Best Practices of Routine Extractables Testing

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IPAC-RS Materials Webinar Series

- ✓ IPAC-RS Baseline Materials Requirements and a Rationalized Testing Paradigm (26 April 2012)
- ✓ Controlled extraction best practices (10 May 2012)
- ✓ Trace analysis fundamentals (May – June 2012)
4. Routine extraction - Best Practices (13 Sep 2012)
5. Acceptance criteria development (11 Oct 2012)
   - What are drivers for setting acceptance criteria?
   - What are strategies for deriving acceptance criteria?
6. Change management approaches (15 Nov 2012)
   - Why is it important?
   - Case studies

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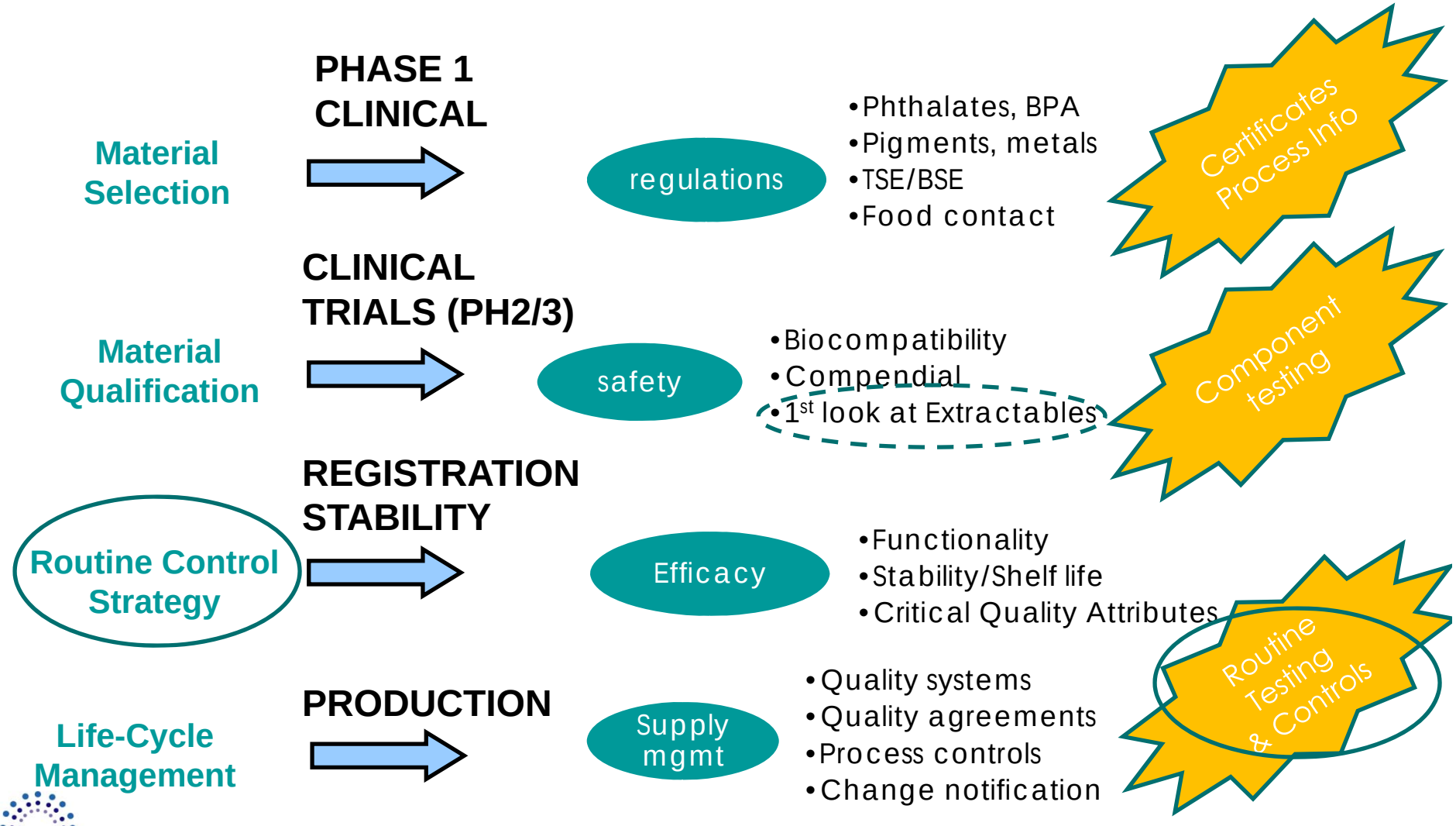
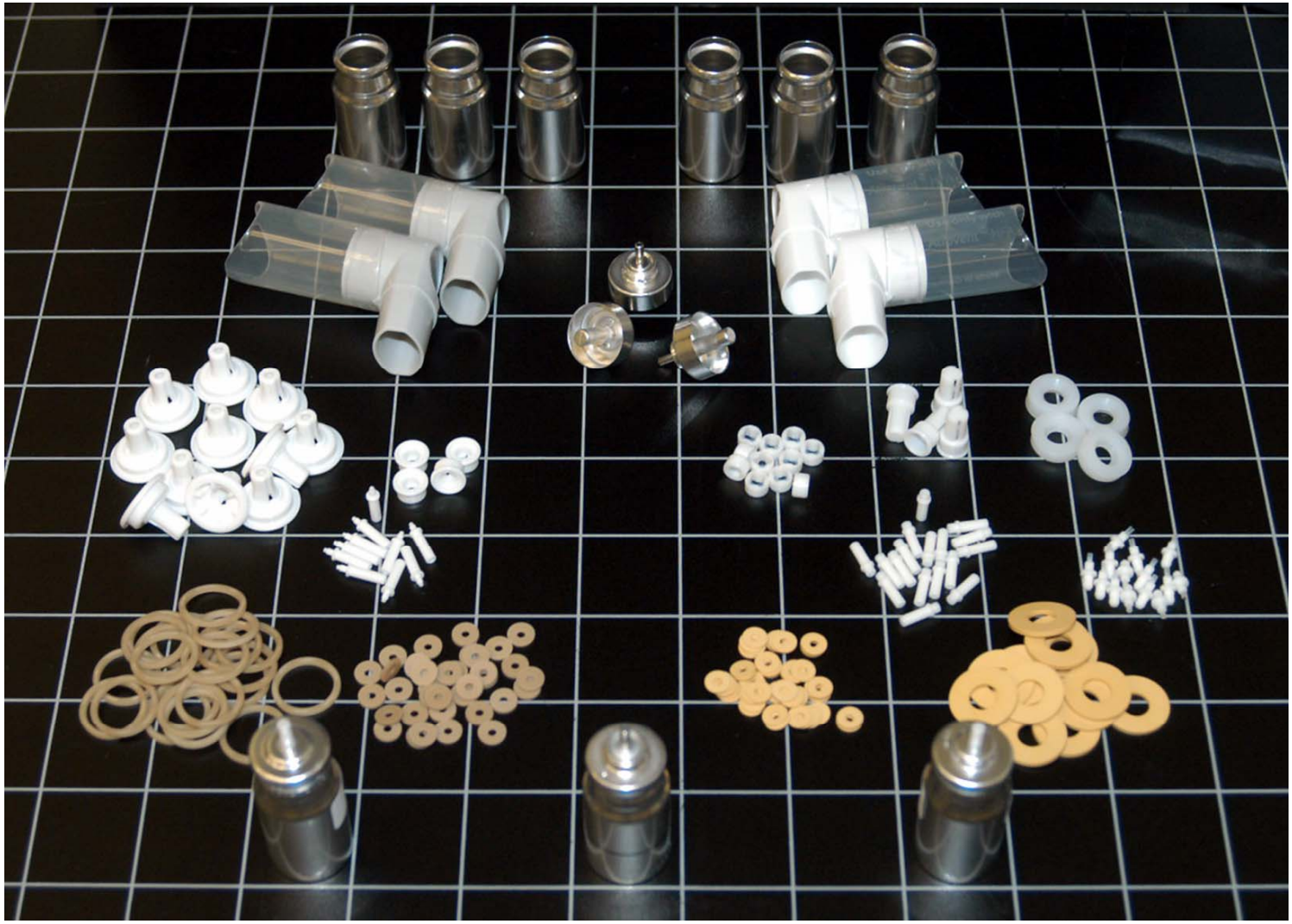
Outline
Routine Extractables Testing

- Introduction and why testing is important
  - Motivation and material types
  - What are “Extractables”, “Leachables” &“Correlation”?
  - How do Controlled Extraction Studies differ from Routine Extractables Testing?
- The Who, What, Where, When and How of Routine Extractables Testing
  - Consider each question
  - Method Development and Validation
- Role in Life Cycle Management
- Summary

Knowledge Space and The Drug Product Development Process

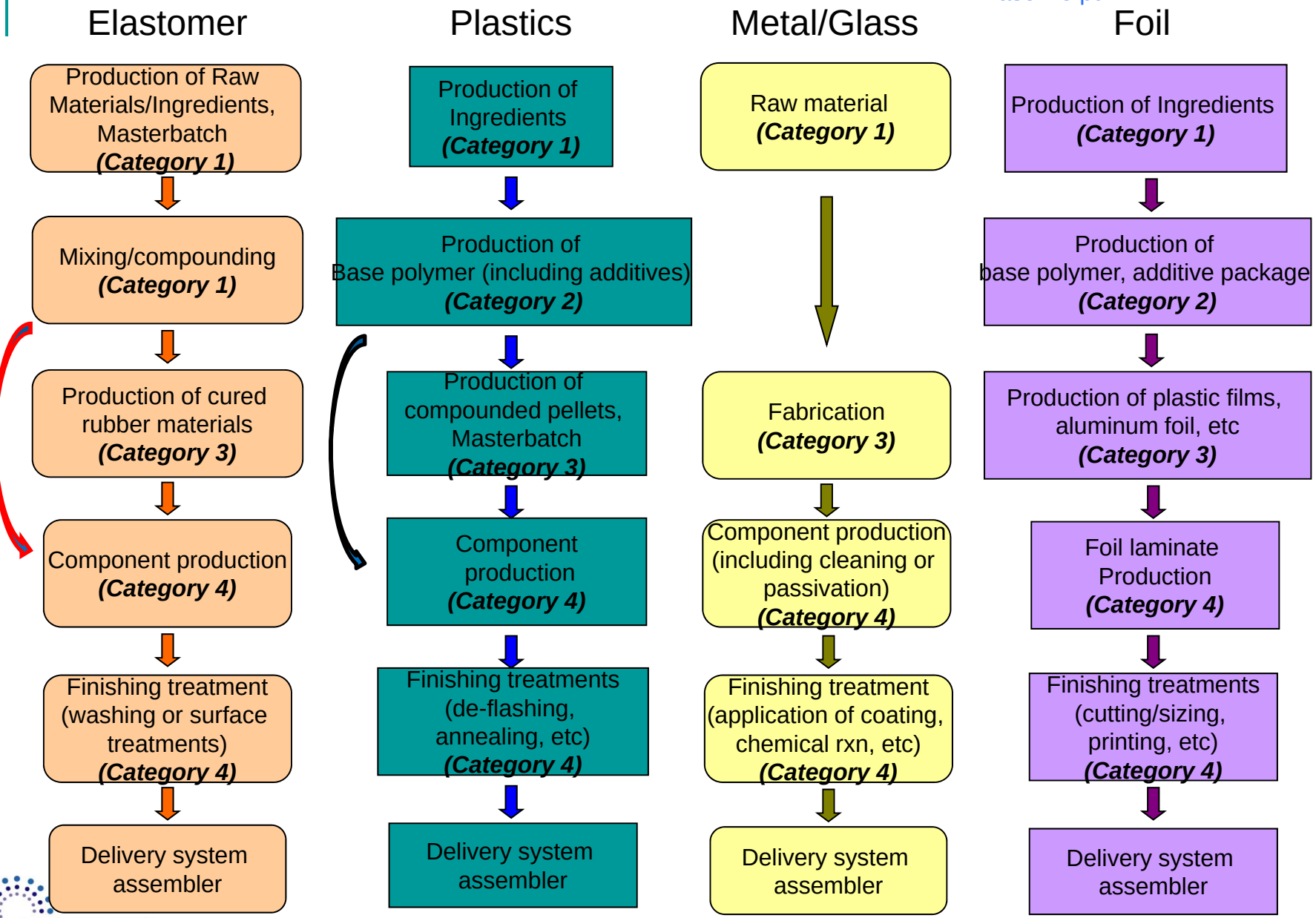


Material Types - examples



Material Types and Testing by Category

http://www.ipacrs.com/PDFs/Baseline.pdf



Material Types and Testing by Category

Test	*Category 1*	*Category 2*	*Category 3*	*Category 4*
Biocompatibility—compliance with ISO 10993*			YES	YES
USP <87>, <88>, and <1031>*			YES	YES
Physicochemical Testing*			YES	YES
Controlled Extraction Studies*	Composition Information	YES	YES	YES
Routine Extractables Testing Per *batch*, unless otherwise justified			YES	YES

