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Testing of packaging systems for Large Volume Parenterals: Extractables Study Design and Challenges

Karen Pieters, E&L Expert

Overview

- Definitions
- Regulatory guidelines
- Where could extractables and leachables come from in Flexible bag systems?
- Challenges for Large Volume Parenterals
- Material assessment versus packaging assessment

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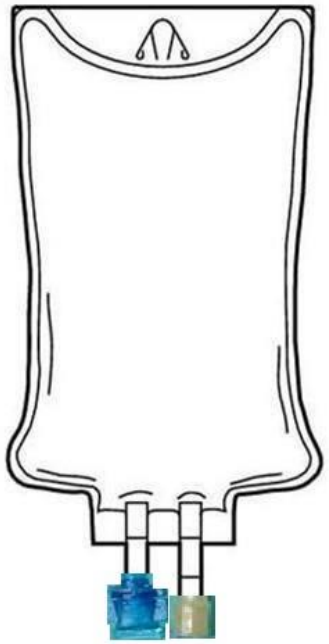
Definitions

Definitions: Large volume parenterals

- Large volume parenterals: single unit doses > 100 mL for parenteral use
- Large volume vs. small volume containers:



Large volume –
Single dose

Small volume –
Multiple number of doses

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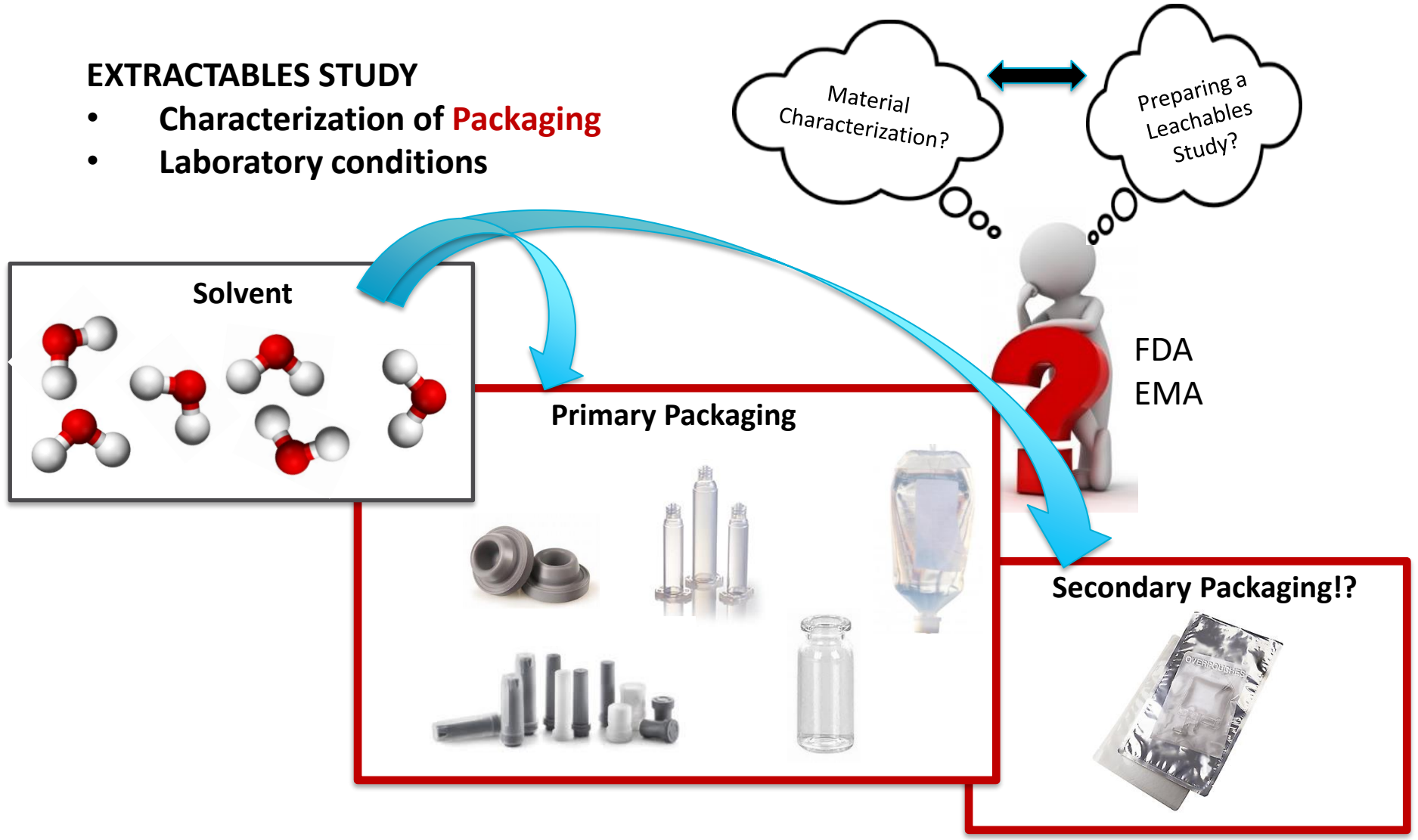
Definitions: Extractables

