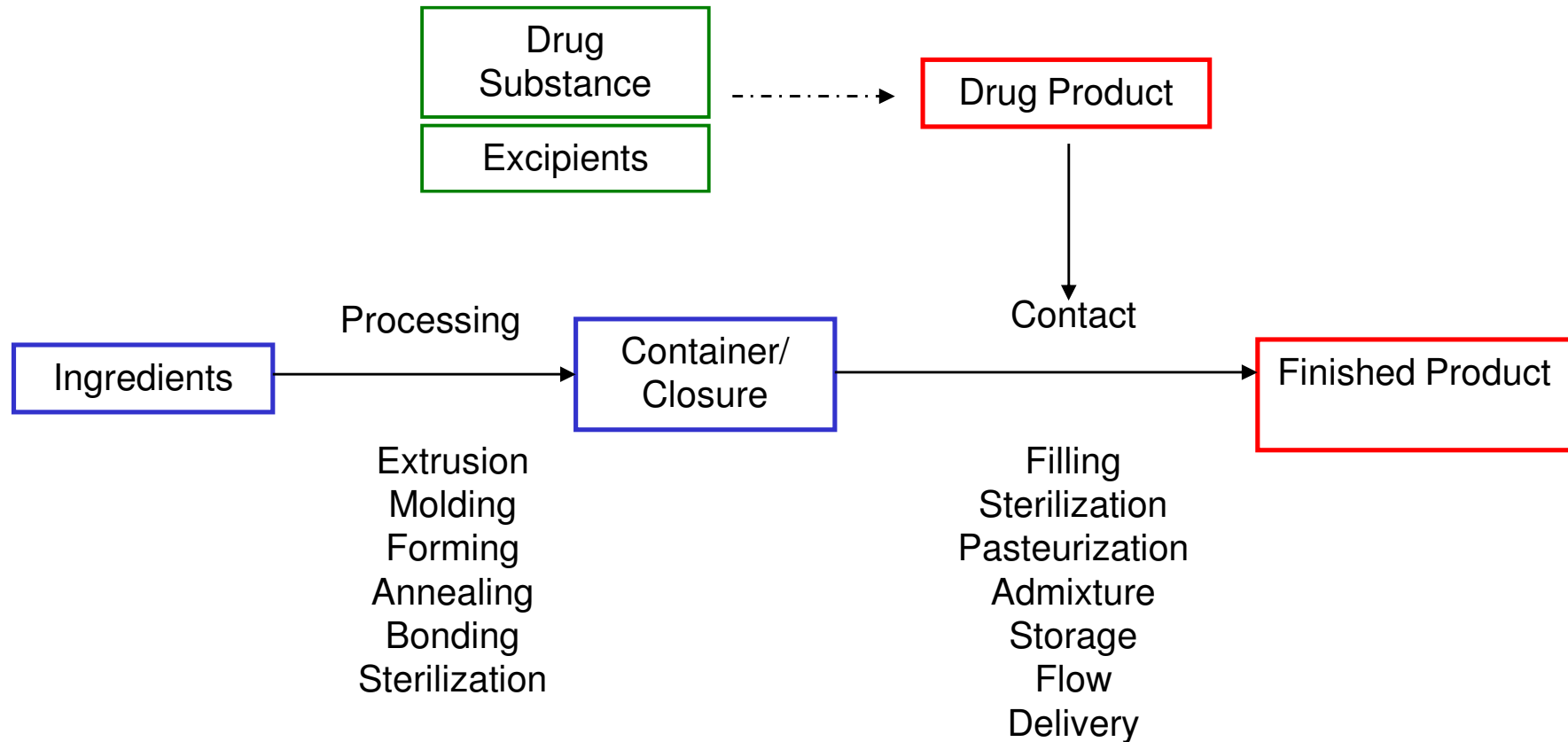
2. When do you need comprehensive studies? - Phase II – III, Commercial Pack Development

A large red arrow pointing to the right, containing the text '4. Controls Defined' in bold black font.

4. Controls Defined

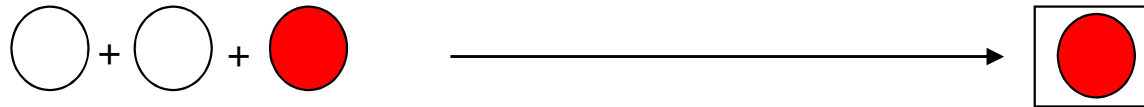
- Need for extractables profiling as a routine control
- Specifications for pack components and suppliers

3. Preliminaries –The Genesis of Finished Product- Sources of Contaminants

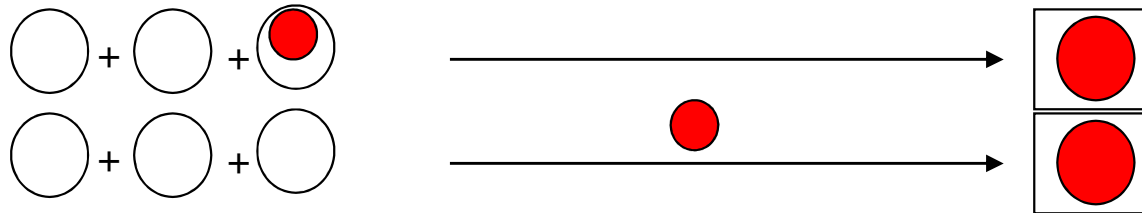


An extractable can become part of the finished container/closure system at any point during the transformation by any number of direct and indirect processes.