* Test once at the beginning of materials selection, or if significant change has occurred

http://www.ipacrs.com/PDFs/Baseline.pdf

Risk associated with OINDP (US Perspective)

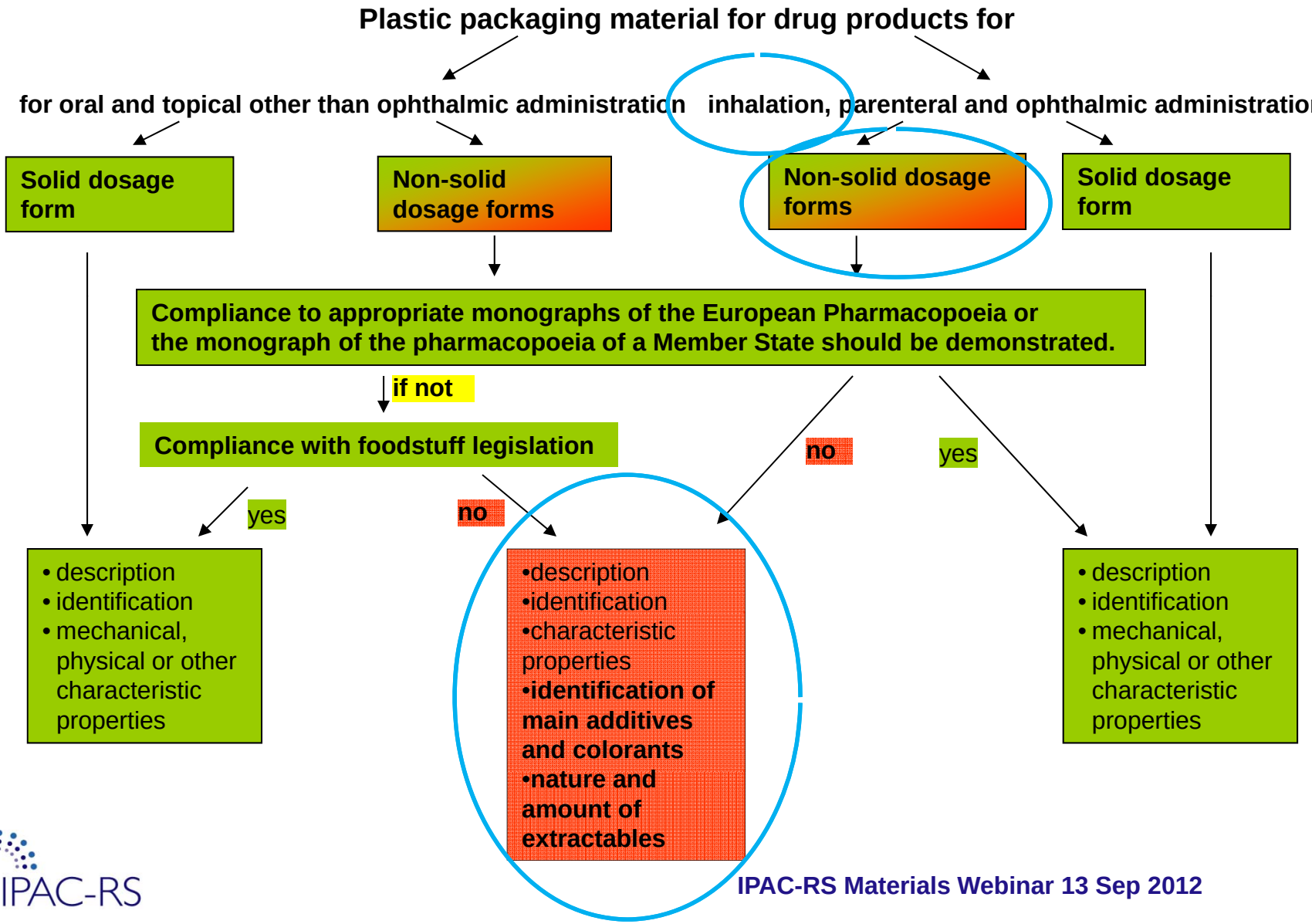
Table 1 Likelihood of Packaging Component-Dosage Form Interactions for Different Classes of Drug Products

Examples of Packaging Concerns for Common Classes of Drug Products

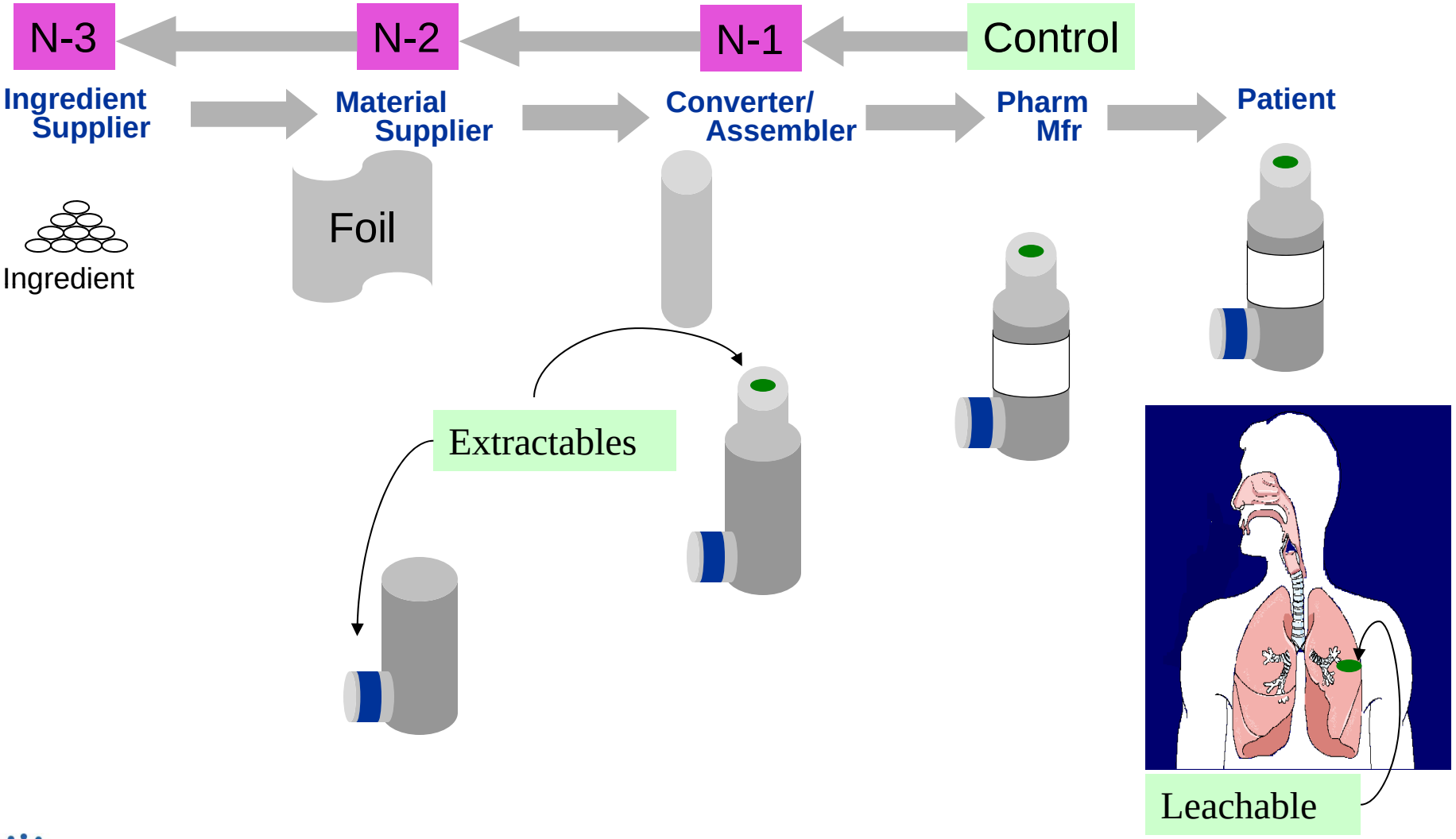
Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	**Medium**	**Low**
Highest	Inhalation Aerosols and Solutions; Injections and Injectable Suspensions[a]	Sterile Powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules

Extracted from 1999 FDA guidance document entitled "Container Closure Systems for Packaging Human Drugs and Biologics"

Risk associated with OINDP (EMEA Perspective)



Quality Throughout the Supply Chain



Extractables and Leachables

Extractables …

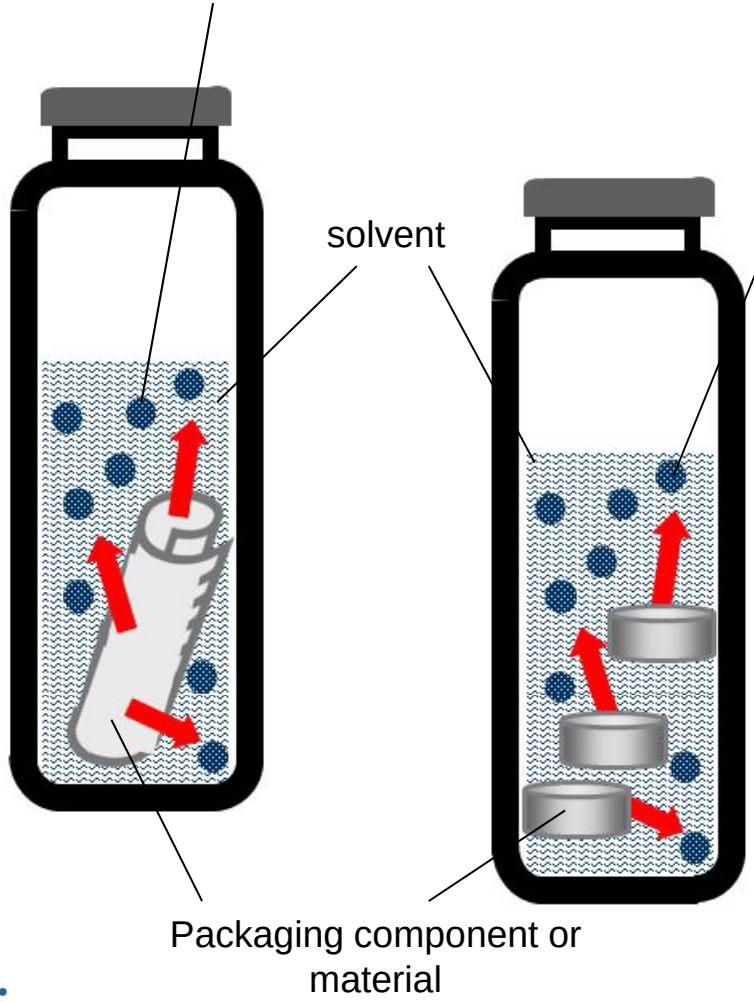
are compounds that are forcibly removed or extracted from components (or coatings) of the container closure/delivery system in a lab setting, often at extreme conditions with solvents and/or heat.