EXTRACTABLES STUDY

- **Characterization of Packaging**
- **Laboratory conditions**



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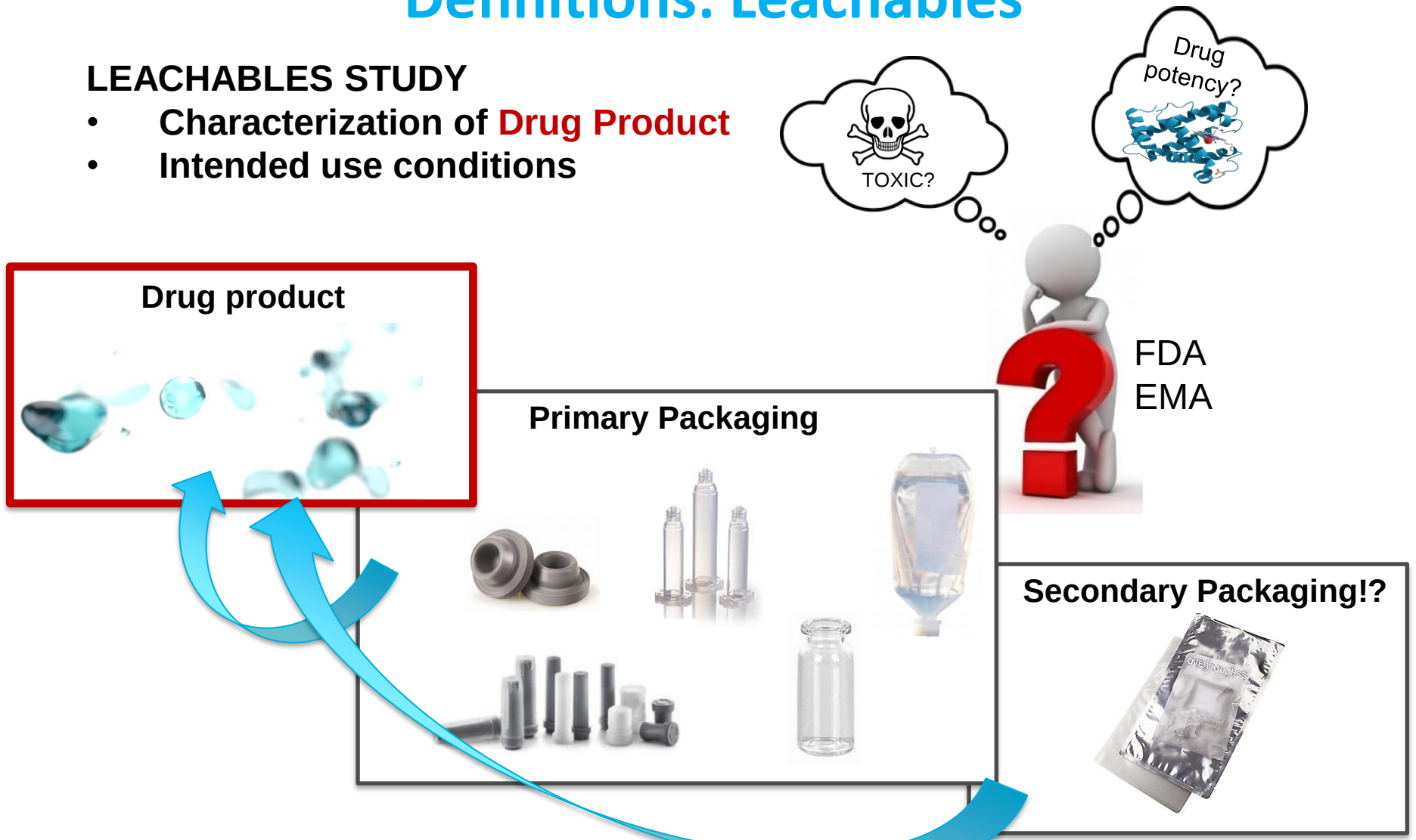
Definitions: Leachables

LEACHABLES STUDY

- **Characterization of Drug Product**
- **Intended use conditions**



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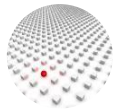
Difference between extractables and leachables

Analytics

Extractables study	Leachables Study
 PHARMACEUTICAL CONTAINER	DRUG PRODUCT 
 What **CAN** come out	What **DOES** come out 
 **FOCUS: Identification**	**FOCUS: Quantification** 
 Worst case condition	Normal conditions 
 Screening	Targeted & Screening 

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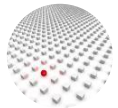
Difference between extractables and leachables

Analytics | **Safety Thresholds** | **Toxicology**

Extractables study		Leachables Study	
	PHARMACEUTICAL CONTAINER	DRUG PRODUCT	
	What **CAN** come out	What **DOES** come out	
	**FOCUS: Identification**	**FOCUS: Quantification**	
	Worst case condition	Normal conditions	