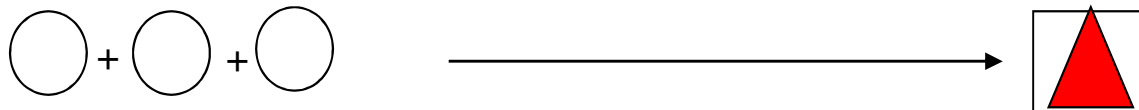
3. Preliminaries – Classification of Extractable substances from packaging material



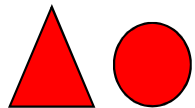
Primary: Extractable is an intentional ingredient.



Secondary: Extractable is an impurity in an intentional ingredient or a processing residual.



Tertiary: Extractable is produced as a result of processing.



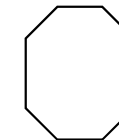
Extractables



Ingredient



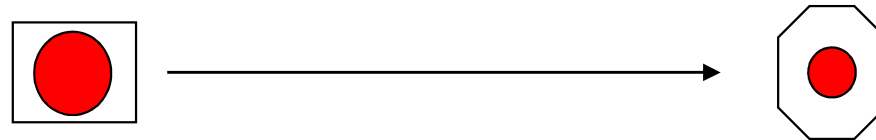
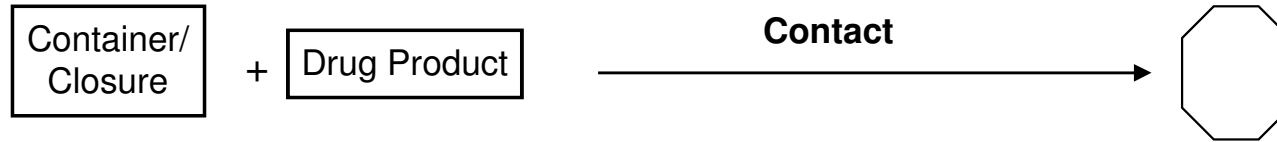
Container/Closure



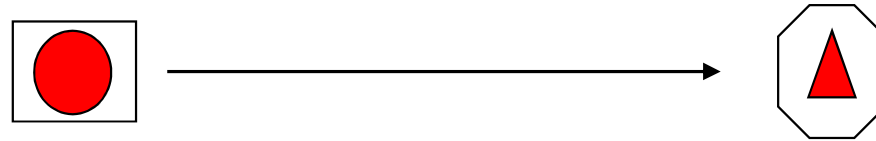
Finished Product

Denis R. Jenke, PDA J. Pharm. Sci. And Tech. 59 (4) 2005

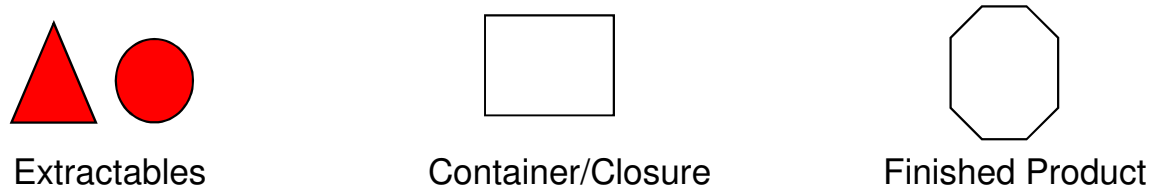
3. Preliminaries – Classification of Extractable substances



Passive: Extractable substance is not chemical modified by drug product contact and a present leachable.



Reactive: Extractable substance chemically modified by product contact and a present leachable.



Denis R. Jenke, PDA J. Pharm. Sci. And Tech. 59 (4) 2005

4. Take Care – Misconceptions associated with Extractables and leachables

- Certain misconceptions about extractables/leachables can lead a manufacturer/supplier to believe that the information obtained is either not relevant or is improperly used.
 - a. Extractables = Ingredients
 - b. Leachables = Extractables
 - c. Outcome in Leachables assessments


- a. **Extractables = Ingredients:** It's wrong to conclude that a list of material or systems ingredients from the supplier is in fact the same as a full and complete extractables assessment.
- ✓ **Extractables may arise as processing aids, process contaminants, ingredient contaminants and impurities, process-induced decomposition or reaction products of ingredients.**

4. Take Care – Misconceptions Associated with Extractables and Leachables

- b. **Leachables = Extractables** : The chemical conversion of extractables under conditions of contact with finished drug product is in common well known and documented in the literature.
- For example, if an antioxidant present in a material or system is oxidized during contact with a finished drug product, the more soluble oxidation product accumulates in the drug product (and thus is the leachable) and not the extractable antioxidant
 - ✓ **Leachables = Extractables** : An assessment based on extractables and their levels in extracts may deal with a significantly overstated case, because they may not partition into the finished product.
 - ✓ Thus a final product deemed to be unsafe or noncompliant based on extractables but safe based on leachables !!!
This could be the outcome of a stability-leachable study.