Leachables …

are compounds that migrate from the components (or coatings) of the container closure/delivery system over the shelf-life of the product under ambient storage conditions.

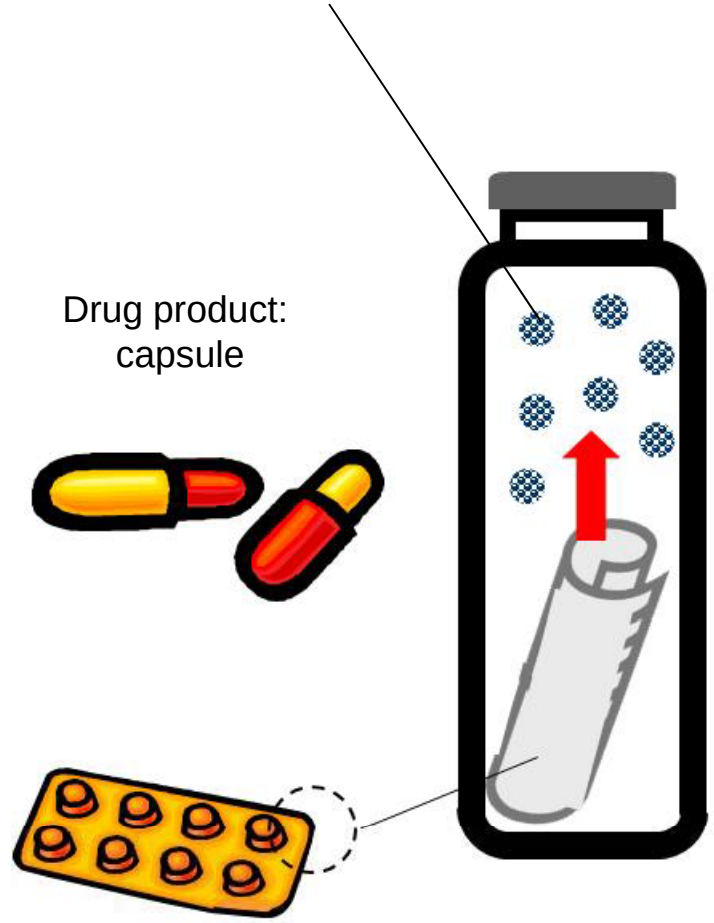
Many leachables can be controlled by careful monitoring and an understanding of extractables.

Semi-Volatile and non-Volatile Extractables



Components (or coatings) of the container closure/delivery system are exposed to appropriate solvent(s), often at extreme heat or pressure conditions for minutes or hours.

Volatile Extractables



Chemical entities migrating through the gas phase.

Subset of extractables obtained by studies that do not use a solvent.

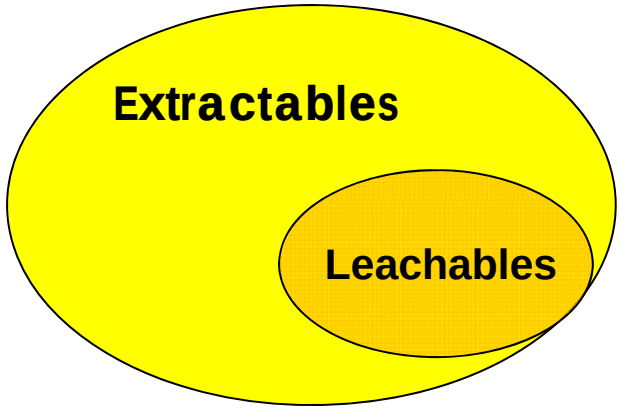
Potential Sources of Extractables

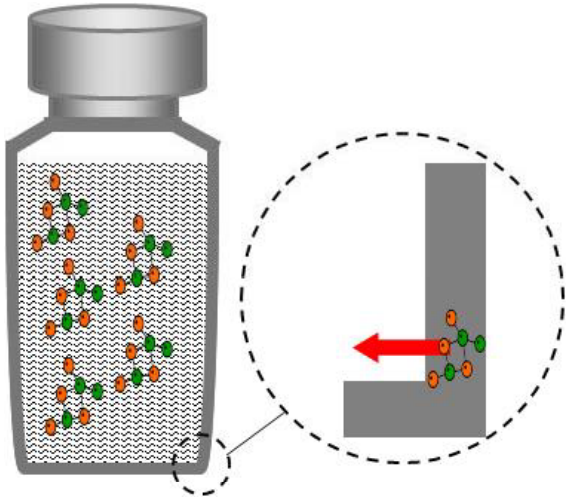
- Polymeric components (Plastics, rubber, etc.)
  - Additives, e.g. antioxidants, stabilizers, plasticizers, pigments, etc.
  - Trace level contaminants and reaction/degradation products of additives (e.g. PAHs and nitrosamines)
  - Monomers and oligomers derived from incomplete polymerization
- Manufacturing Processing aids - Mould release agents, antistatic and antislip aids, and lubricants
- Coatings on metal components - Intentional coatings or surface residues such as heavy manufacturing oils or degreasing agents
- Sources in direct contact with the outer surface of semi-permeable plastic containers - Labels including adhesives, glues and inks
- Volatiles from storage environment, not in direct contact:
  - Cardboard containers, plastic bags or plastic coatings
  - Compounds from container closure system processing during packaging

Extractables & Leachables

- In many drug products, leachables are a subset of, or are related directly or indirectly to extractables:
  - Additives, monomers/oligomers, surface residues
  - Reaction products (*e.g.*, with excipients)
  - Degradation products
  - Leaching can be promoted by components of the formulation, e.g. propellants in MDIs.

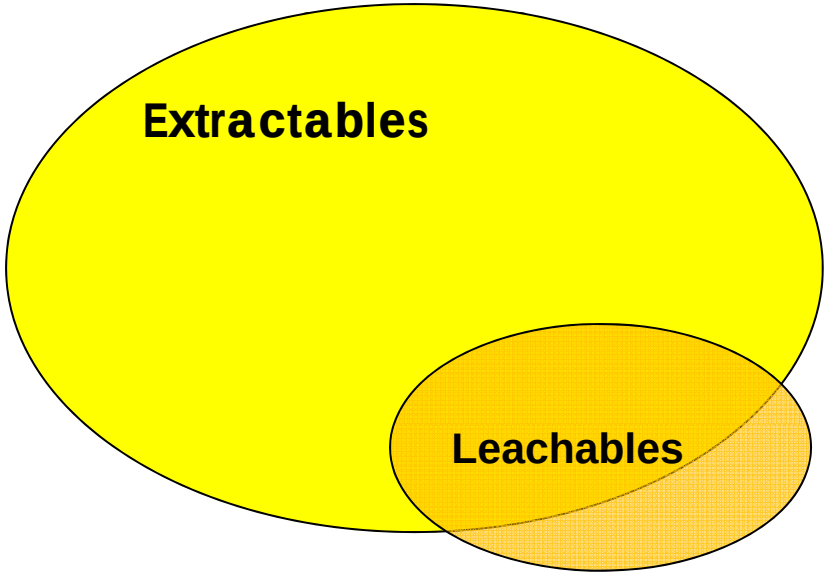
For Metered Dose Inhalers, the extractables and leachables domains are often the same.





Extractables & Leachables

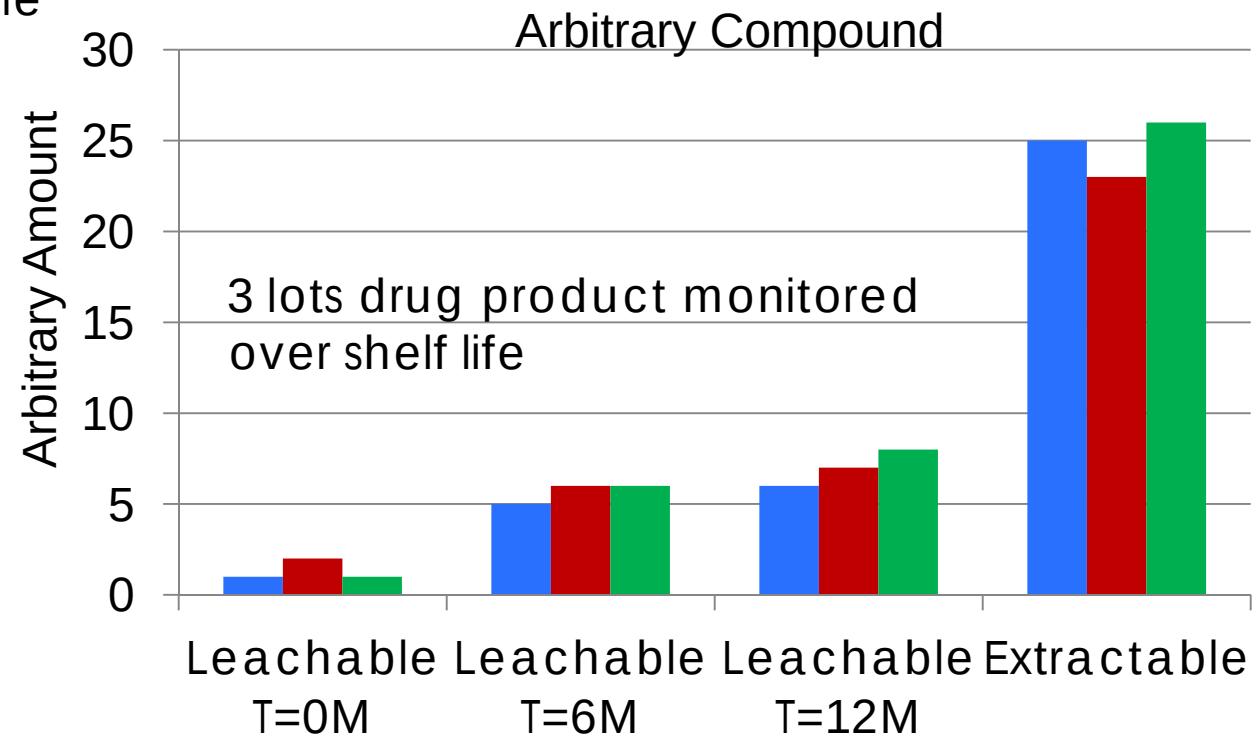
In certain cases, leachables can be derived from sources external to both primary and secondary packaging systems, *e.g.,* processing equipment, intermediate containers. Such sources may or may not have been investigated for extractables (*i.e.,* potential leachables).



Example: Filters and/or plastic tubing associated with the manufacture of a biologically active ingredient leach organic and/or inorganic species which appear in final drug product.