Screening	Targeted & Screening
	

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Regulatory Guidelines

Regulatory Requirements

1999: "CONTAINER/CLOSURE SYSTEMS FOR PACKAGING HUMAN DRUGS AND BIOLOGICS"

Classification, based on likelihood of interaction and route of administration

2005: "GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS"

"Decision Tree" what information to provide for different dosage forms

2014: USP <1661>, <1663> (Extractables), <1664> (Leachables)

Regulatory Requirements

USP <1663> Monograph

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

This is an INFORMAL Monograph

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

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Regulatory Requirements

PQRI – Parenteral & Ophthalmic Drug Products

Best Demonstrated Practice Recommendations: Chemistry & Toxicology

This is a RECOMMENDATION

(To be published)

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Regulatory Requirements

ISO 10993-1: categorization as 'Externally communicating device'

ISO 10993-18: Chemical characterization of medical devices:

The nature of use for some medical devices (e.g. indirect contact devices such as saline infusion bags) can obviate the need for extractables testing, as the conditions of use associated with the maximum human exposure to leachables can be replicated and the clinical use solutions can be analysed in a straightforward manner. In such cases, extractables testing could reasonably be replaced by leachables testing.

Contact category	Recommended extraction conditions	Credible alternatives
Limited contact devices	Simulated use conditions[a]	Exaggerated conditions
Prolonged contact devices	Exhaustive conditions	Exaggerated conditions[b,c]
Long-term contact devices	Exhaustive conditions	Exaggerated conditions[b,c,d]

[a] Note that some legal authorities (e.g., U.S. FDA) can request exaggerated extraction, unless otherwise justified.

[b] Examples of instances where exhaustive extraction would not typically be required include:

— single use devices used for less than 24 h, where repeat use of a new device each day would result in categorization as prolonged or long-term contact;

— single use devices used for several days, where repeat use of new devices would result in categorization as prolonged or long-term contact;

— reusable devices, where a patient may be exposed to repeated use of the same device, resulting in categorization as prolonged or long-term contact; when an exaggerated extraction is used for a reusable device, the extraction should properly account for the duration of each individual use.

[c] Exaggerated conditions can be appropriate for external communicating or non-absorbable surface contact devices, with justification.

[d] An example is a device comprised entirely of non-absorbable metal (e.g. a vascular stent), because migration of constituents from within the material is not possible, and the constituents of interest are related to the surface only and exaggerated extraction can be adequate to generate a complete extractables profile.

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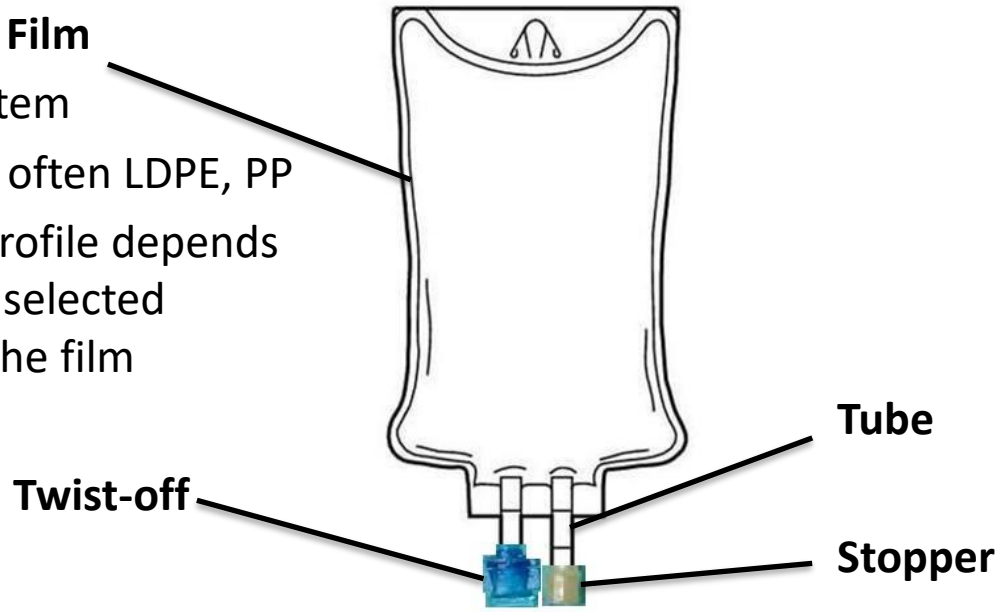
Where could Extractables/Leachables come from in Flexible bag systems?

Primary containers: Flexible Bag

Primary packaging Film

- Multilayer system
- Internal layer: often LDPE, PP
- Extractables profile depends largely on the selected materials for the film



Be careful in selecting high quality materials, even though the contact is minimal, the impact on the extractables profile might be relevant!