4. Take Care – Misconceptions Associated with Extractables and leachables


c. **Outcome** : In a leachable assessment, the desired outcome is the null outcome, that is, that the drug product's interaction with a plastic material results in no leachable being present in the drug product at levels where the leachable can adversely affected product safety or efficacy.

-  The null outcome of an extractables assessment is undesirable from two perspectives:
- ✓ Such an outcome suggests that the assessment was flawed.
- ✓ Such an outcome detracts from the objective of the assessment.

4. Take Care – Misconceptions Associated with Extractables and leachables

- ICH Q3B : “IMPURITIES IN NEW DRUG PRODUCTS”

-  This guideline addresses only those impurities in new drug products classified as **degradation products of the drug substance or reaction products of the drug substance** with an excipient and/or immediate container closure system.

-  Impurities arising from excipients present in the new drug product or **extracted or leached from the container closure system** are **not covered** by this guideline.

Guidelines to address the general question “are these extractables of concern or not?” and “How low do you go?” Answering this question by doing a toxicological risk assessment!!!

5. How? Global and tailored approaches

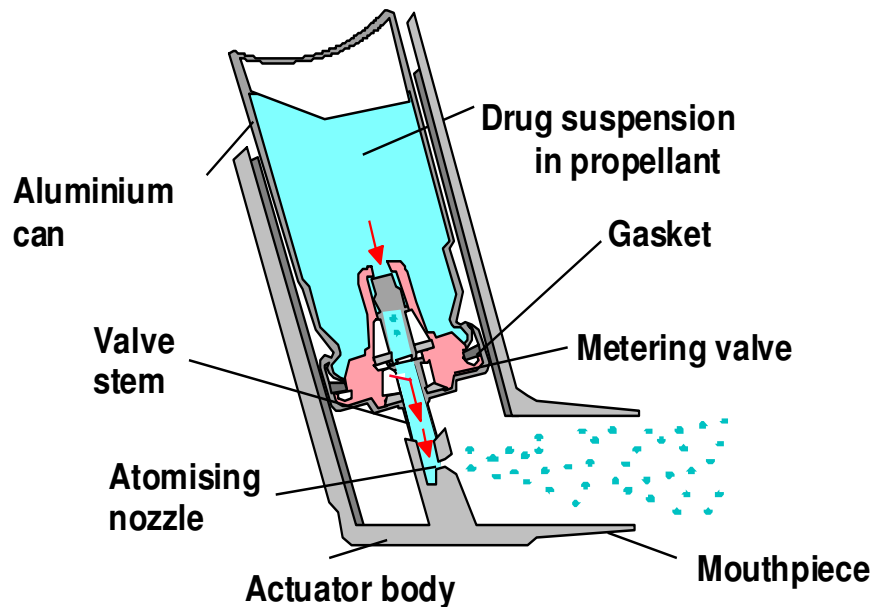
“I need a Leachable and Extractable Test”



What shall I do?

5. How – Collect Information's

Example of Complex Container Construction



- Classify your DP: High or low risk product.
- Identification of container material and critical components which are stay in contact with drug product.
- Active product contact surface of the container material.
- Understand polymer chemistry

5. How? Global and tailored approaches – Analytical challenges

- Employ vigorous extraction with multiple solvents of varying polarity
- Incorporate multiple extraction techniques
- Include a defined and systematic process for identification of individual extractables
- Extraction methods should be guided by Analytical Evaluation Threshold (AET)
- Perform the study with treated container material (e.g. irradiated for sterilisation purposes)

5. How: Global and tailored approaches - Strategy Extractables

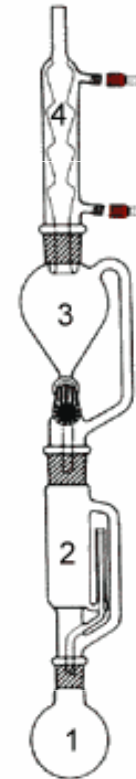
- The controlled extraction study has 4 parts:
 - Qualitative
 - Quantitative
 - Assessment of data
 - Evaluate toxicity of potential extractables.