Control of Leachables by Extractables Testing

- First step: Qualitative Correlation: Compound is detected as a leachable in drug product and is sourced from the container closure system/delivery device or drug product
- Second step: Quantitative Correlation: Leachable compound monitored over time; amount found is less than what is available as an extractable



Correlation of Extractables and Leachables

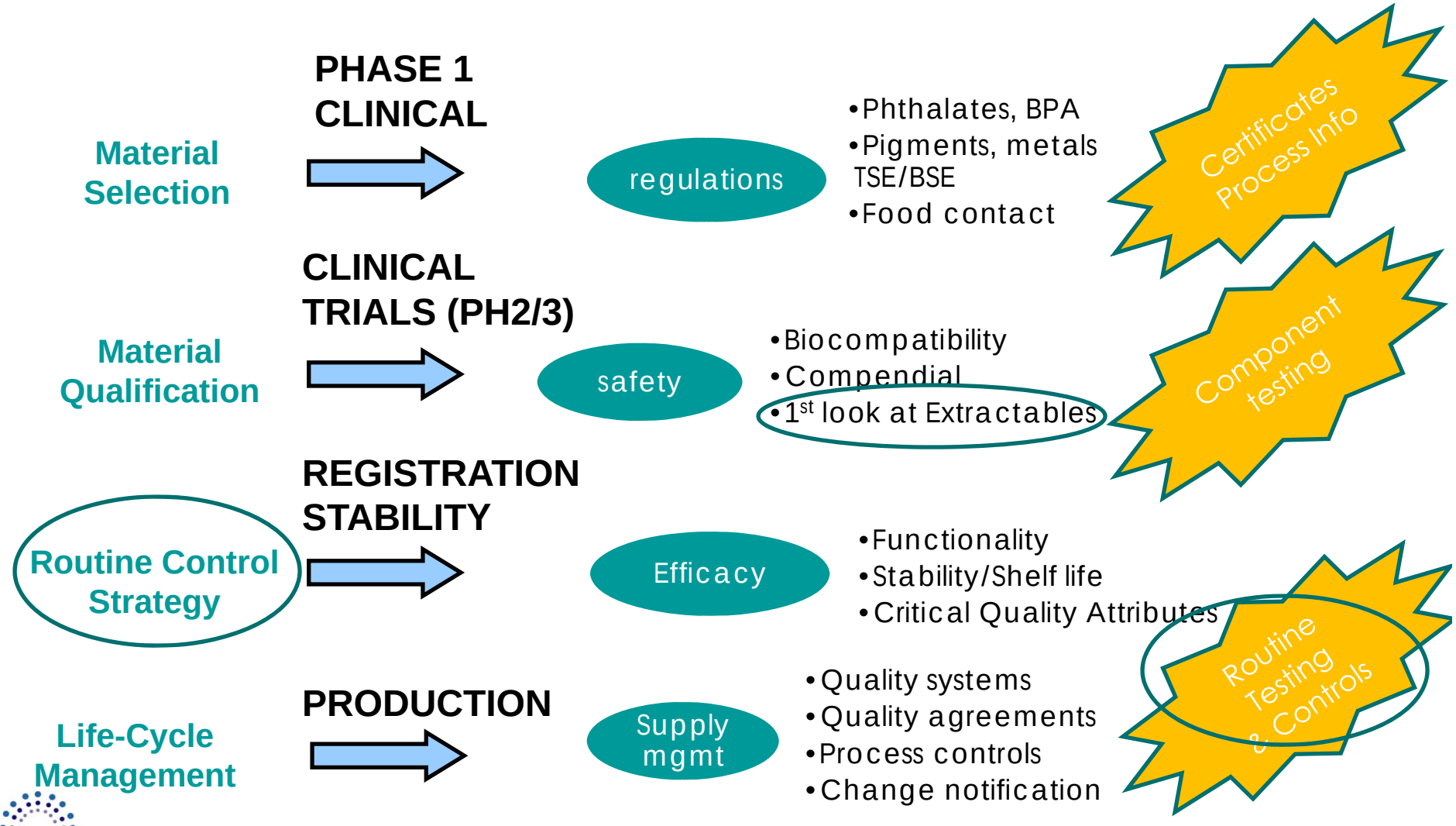
Predicted Maximum Levels of Extractables and the Corresponding Leachables Following Storage of MDI with ethanol for 18 months

Target Leachables	Maximum Predicted Total Extractables (µg/valve)	MDI Drug Product Leachables (18 Month Inverted; 30 °C/70%RH) (µg/canister)		
		Lot A	Lot B	Lot C
Peroxide related leachables	3.2	2.4	0.9	0.7
Myristic acid	332	107	95.0	87.2
Ethyl myristate	<LOD	44.4	16.3	15.3
Palmitic acid	710	188	123	124
Ethyl palmitate	<LOD	111	67.9	54.5
Stearic acid	1230	289	184	165
Ethyl stearate	<LOD	113	60.9	70.2
PBT dimer	5620	192	185	178
PBT trimer	1810	20.6	20.1	19.2
PBT tetramer	270	0.4	<0.4	0.6
PBT pentamer	227	<LOD	<LOD	<LOD

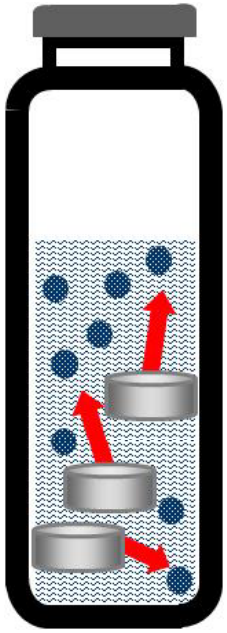
Indirect Leachables

Example Data is Courtesy of BI

Knowledge Space and The Drug Product Development Process



Controlled Extractables study – EXAMPLE
Many target compounds - Single time



Material characterization

Simulation

Plastic packaging component (3 batches)

Soxhlet Extraction (24 h)

Non polar extraction solvent: Hexane

Polar extraction solvent: Ethanol

Formulation simulant: Acidic Ethanol/Water

Sample preparation

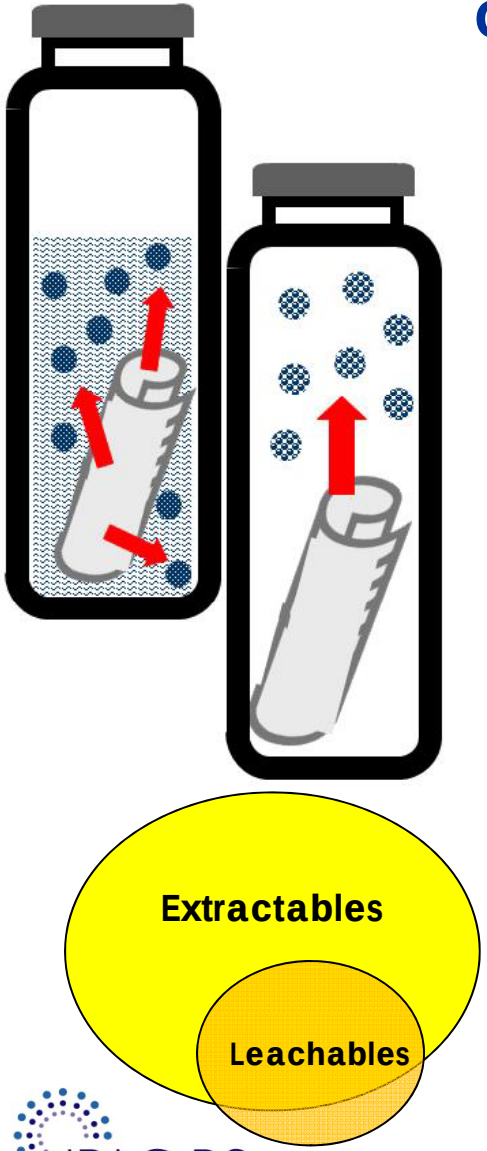
GC/FID

GC/MS

HPLC/UV

HPLC/MS(MS)

Evaluation of results from Controlled Extraction studies



Qualitative and quantitative results of extractables studies

- Results for volatiles & organic extracts:
  - ⇨ Material characterization
  - ➢ Revisit supplier information describing component formulation
- Results for formulation simulant:
  - ⇨ Potential leachables list
  - ➢ Toxicologists evaluate extractables profiles to identify any potential safety concerns

Overall, the Controlled Extraction studies give us potential target compounds for routine extractables testing.

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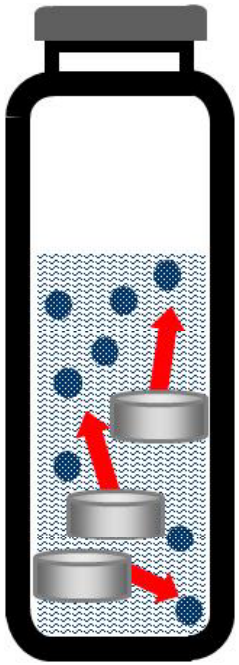
Routine Extractables testing – EXAMPLE
Selected Targets Only – Ongoing testing



Quantitative characterization

Component
(Every batch unless otherwise arranged)

Validated Methods

Efficient Extraction
(minutes - hours)

Volatiles extraction solvent: non-polar

Semi volatiles/Non-volatiles extraction solvent: Ethanol or other Polar

Other if needed

Sample preparation

Sample preparation

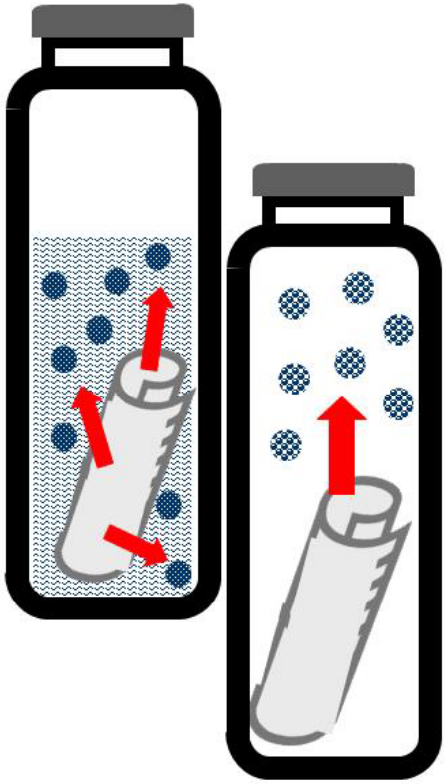
GC/FID

GC/MS if needed

LC/UV

Other if needed

Evaluation of results from Routine Extraction studies



Quantitative results of extractables

- Results for **several targeted** compounds:
  - Supplier compares to a release specification
  - Track results over time to ensure consistency and identify any trends in data/process

Extractables

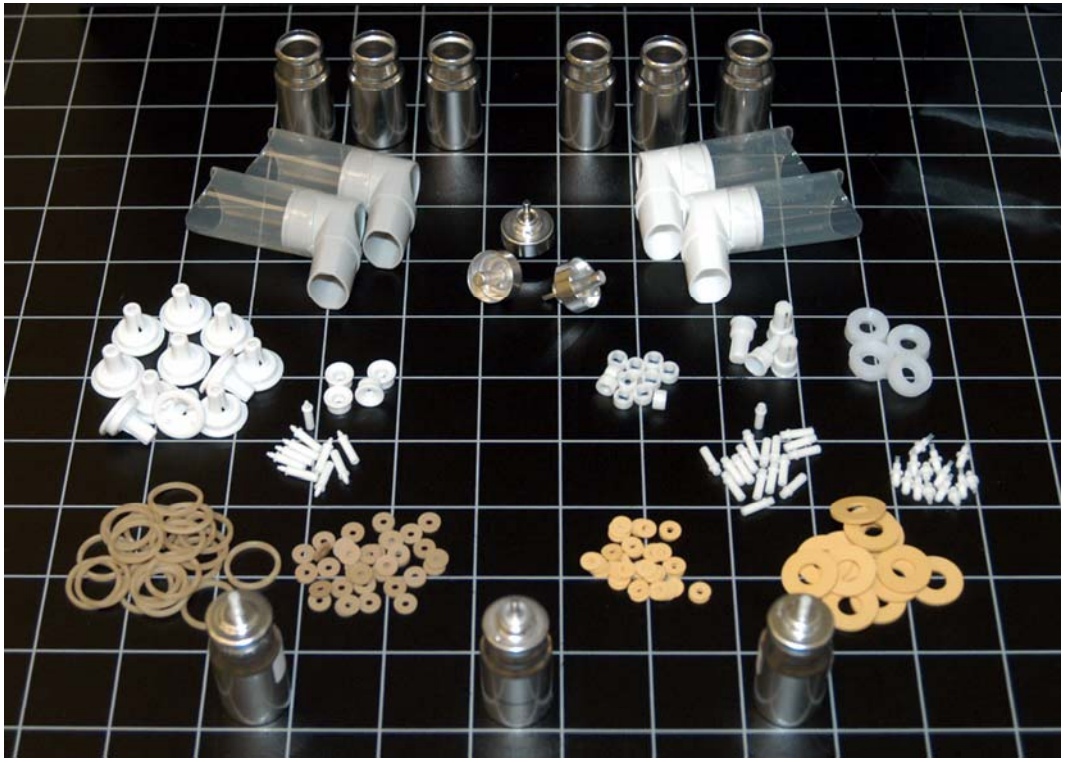
Routine Extractables for OINDP–

OINDP=Orally Inhaled and Nasal Drug Products

What is tested?