Dibenzylamine, Dibutylamine: used in solvents for polymers such as polyisoprene
=> precursors for nitrosamines

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Labels/printing

Due to the semi-permeable character of the primary film, compounds from printing/labels can easily migrate through the primary packaging system

- Label
  - Adhesive
  - paper
  - Ink
  - Varnish

Typical extractable compounds:

Curing agents (e.g. Benzophenone, Irgacure 184)

Solvent residues (e.g.Toluene, acetone)

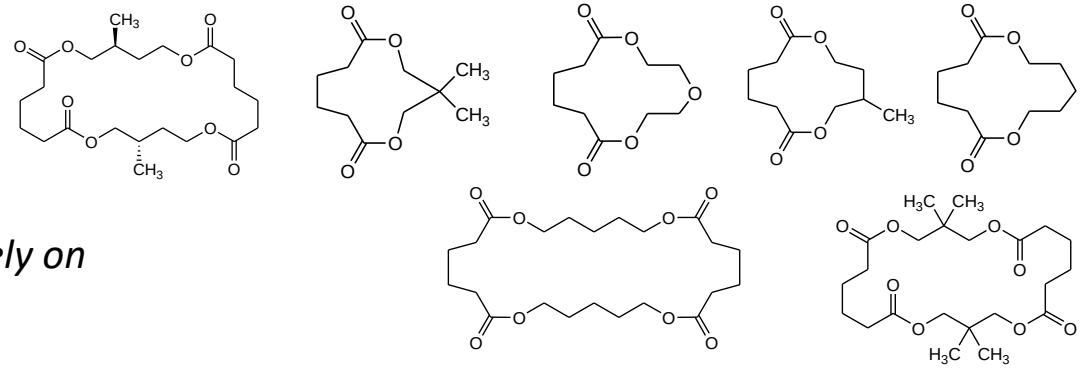
Adhesive residues (e.g. Acrylates)

Paper residues (e.g. (dehydro)abietic acids, abietates)

Overwrap/Overpouches

Due to the semi-permeable character of bags, compounds from overwraps/overpouches can easily migrate through the primary packaging system

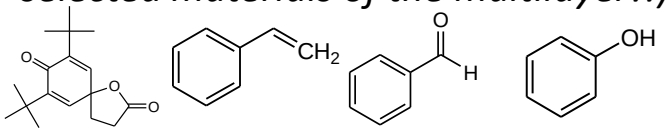
- Overwrap
  - Multilayer System
  - Aluminum as barrier layer for protection against light
  - PU adhesives might be used to keep the different layers together



Typical extractable compounds:

Bislactone Compounds from PU adhesive

Residues from other layers (depends largely on selected materials of the multilayer!!)



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Where could Leachables come from in large volume parenterals?

High impact on leachables profile of

- Secondary packaging materials: overpouches, labels, ink
- Tubes, ports, stoppers

due to

- Semi-permeability of the primary container
- High solubility of polar migration compounds in aqueous solutions
- Closed environment created by secondary packaging that ‘traps’ the extractables
- Final sterilization (e.g. steam sterilization) of the filled packaging system

Be careful in selecting high quality materials, even though the (direct) contact is minimal, the impact on the leachables profile might be relevant!

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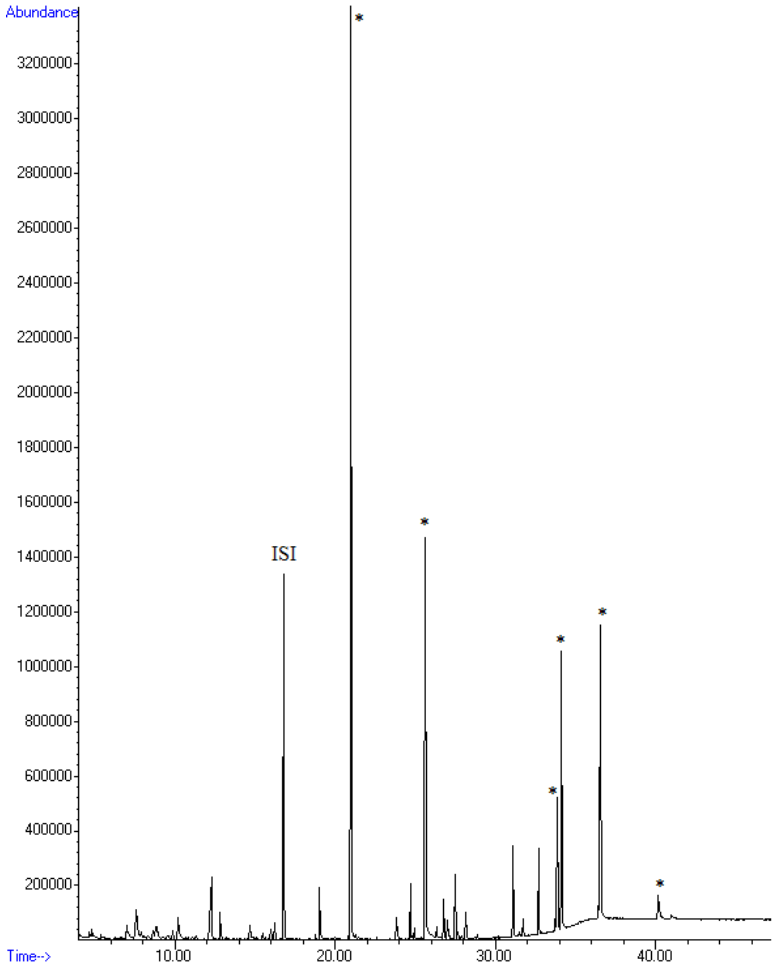
Case study