 **Focus on Identification**

5. How? Global and tailored approaches - Analytical Tools

- Extraction
 - Soxhlet extractors, reflux extraction
 - Microwave oven extraction
 - Ultrasound-assisted extraction
 - Accelerated Solvent Extraction (ASE)

- Clean up procedures and sample enrichment
 - Liquid-phase extraction
 - Solid-phase extraction
 - One-line turbo flow extraction column used in LC-MS
 - **Solid Phase Multiple Extraction, SPME (Twister)**

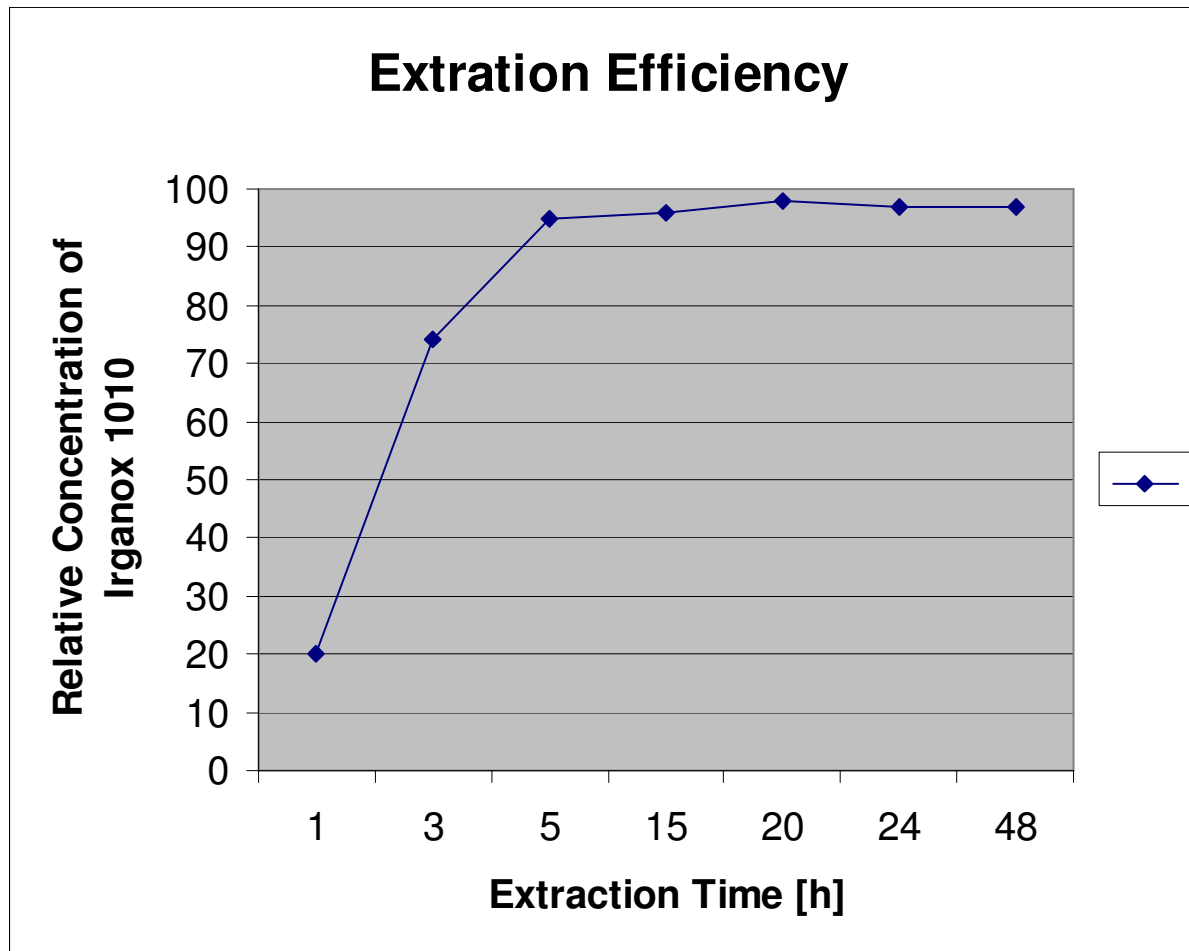


5. How? Global and tailored approaches - Analytical Tools

- Solvents should be chemically inert
- Soft Solvents are:
 - Aqueous buffers (vary pH)
 - Mixtures of water and alcohols
- Harsh solvents are:
 - Methanol, Ethanol, Isopropyl alcohol
 - CH_2Cl_2
 - Hexane, Heptane, MTBE

5. How? Global and tailored approaches - Analytical Tools

- Reflux Extraction of Irganox 1010 from LDPE –Container (Isopropyl alcohol)



5. How? Global and tailored approaches - Analytical Tools

■ MALDI-TOF or SIMS-TOF

- Possibility of analyzing materials without prior workup
- Very sensitive for polar and medium polar compounds
- Get first mass information about additives without chromatographic separation
- Structure education
- Accurate mass information and elemental composition

MALDI: Matrix Assist Laser Desorption Ionization

TOF: Time of Flight Mass Detector

SIMS: Secondary Ion Mass Spectrometer

5. How? Global and tailored approaches - Analytical Tools

■ **GC-MS/FID / HS-GC-MS/FID / TDS-GC- MS/FID**

- Powerful tools for structure education within complex mixture.
- Quantitation
- Non-volatile matrix: no need for cleanup techniques.
- Possibility of external calibration: **Multiple Headspace Extraction method (MHE)**.
- **Electron Impact Ionization (EI)**, commercially available library data bases for hit identification.