Individual components which are in direct contact with drug product formulation, delivery device and patient:

Foil



Routine Extractables – Components are tested **for what**?

- Compounds identified during **Controlled Extraction Studies**
- Compounds detected as **Leachables** which are > Qualification Threshold or Safety Concern Threshold, according to PQRI definitions*
- **Additives** that are functionally **essential**
- **Other** compounds desired from Pharma, Regulatory Agency, or Material Supplier

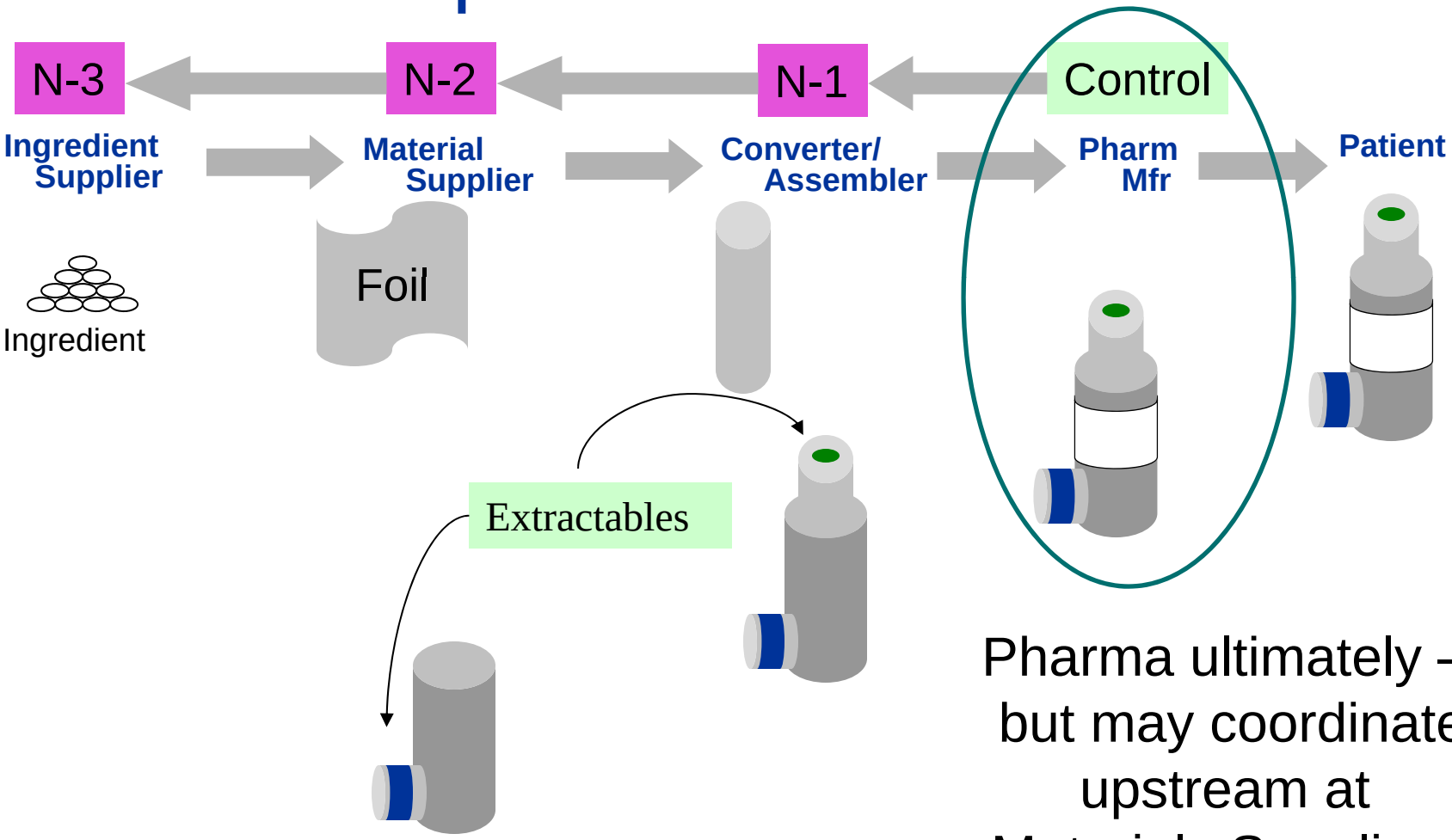
*PQRI (Product Quality Research Institute) Leachables and Extractables Working Group: Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products, 8 September 2006

Routine Extractables – Components are tested **for what**?

Example Extractable	Example Leachable	Safety Concern and Functional Considerations	Routine Extractables Testing
Ethanol	Ethanol	Safe, no tox concerns, needed for manufacturing of product	Likely not needed due to compound being safe
Polyaromatic hydrocarbons or nitrosamines	Not detected	Compounds have tox concerns at known low levels; no functional need	May (or may not) need due to known safety concerns and manufacturing controls
Antioxidant	Detected or not detected	Compound is essential for function or manufacturing of the part; no tox or safety concerns at detected levels	May need because compound is essential for part
Other additive	Detected	Compounds have safety/tox concerns above detected levels; no functional need	May need; Consult PQRI* recommendations; take leachables levels into account

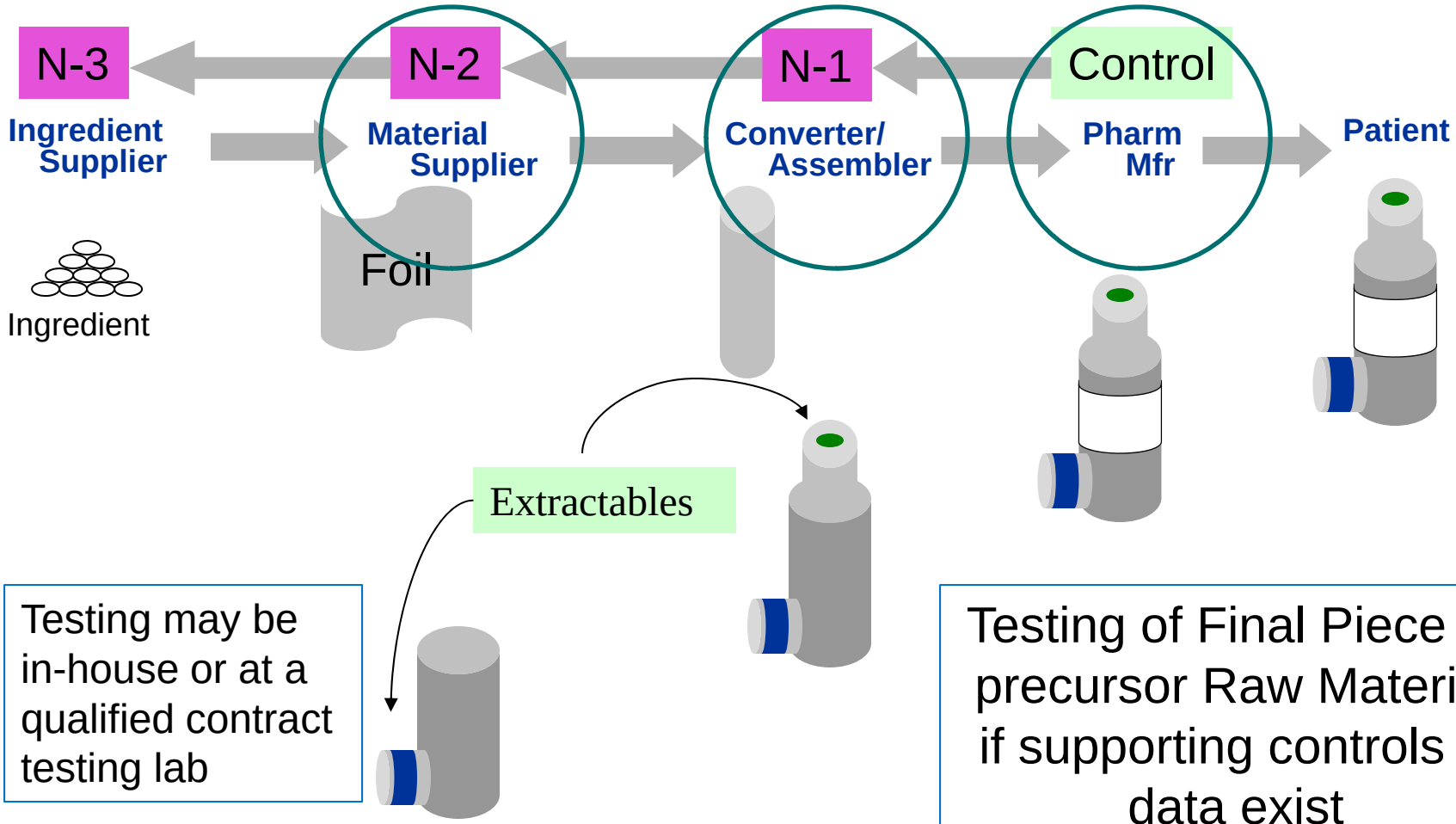
*PQRI (Product Quality Research Institute) Leachables and Extractables Working Group: Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products, 8 September 2006

Routine Extractables – **Who** is responsible for tests?



Pharma ultimately – but may coordinate upstream at Materials Suppliers

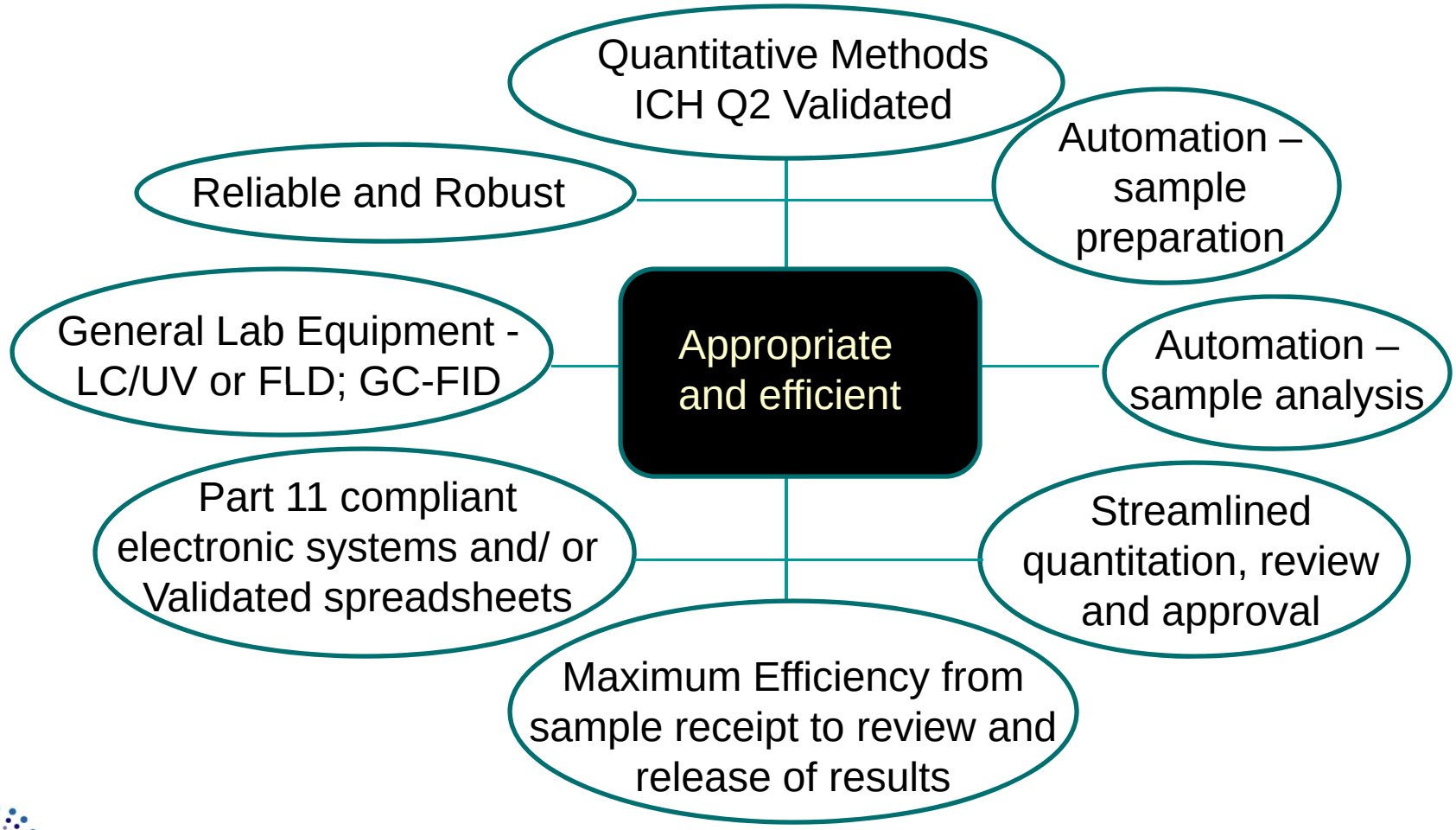
Routine Extractables – **Where** & **When** does testing occur?