- 0.9% NaCl stored in 100 mL PP bags packed in aluminium overpouch
- Sterilized by steam sterilization
- Highest leachables attributable to the overpouch (*)

1,4,11,14-Tetraoxacycloeicosane-5,10,15,20-tetraone	[64066-17-7]	$C_{16}H_{24}O_8$	344.36
1,4,7-Trioxacyclotridecane-8,13-dione	[6607-34-7]	$C_{10}H_{16}O_5$	216.23
1,4,7,14,17-Pentaoxacyclotricosane-8,13,18,23-tetraone		$C_{18}H_{29}O_9$	388.41
3,6,9,16,19,22-Hexaoxa-1(1,4)-benzenacyclotricosaphane-2,10,15,23-tetraone		$C_{22}H_{28}O_{10}$	452.45
Cyclic polyester; Di(Adipic acid diglycol bislactone)		$C_{20}H_{32}O_{10}$	432.46



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Challenges for large volume parenterals

Challenges for Large Volume Parenterals

Large volume parenteral applications typically come with a high dose

This may result in a challenging analytical and toxicological evaluation

Authorities may look at large volume parenteral applications with high concern.

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Threshold Levels

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 recommendations for Parenteral Drug Products (PDP)

- SCT specific to route of administration
- Chronic therapy

	General Toxicity	Sensitizers/Irritants	Mutagens
Threshold Level (µg/day)	5	5	1.5 (PDP-SCT)

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Threshold levels

ANALYTICAL EVALUATION THRESHOLD (AET)

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

Converting the SCT into an analytically relevant concentration

$$\textit{Final AET} = \frac{AET}{UF}$$

Screening methods are estimated/semi-quantitative: uncertainty factor (UF)

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

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Threshold levels

High dose (> 100 mL) → **Low AET (< 15 µg/L)**

- Example:
  - bag system filled with sodium citrate solution
  - Filling volume: 250 mL
  - Maximum administered: 2 bags/day

Tox. Endpoint	Sensitizers/Irritants	Mutagens
Threshold Level (µg/day)	5	1.5
AET (µg/L)	10	3
AET (µg/bag)	2.5	0.75

- Low AET levels result in
  - More compounds detected
  - More compounds to be identified

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Threshold levels

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 mutagenic impurities**
- **Excess 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

However….

No staged approach can be applied for irritants and sensitizers, since they have an immediate effect

Thus…

All compounds exceeding 5 µg/day should be evaluated for irritation/sensitization

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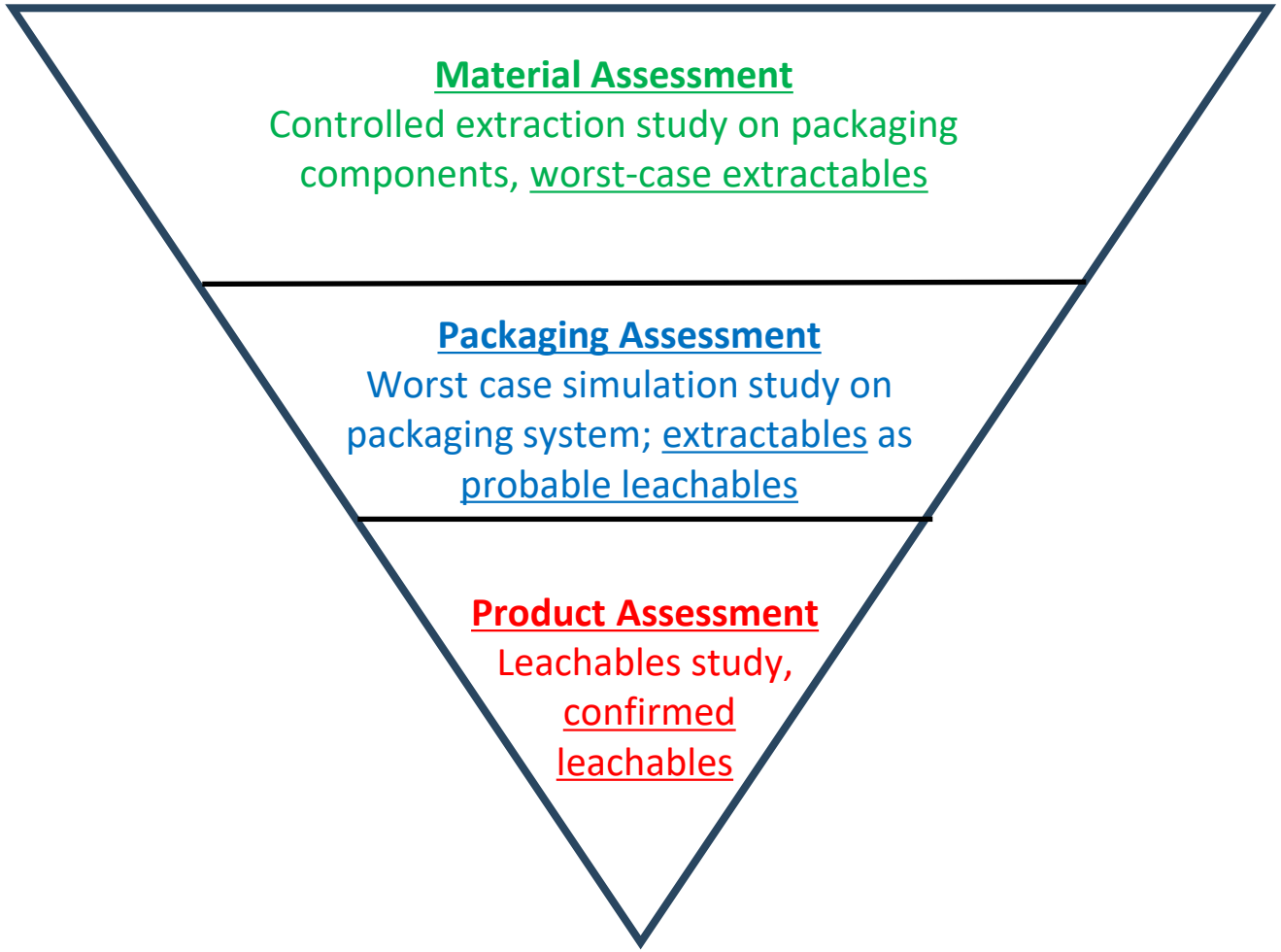
Material assessment vs. Packaging assessment