5. How? Global and tailored approaches - Analytical Tools

■ LC-MS/MS combined with DAD

- Possibility of analyzing extracts without prior workup
- Multiple detection technique
- Very sensitive for polar and medium polar compounds
- Different ionization techniques such as ESI or APCI for positive and negative ionization
- Structure elucidation of components in comparison to references



DAD: Diode Array Detection - Sensitive quantitation on trace level
ESI: Electrospray Ionization
APCI: Atmospheric Pressure Ionization

5. How? Global and tailored approaches
 - Examples: How can I identify an Extractable / Leachable using GC-MS or LC-MS/MS?

Category	Aspects
1	Confirmation of molecular weight
2	Interpret isotopic pattern
3	Fragmentation behaviour
4	Confirmation of the elemental composition
5	Mass spectrum matches automated library or other reference spectrum
6	Mass spectrum and chromatographic retention index match authentic specimen

A confirmed identification means the combinations of following categories:

- 1., 3., and 4 (6)

or

- 5. and 6.

or

- 1., 3. (or 5.) and 6

5. How? Global and tailored approaches - Analytical Tools

■ ICP-MS / ICP-OES

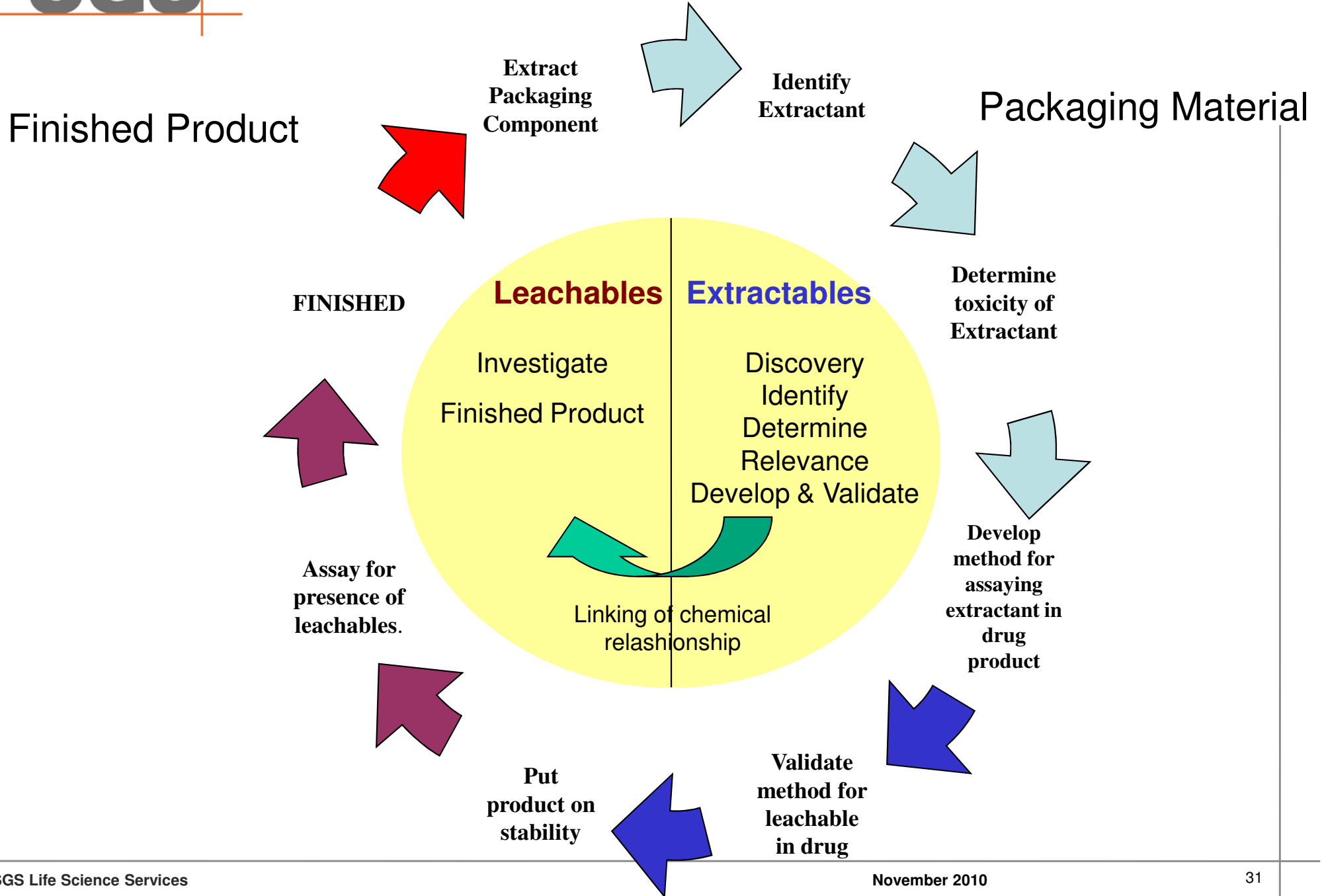
- Very sensitive, element specific
- Fast results for quantification of multiple elements
- Useful for analysis of inorganic material

■ TOC

- Sum-parameter of organic components
- Confirms that list of organic extractables is comprehensive