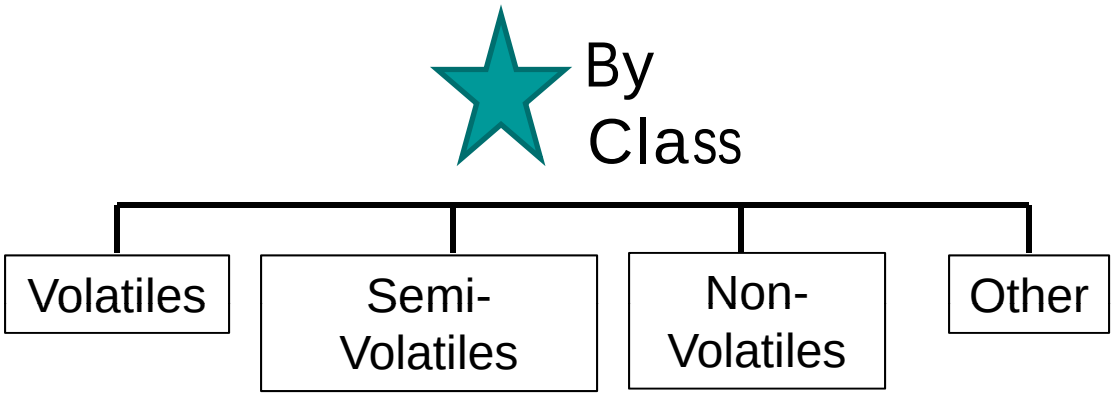
Testing may be in-house or at a qualified contract testing lab

Testing of Final Piece or precursor Raw Material if supporting controls & data exist

Routine Extractables – Components are tested **how**?



Routine Extractables – Components are tested **how**?



By Amount Present (or a desired Lower Limit)

Extractable Compound Type	Likely Range of Detection Limits
Abundant Known Additives with no Safety Concerns	High ppm
Known Additives or Breakdown Products or Moderate Safety Concerns	Low ppm
Special Interest Compound (PAHs or Nitrosamines) or High Safety Concern	ppb
Unknowns	ppm

Routine Extractables – Method Development Parameters?

- Define Target Compounds from Controlled Extraction Studies and Leachables
- Class (volatile, semi- or non-volatile, other)
- Expected levels of target compounds
- Detection Limits
- System Suitability requirements

Routine Extractables – Method Development Parameters?

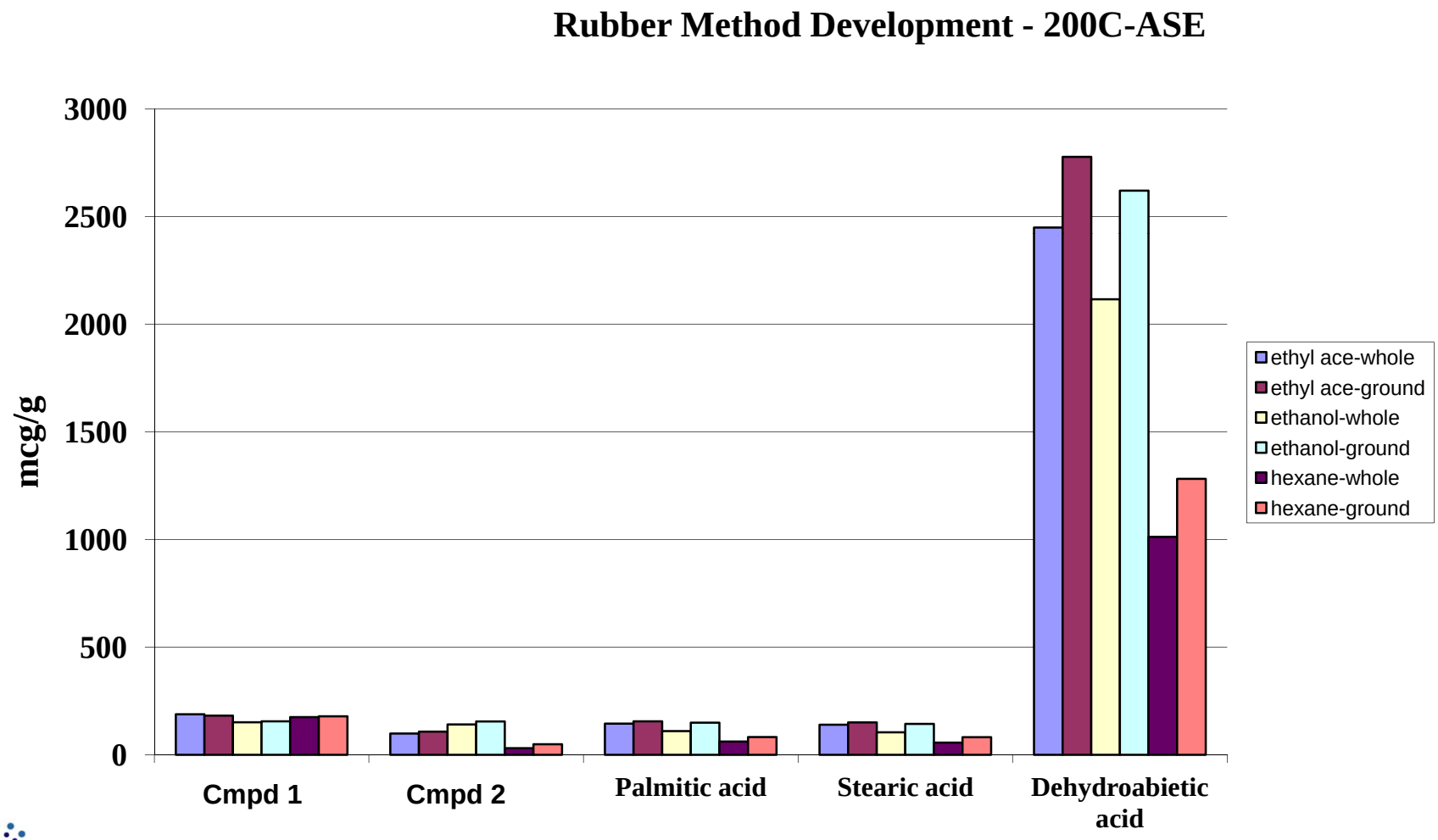
Other Practical Considerations

- Cost – equipment purchase required?
- Is the equipment expensive to maintain?
- Are consumables cheap and readily available?
- Are standards available at a reasonable cost?
- Will analyst training be difficult?
- Method to be run at more than 1 site?
- Too complicated? Too long to obtain results?

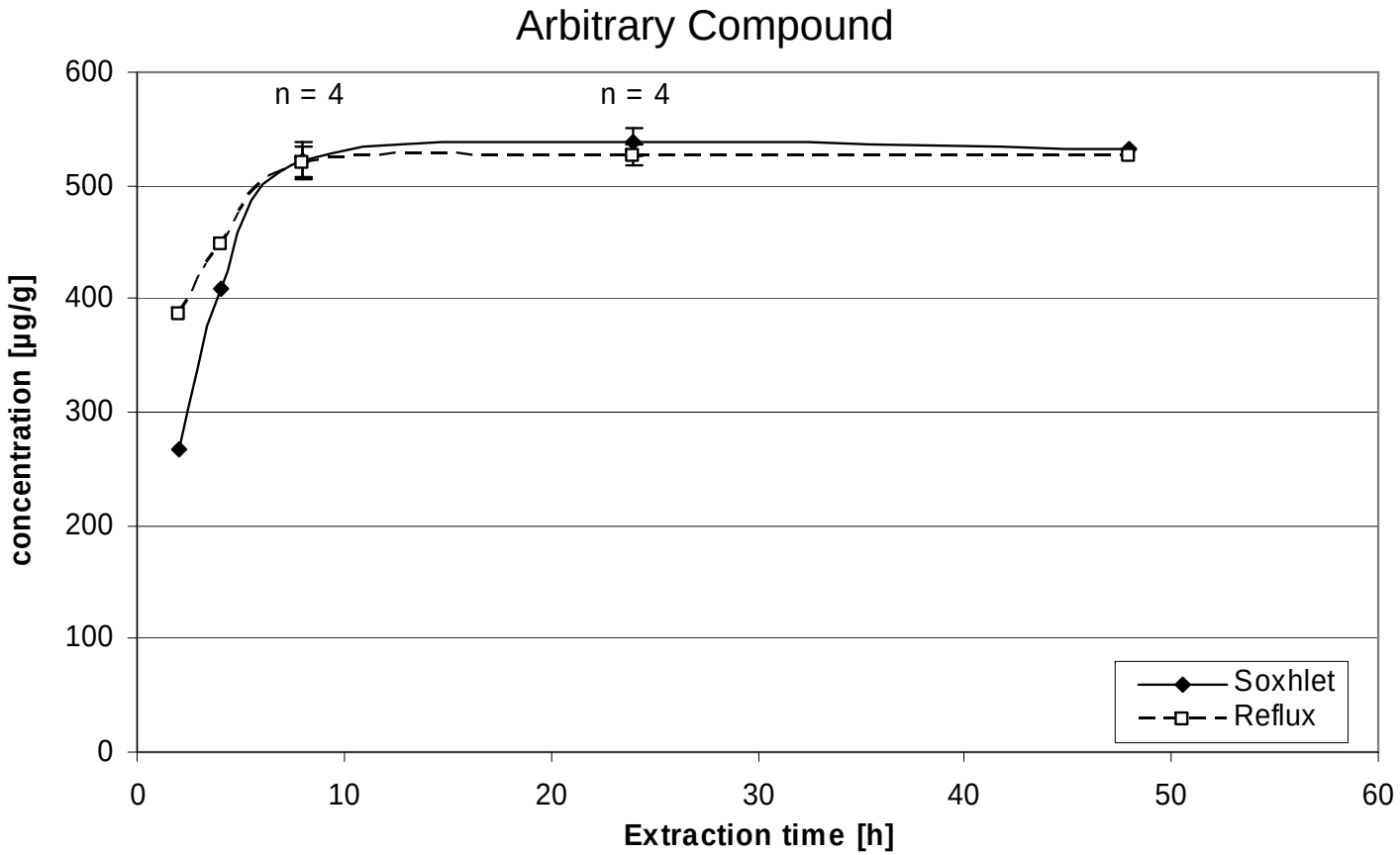
Routine Extractables – Method Development Parameters?