Safety Assessment Triad



Source: Challenges associated with the safety assessment of Extractables/Leachables in Large Volume Parenterals (LVPs) and potential chemistry approaches, Dr. Dennis Jenke, PDA workshop E/L, Rome, September 2016

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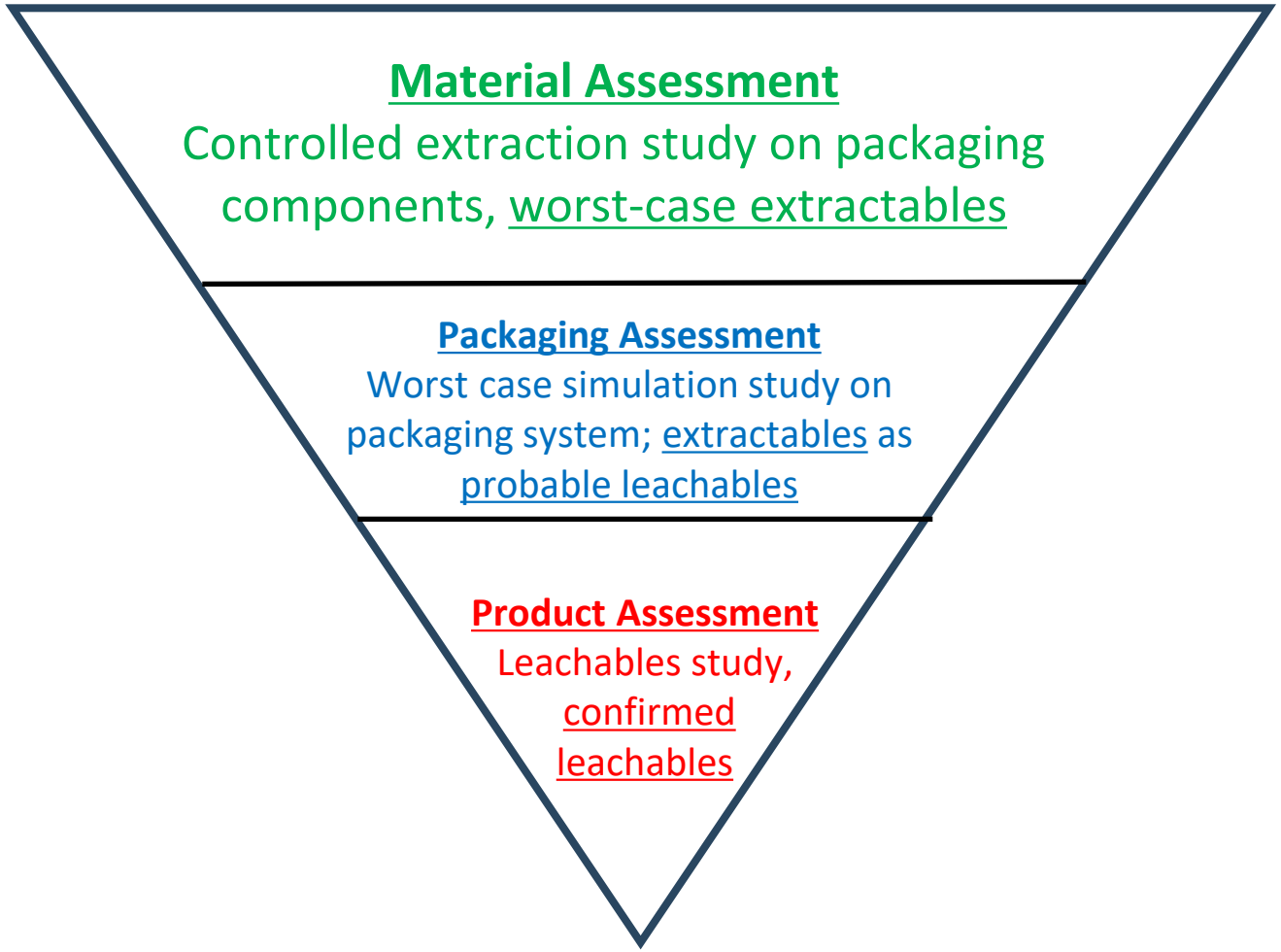
Safety Assessment Triad