ICP: Inductively Coupled Plasma
OES: Optical Emission Spectrometry
MS: Mass Spectrometry
TOC: Total Organic Carbon

5. How? Global and tailored approaches - Milestones of an extractable / leachable assessment

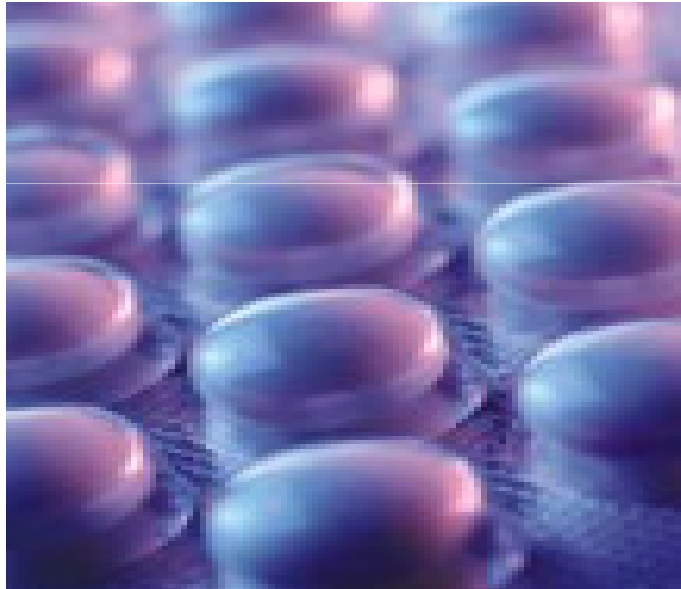


5. How? Global and tailored approaches - Strategy Leachables

- Based on Extractable study suitable test methods for testing of potential leachables in drug product have to be developed
- Recovery of reference compounds could be optimized by spiking into a drug product formulation matrix.
- Based on **Toxicological Expertise** limits for potential leachables have to be defined
- The potential for the presence of “special case” compounds should be considered

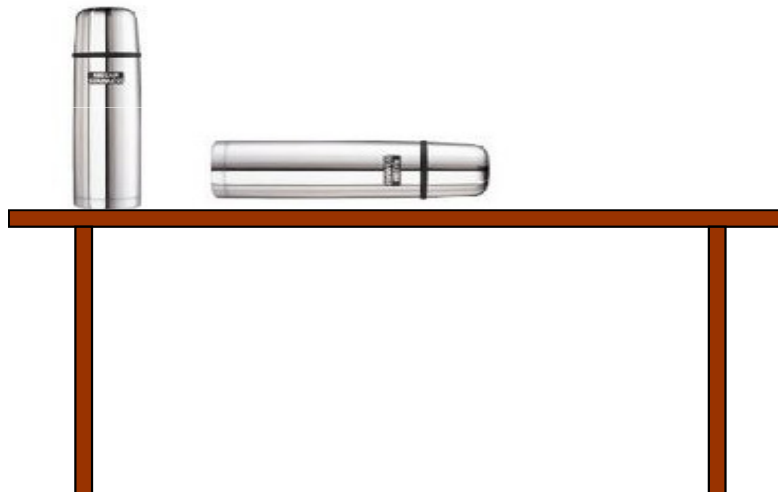
5. How? Global and tailored approaches - Strategy Leachables

- Validate the analytical methods
- Methods for leachables studies are specific to the finished product
- Determine shelf-life acceptance criteria for leachables based on the toxicological risk assessment



5. How? Global and tailored approaches - Strategy Leachables

- Perform stability studies according ICH (accelerated)
 - With the drug product
 - With placebo formulation
 - With other “inert” primary packaging material containing the drug product for comparison
 - Change storage position of the packaged drug product:



5. How? Global and tailored approaches - Strategy Leachables

- Storage Conditions and Suggested Points for Leachables Analysis

Condition	Temperature [°C]	Relative Humidity [%RH]	Time Points [months]
Long Term ¹	25 ±2	60 ±5	0, 6, 12, 24, 36
	30 ±2	65 ±5	
Intermediate	30 ±2	65 ±5	0, 6, 12, 24, 36
Accelerated	40 ±2	75 ±5	0, 3, 6, 9 12

¹ Either set of conditions can be used for Long Term Storage

5. How? Global and tailored approaches - Strategy Leachables

■ **Extractable and Leachable Correlation**

- Establish qualitative correlation between profiles, it must be shown that compounds detected in the leachable studies were also present in the Controlled Extractables Studies
- It must be shown that levels of leachables obtained from leachables studies are generally less than the levels of extractables obtained in the quantitative Controlled Extraction Studies
- Use multiple batches in Extractables and Leachables Studies

6. How low should we go?

Analytical Evaluation Theshold

- Take targets from your extractable assessment
- Choose an useful internal standard
- Determine an **A**nalytical **E**valuation **T**heshold (AET)
- The AET should be $>$ LLOQ

6. How low should we go?

- Analytical Evaluation Threshold

- Extractable studies should be guided by an **Analytical Evaluation Threshold (AET)** that is based on an accepted safety (SCT) evaluation threshold.
- The value or above which a chemist should begin to identify a particular leachables and extractable and report for potential toxicological assessment
- Advantage of AET:
 - The sensitivity for leachable and extractable methods can be postulated.