- **Sample Preparation Trials**
  - Several extraction solvents
  - Ground and whole parts
  - Multiple extraction methods
    - Soxhlet
    - Reflux
    - Sonication
    - Accelerated solvent extraction (ASE)
    - Super-critical fluid extraction (SFE)
    - Microwave
  - Sample Concentration Steps, solvent reduction
  - Exhaustive – asymptotic over time

Sample Prep Examples: Solvent and Ground vs. Whole



Sample Prep Examples: Exhaustive = asymptotic over time

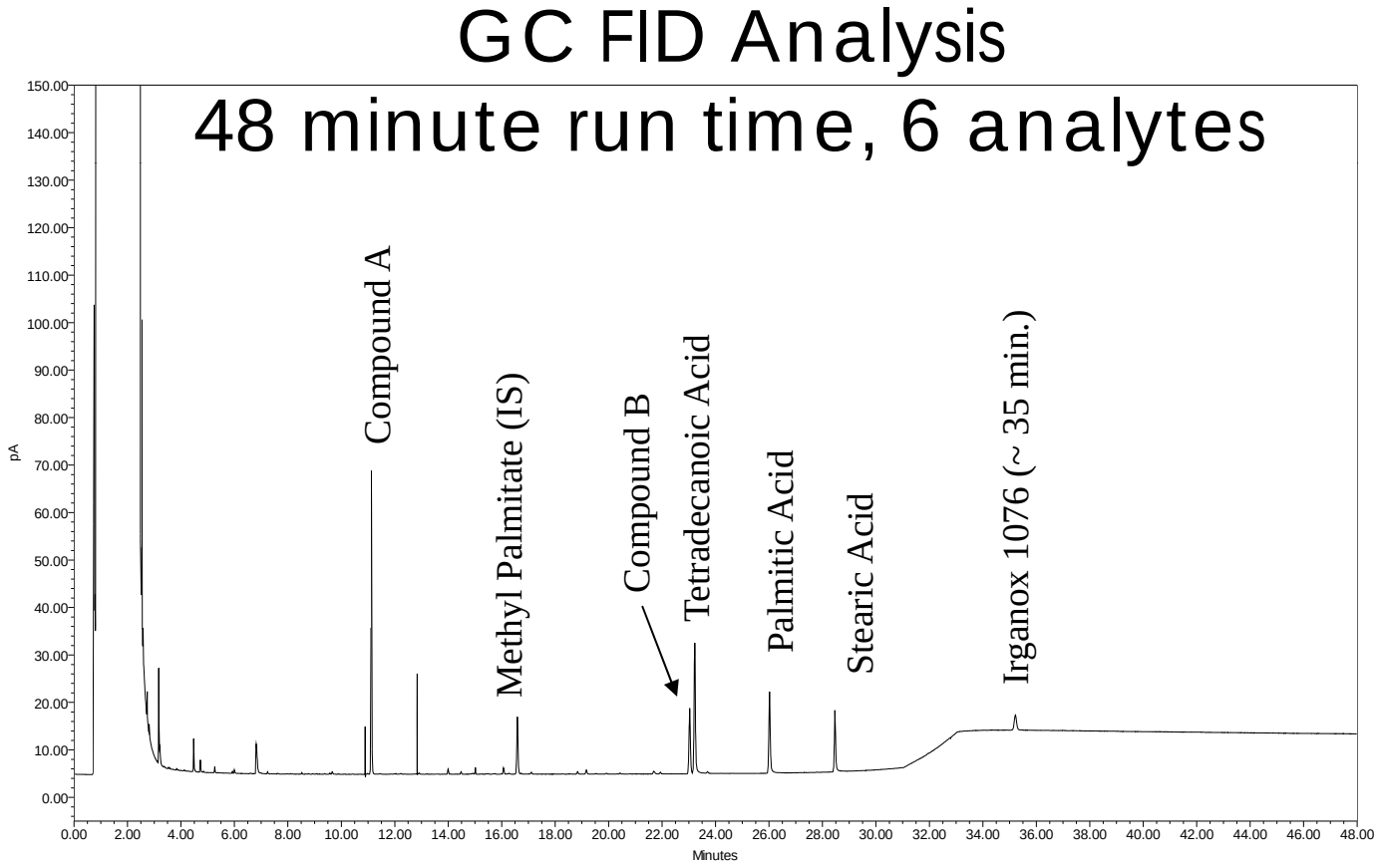


Sample Analysis Examples– GC Parameters?

- **Sample Analysis Trials**
  - Volatiles - GC-FID primarily
    if necessary for sensitivity or selectivity:
    GC-Mass Spec (MS)
    GC-Nitrogen Chemiluminescence (NCD)
    GC-Thermal Energy Analyzer (TEA)

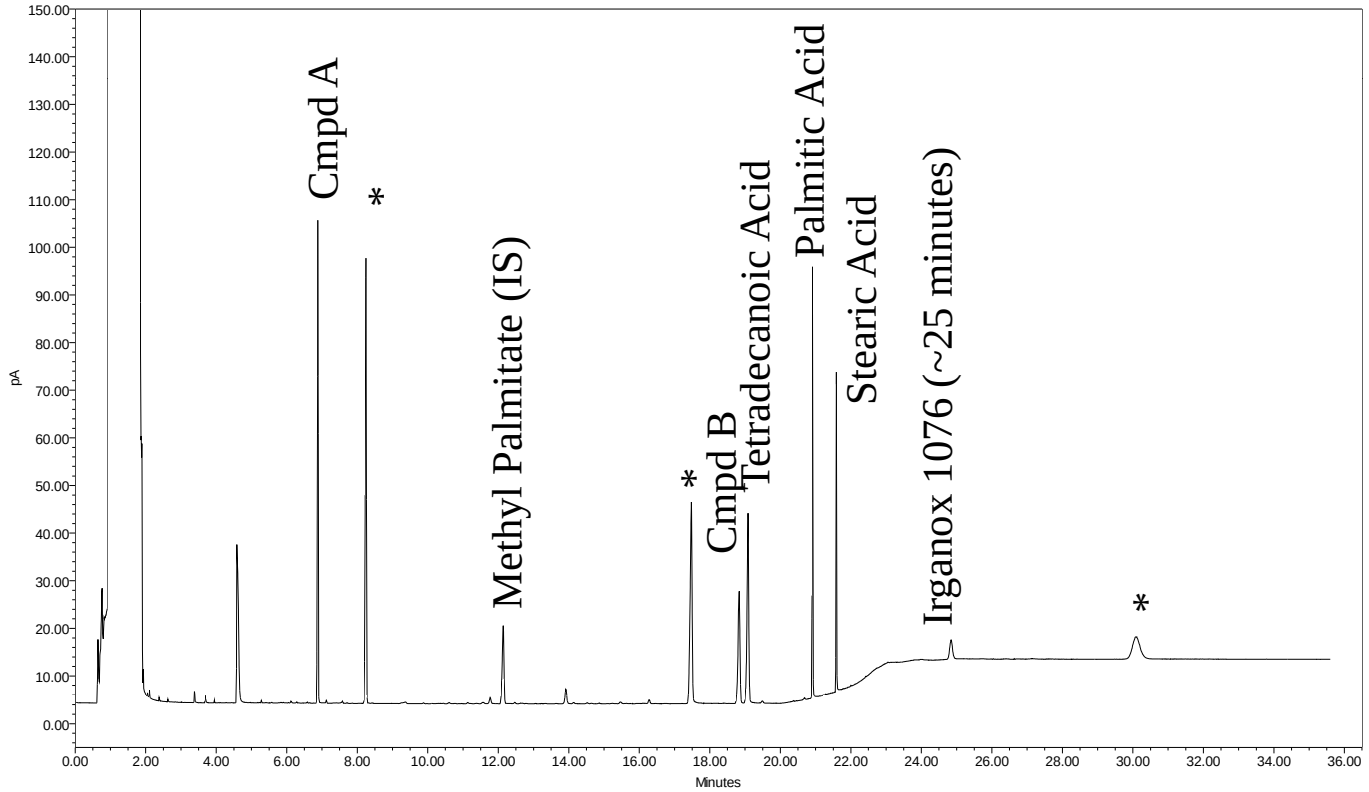
Common GC Variables	
Injection port temperature	Injection volume
Columns – type and dimensions	Column flow rate
Temperature Ramps	Carrier Gas

Sample Analysis – Runtime example for GC FID SLOW



Sample Analysis – Shortened Runtime–increased throughput FASTER

GC FID Analysis
36 minute runtime, 6+3 analytes



Sample Analysis Examples – LC Parameters?

- **Sample Analysis Trials**
  - Semi-volatiles and non-volatiles – LC-UV
    Depending on chromophores, sensitivity, and interferences may need:
    LC-diode array (DAD)
    LC-fluorescence (FLD)
    LC-charged aerosol (CAD)

Common LC Variables	
Flow rate	Injection volume
Column temperature	Columns – type and dimensions
% A / B ramps	pH
Buffer concentration	Mobile phase composition

  - Consider UPLC for speed over HPLC

Routine Extractables – Other Compounds?

Special Concern Compounds –Nitrosamines, 2-Mercaptobenzothiazole (MBT) and Polyaromatic hydrocarbons (PAHs)

Methods with very low detection limits may be needed:

- Concentration steps during sample preparation
- GC/MS or GC/TEA detection methods to minimize interferences and maximize sensitivity

Other Compounds such as Metals –

ICP-AA or ICP-OES for metal-specific quantitation

Routine Extractables – How important are Standards?

- Retention Time Marker Standards:
  - Stable and available
- Quantitation Standards:
  - Known Purity from Supplier or Independently Determined
  - Ideally, Reference Standards Exist
  - Raw Compound in Storage Vial – Stability Established
  - Standard Solution - Stability Established in Diluent
  - Readily available

Routine Extractables – How important are Standards?

- Internal Standards:
  - No interference with target compounds
  - Used to quantitate target compounds either within analysis or by established response factor
  - Compatible with dilution solvent
  - Good peak shape with chosen chromatography or analysis method
  - Readily available

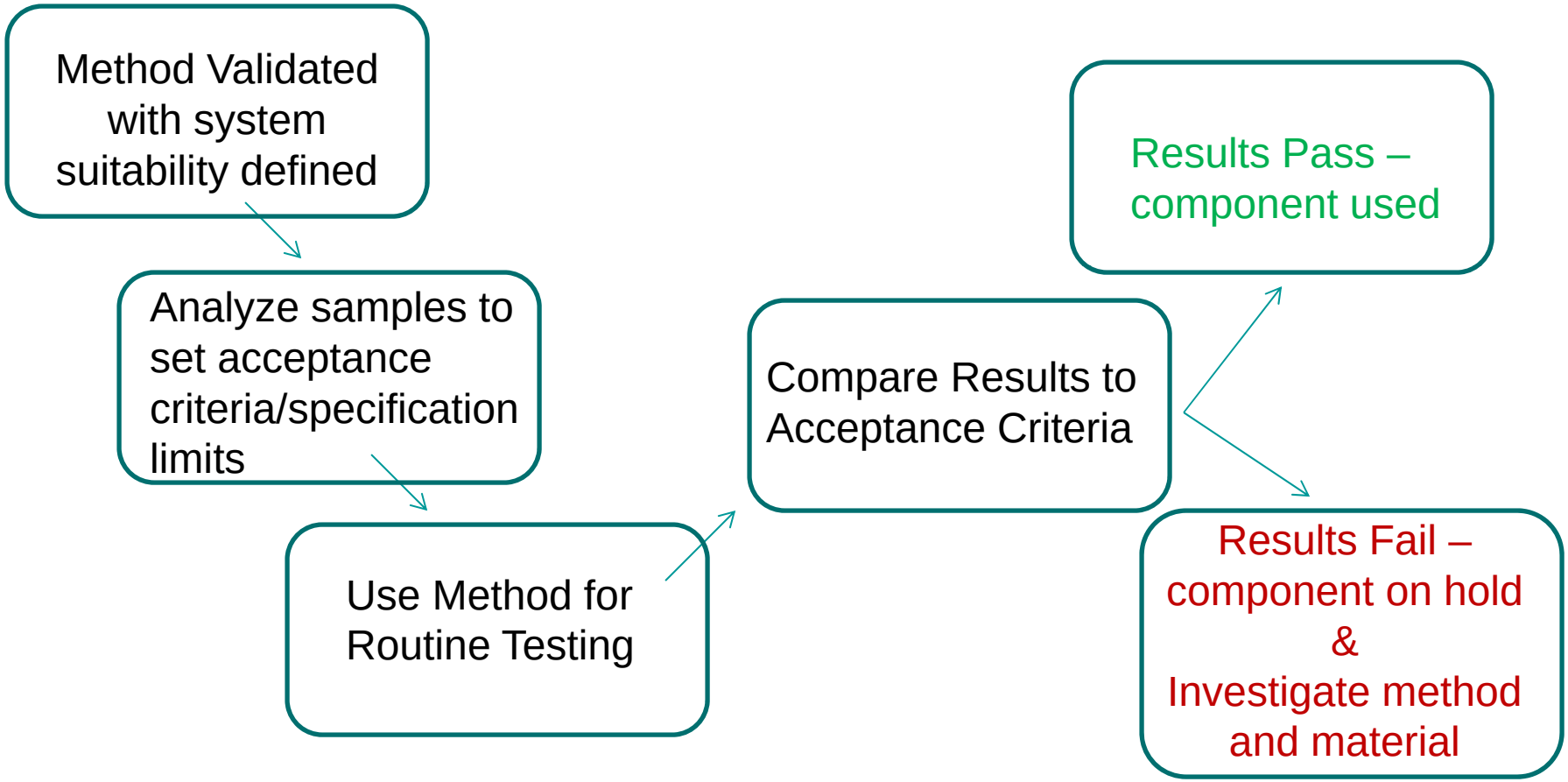
Routine Extractables – Method Validation Parameters?