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Material assessment: controlled extraction study

- Different components of the packaging system are assessed separately
- Subjected to sterilization processes (e.g. gamma-irradiation)
- Use worst case extraction conditions: closed vessel, reflux, …
- Extraction solvents: worst-case extraction solvents or generic solvents:
  - water low pH,
  - water high pH,
  - organic solvents, …

+	-
Track the source of leachables	Long lists of extractables for each material
Achieve lower reporting limits (AET)	How to select target leachables?
Reject materials with safety concerns	

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Material assessment

PURPOSE

Chemically characterize candidate materials to establish their composition.

- Identify as Many Compounds as Possible
- Identify “Bad Actors” in the Materials

FOCUS ON IDENTIFICATION

- ***Screening***
  - Use of multiple orthogonal analytical techniques suitable for the purpose of discovering and identifying a wide range of extractables compounds.
  - Proprietary Screener Database available at Nelson Labs containing > 5000 extractables/leachables compounds

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Case study

- Bag system consisting of:
  - Primary packaging film, printed
  - Primary packaging tube
  - Twist-off port
  - Secondary packaging: aluminium overpouch

- Used for storage of antibiotic, pH 4.5

- Extraction by closed vessel extraction and neat headspace enrichment

- Extraction solvents:
  - 10% Isopropanol in Ultrapure Water to mimic the organic content of the DP (10°C below boiling point for 24h)
  - Ultrapure Water, pH 4.5 to mimic the aqueous character and pH (autoclave, 121°C for 30 min)

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Case study

Calculation AET:

- Maximum daily dose: 1200 mL or 12 bags of 100 mL
- Different filling volumes: worst-case amount of surface area film and number of ports is used
- express AET in unit of surface area in order to extrapolate to other filling volumes

SCT for genotoxic impurities	1.5 µg/day
Maximum contact surface/test items exposed to the patient	2292 cm^2 (primary film) 280 cm^2 (tube) 12 twist-off ports 7500 cm^2 (secondary film)
Analytical Evaluation Threshold **(1.5 µg/day / 2292 cm^2)** **(1.5 µg/day / 280 cm^2)** **(1.5 µg/day /12 test items)** **(1.5 µg/day /7500 cm^2)**	0.00065 µg/cm^2 or 6.5 µg/m^2 (primary film) 0.0054 µg/cm^2 or 54 µg/m^2 (tube) 0.125 µg/test item (twist-off) 0.0002 µg/cm^2 or 2 µg/m^2 (secondary film)

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Case study

Results:

Component	Number of compounds above the AET		
	HS-GC/MS Volatiles	GC/MS Semi-Volatiles	HRAM-UPLC/MS Non-Volatiles
Primary film, printed	26	48	39
Twist-off port	18	38	26
Tube	21	6	2
Secondary film (overwrap)	41	54	63
TOTAL	**106**	**146**	**130**