6. How low should we go? - Analytical Evaluation Threshold

- For Inhalers (OINDP) the **Safety Concern Threshold** is:

SCT = 0.15 µg/day for an individual leachable.

It was derived from toxicological data bases and was set equal to the AET:

- SCT = AET

OINDP Orally Inhaled Nasal Drug Products

3. 6. How low should we go?

- Example: Estimation of the AET

■ Example:

- 5 doses per day
- 200 doses per canister
- 0.1g component (material/container)

■ Estimate AET:

- convert SCT (0.15 μg TDI) to $\mu\text{g}/\text{canister}$
 - $\frac{0.15 \mu\text{g}/\text{day} \times 200 \text{ doses}/\text{canister}}{5 \text{ doses}/\text{Day}} = 6.0 \mu\text{g}/\text{canister}$
 - $\frac{6.0 \mu\text{g}/\text{canister}}{0.1\text{g component}} = 60 \mu\text{g}/\text{g}$

■ The response of a final AET can be based on an appropriate internal standard.

■ But what's about the analytical uncertainty?

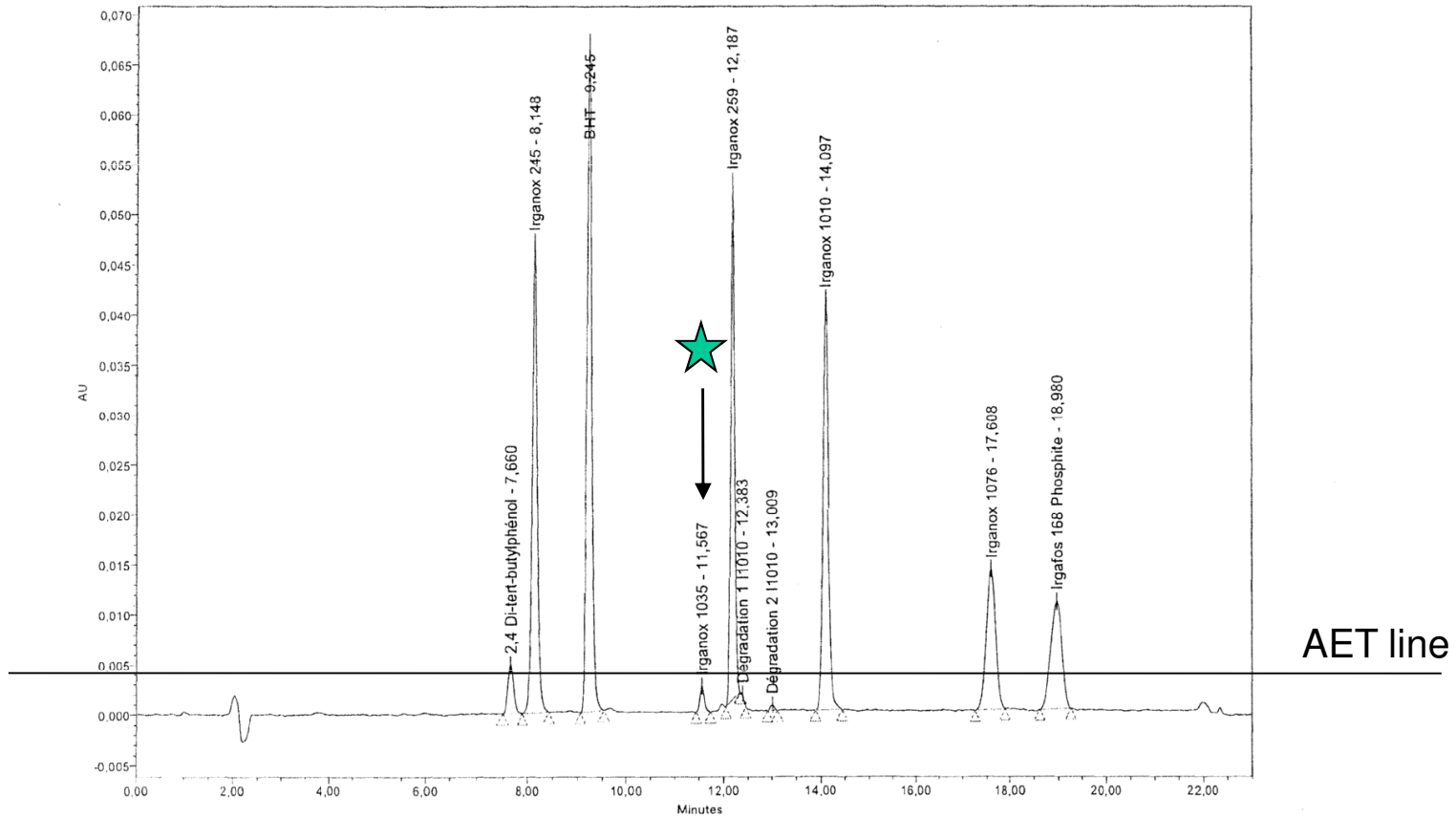
3. 6. How low should we go?