- Quantitative by FDA or ICH Q2:
  - Specificity/Selectivity – no overlapping peaks
  - Linearity/Range
    - Based on anticipated levels in samples
    - May differ by an order of magnitude between compounds
  - Limit of Quantitation, Limit of Detection
    - Appropriate for different compounds
  - Accuracy at several levels
    - 50%, 100% and 150% of expected levels and near the LOQ

Routine Extractables – Method Validation Parameters?

- Quantitative by FDA or ICH Q2:
  - System (Injection) Precision for instrument
  - Method Precision
  - Intermediate Precision (2nd analyst/instrument)
    - Especially important if method will be run at more than 1 site
  - Robustness to minor changes in parameters
    - Especially important if equipment is not dedicated or environmental conditions are variable
  - Standard Solution and Sample Solution Stability
    - Light & temperature may play a role
    - Reactive species

Life Cycle of Routine Extractables Testing–



Routine Extractables – **Robustness** is key – Example risks of failed **system suitability**

1-6 hours of troubleshooting time
1-2 hours lost time – review/signatures
24 hours lost instrument time

Repeated failures can lead to:
Delay in results
Delay in shipping
Delay in drug product manufacture

Robust routine extractables methods are essential !

Routine Extractables – **Specification Limits/Acceptance Criteria**

Data Driven Process (preferred by regulators and industry)

At least 3 sample lots but ideally >20 sample lots analyzed

Range of manufacturing conditions and operating ranges

Range of temperature and humidity environmental conditions

Upstream supplier controls and information in regulatory filings

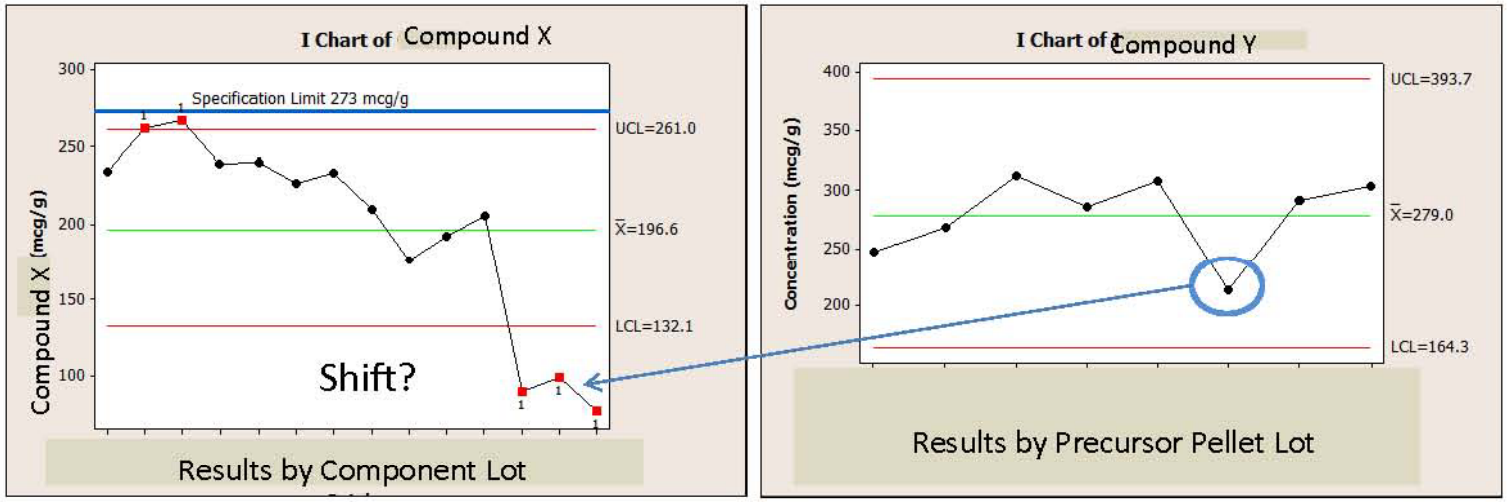
Analytical variability (instrument and analyst)

Routine Extractables – Detect change in manufacturing condition or raw material?

GC-FID Analysis of Plastic Part Example

N-1 Supplier (Molder)

N-2 Supplier (Resin/Pellet)



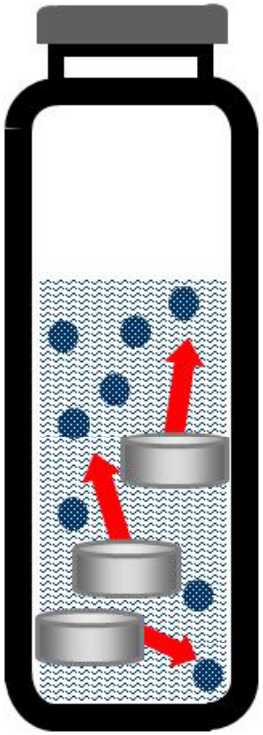
Examples of change...

- Material composition—change of ingredient or supplier
- Material processing—change of conditions or processing aids
- Component processing—change of conditions, tooling or finishing steps
- Test Method change - discontinued column, instrument

Which must be discussed between Supplier and Pharma and a risk assessment performed.

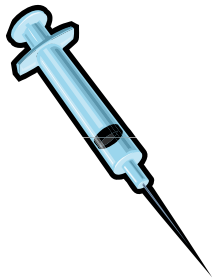
Revalidation of test method or new acceptance criteria may be necessary.

Detailed Summary - Routine extractables testing for OINDP



- Critical components are qualitatively and quantitatively profiled for **extractables, for the purpose of release according to acceptance criteria** established through:
  - Understanding of composition, ingredients, and compounding/fabrication processes.
  - Comprehensive controlled extraction studies.
  - Leachables/extractables correlation.
- Helping to ensure that the leachable profile in the drug product is maintained within appropriate limits.

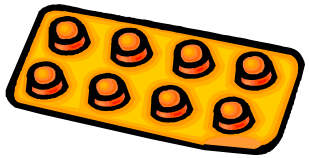
Source: PQRI (Product Quality Research Institute) Leachables and Extractables Working Group: Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products, 8 September 2006



Summary

- Combination products that include OINDP and injectables are generally categorized as having a high level of concern for **patient safety** and require **high quality materials** and **controlled processes** throughout the supply chain.

- Ongoing routine extractables **testing** is a method of ensuring patient safety and **manufacturing consistency**.



Material Testing – Regulatory Guidance

Key Regulatory Guidances

- Health Canada/EMEA Guidance – Pharmaceutical Quality of Inhalation and Nasal Products (Extractables/Leachables) 2006
- FDA - MDI/DPI Draft Guidance (Inhalation Product Performance & Characterizaton) 1998
- FDA – Guidance on Inhalation solution, suspension, spray and nasal spray products 2002
- FDA - Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (Packaging Characterization) 1999
- CHMP, CVMP - Guideline for Plastic Immediate Packaging Materials (Packaging Characterization) 2005
- FDA – Draft Guidance Analytical Method Development and Validation 2000
- ICH Q2 – Validation of Analytical Procedures 2005

Material Testing – Non- Regulatory Guidance

References

Leachables and Extractables Handbook. Safety Evaluation, Qualification, and Best Practices Applied to Inhalation Drug Products. D.J. Ball, D.L. Norwood, C.L.M. Stults, L.M. Nagao eds. John Wiley & Sons, Inc. Hoboken, NJ. 2012.

Safety Thresholds and Best Practices for Leachables and Extractables in Orally Inhaled and Nasal Drug Products. PQRI L&E Working Group. Product Quality Research Institute. 2006.

Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products: An Overview of the PQRI Recommendations. D. L. Norwood, D. Paskiet, M. Ruberto, T. Feinberg, A. Schroeder, G. Poochikian, Q. Wang, T. J. Deng, F. DeGrazio, M. K. Munos, L. M. Nagao. *Pharmaceutical Research,* 25(4), 727-739 (2008)

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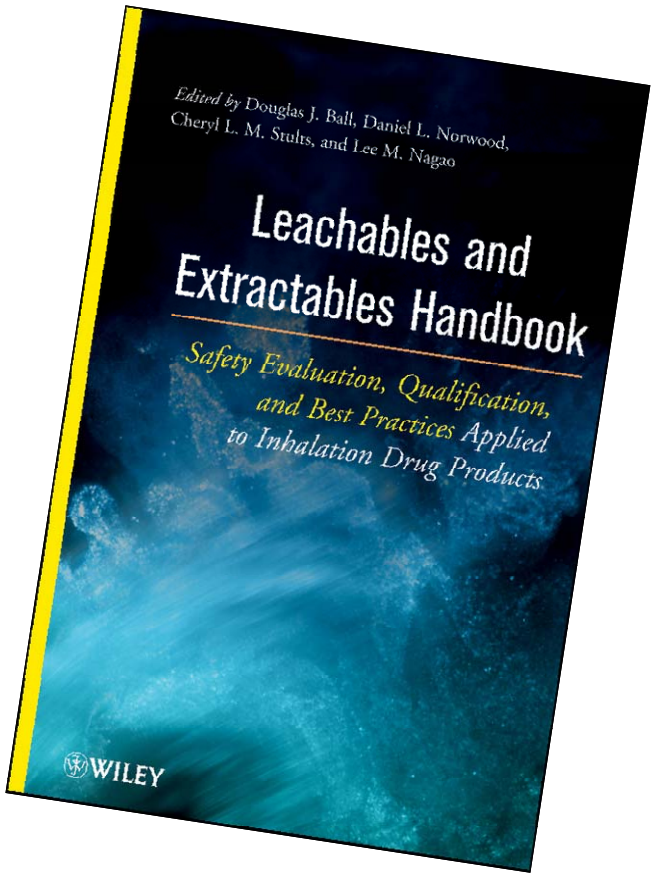
Leachables and Extractables Handbook:
Safety Evaluation, Qualification, and Best Practices Applied to Inhalation Drug Products

Douglas J. Ball, Daniel L. Norwood, Cheryl L.M. Stults, Lee M. Nagao

Combining a practical and experience-based approach, this book helps pharmaceutical professionals evaluate the safety of and manage leachables and extractables throughout the pharma product lifecycle.

- Addresses concepts, background, historical use and development of safety thresholds and their utility for qualifying leachables in OINDP (Orally Inhaled and Nasal Drug Products)
- Provides guidance for pharmaceutical professionals to qualify and risk-assess container closure system leachables and extractables in drug products
- Familiarizes readers with the development of safety qualification thresholds, with an emphasis on a practical approach and illustrates principles for defining toxicological safety qualification thresholds that are applicable to OINDP and potentially applicable to other drug products
- Includes regulatory perspectives
- Contains key terms and definitions, case studies and sample protocols



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