Total of **382** compounds to be evaluated

Narrow down the number of target compounds for leachables study

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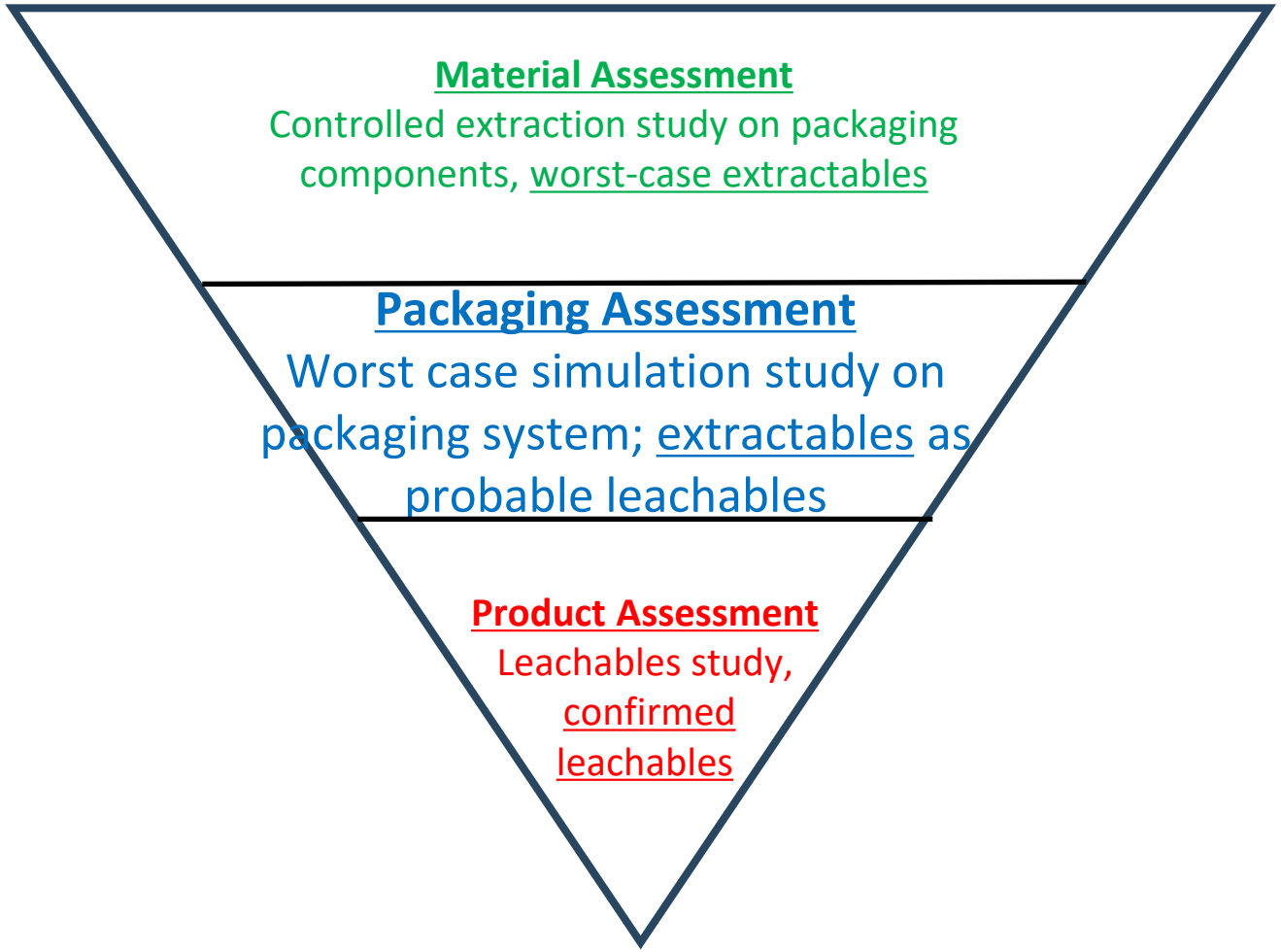
Safety Assessment Triad



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Packaging assessment: Simulation study

- Assessment of the packaging system as a whole
- Simulating conditions:
  - Extraction conditions: filling and incubation, accelerated ageing
  - Extraction solvents:
    - solvents simulating or bracketing the final application(s)
    - Drug product (vehicle), if analytically feasible (e.g. 0.9% NaCl, WFI, 5% Dextrose)

+	-
Extractables profile more close to reality	Source of extractables is unknown
Narrow down the list of potential leachables	
Potential to bracket different applications	
Achieve lower reporting limits in clean solvents versus complex drug products	

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Packaging assessment

PURPOSE

- Establish the worst case (highest possible) accumulation of leachables.
- Identify compounds that may need to be monitored as Leachable

BUILDING A BRIDGE BETWEEN MATERIAL ASSESSMENT AND LEACHABLES STUDY

- ***Screening***

A TOX ASSESSMENT OF THE DATA OF THE SIMULATION STUDY MIGHT HELP IN LIMITING THE DESIGN OF THE LEACHABLES STUDY

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Case study

Extraction by filling and incubation with 6% IPA in UPW, pH 4.5

Accelerated ageing for 6 months at 40°C

Safety Concern Threshold	5 µg/day
Maximum daily dose administered to the patient	1200 mL
Analytical Evaluation Threshold (5 µg/day / 1200 mL/day)	4.2 µg/L

Results:

Number of compounds above the AET		
HS-GC/MS Volatiles	GC/MS Semi-Volatiles	HRAM-UPLC/MS Non-Volatiles
3	**17**	**36**

Total of **56** compounds to be evaluated

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Conclusions

- The extractables study for Flexible bag systems should include all components of the packaging system, including
  - Components with minimal direct product contact
  - Secondary packaging

- High dosing regimens result in low Analytical Evaluation Thresholds and higher analytical and toxicological workload

- A three step approach is recommended for the evaluation of large volume parenterals:
  - Material assessment: controlled extraction study
  - Packaging assessment: simulation study
  - Product assessment: leachables study

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