- Estimation of the AET and Analytical Uncertainty

- The PQRI working Group recommends:
 - The estimated AET be defined as %RSD in an appropriately constituted response factor data base
 - or
 - a factor of 50% of the estimated AET.

- Final AET = Estimated AET x (1 – analytical uncertainty)
 - Analytical uncertainty = Max (%RSD or 0.5)

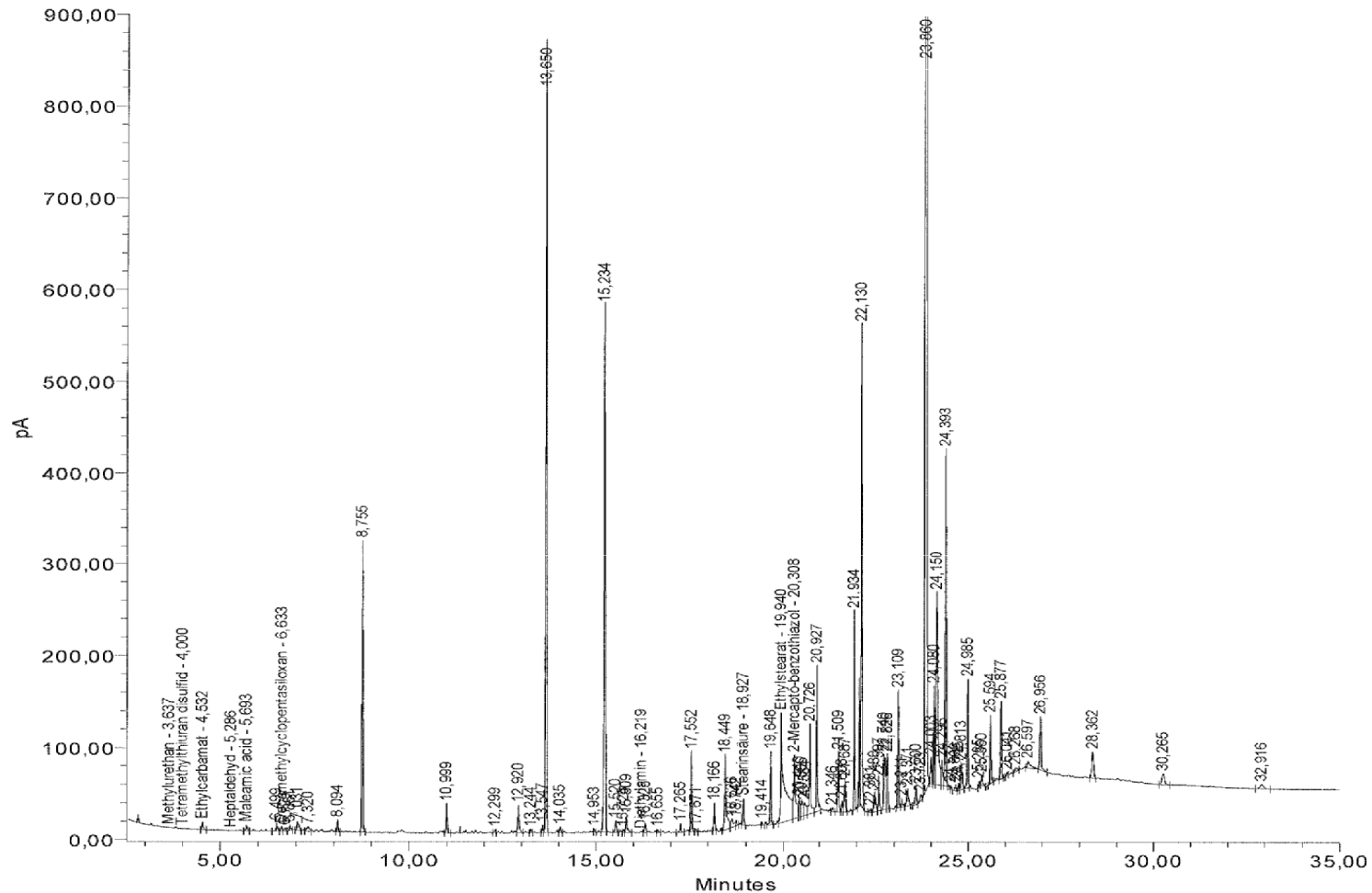
3. How: Global and tailored approaches - Example antioxidants mixture



★ Internal Standard: Irganox 1035 at AET of 30 ppm

6. How low should we go? - Analytical Evaluation Theshold

Do not go to low!



6. How low should we go? - Special Cases

- Following compounds are not be evaluated following the AET concept:
 - N-nitrosoamines
 - 2-mercatptobenzothiazole
 - and some other

7. Routine Extractables Testing should:

- Be performed on critical components using methods on those used in the Controlled Extractables Assessment
- Use validated methods
- Be performed using acceptance criteria
 - This could be part of packaging entrance control

