



Leachables and Extractables from Polymers

Requirements for the Pharmaceutical Industry

Stephane Berghmans
Janssen Pharmaceutica N.V.
Manager Packaging Development



Introduction

Wal-Mart said it would phase out BPA from all the baby bottles it sells, replacing them with different plastics or glass. Retail chains pull BPA-tainted baby bottles from shelves as health risks arise. "Safety is a top priority for Wal-Mart," the company said in a statement. "While the FDA has not established any restrictions on the use of bisphenol A (BPA) in baby bottles, for several years now we have offered a variety of BPA-free products for customers who seek this option. We are working to expand our BPA-free offerings and expect the entire assortment of baby bottles to be BPA-free sometime early next year."

<http://abcnews.go.com/Health/story?id=4683891&page=1>

- 1953: Foundation of Janssen Pharmaceutica
- 1961: Janssen Pharmaceutica becomes part of Johnson&Johnson
- 1994: Fusion of Janssen and Cilag Sales & Marketing to Janssen-Cilag
- 2001: Global Pharmaceutical Research - Johnson&Johnson Pharmaceutical R&D
- 2004: New global pharma R&D structure (J&J PRD, Tibotec, etc...)

- Plastics and rubbers are used in different packaging materials and dosing devices
- These materials are in direct contact with the Pharmaceutical product
- The final use of the product determines the risk of possible interactions with the product
- Extractables and leachables can be harmful and can possibly alter the pharmaceutical product

Potential Sources of Extractables from elastomeric or plastic components:

- Additives and processing aids, e.g. antioxidants, stabilizers, plasticizers, emulsifiers etc.
- Trace level contaminants and reaction products contained in additives
- Monomers and oligomers
- Secondary reaction products from processing
- Pigments
- Contaminants and/ or reaction products from storage/shipping

=> Conduct risk assessment based on this information regarding the identity and amounts of ingredients

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	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

Source: FDA Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics, May 1999

Parenterals

Syringe (body/barrel),
stopper, glass vials,
needle, ampoules, etc



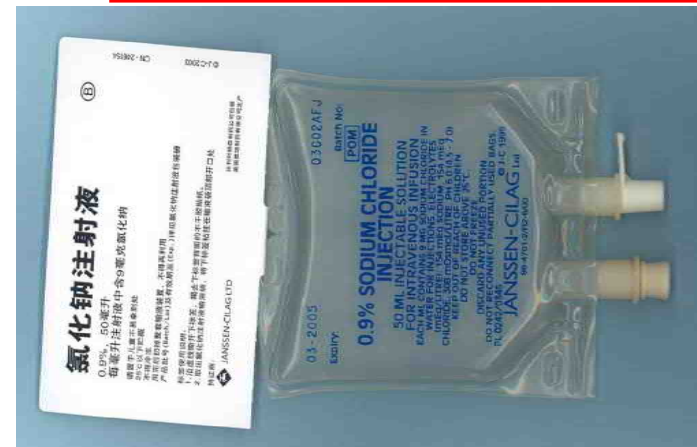
Sterile systems

IV kits

laminated bags,
extension line

Ophthalmic

Bottle, dropper,
closure



Patches

Transdermal film,
backing, pouch foil



Transdermal



E-trans
Systems

Bottle

Bottle, closure, liner



Liquid dosage form



Spray Systems

Bottle, pumps, etc



Tubes

Tubes, closure



Semisolid dosage form

Low interaction - low concern

Blister

Thermoform and
Cold Form Foil



Bottle

Bottle, closure, liner



Solids

Desiccant

Canisters, disks and
pouches





Devices for Non-injectable
Pipette, spoons, cups, etc.



Dosing devices

Devices for injectables
Auto-Injectors, etc.

Inhalation devices
Powder inhalators, etc.



Guidelines



- Minimum requirements :
 - Compliance with EP/USP
 - 21CFR - food approval
 - EU food approved

- Regulation has increased (main concern=safety)

- Extractables = Worst Case Leachables

Extractables

- Use selected extractants
- Use fully processed materials (irradiated, sterilized,...)
- Look for monomer (more emphasis), additives (esp. those with tox concerns - phthalates, cyclohexanone, benzene,...-, reaction products of additives (oxidation, hydrolysis),...
- Assess possible influence of label, glue, inks

Leachables

- With real product
- Effects of Excipients:
 - Cyclodextrines
 - PEG
 - pH
- Longer contact time (shelf life)

- 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

The threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and noncarcinogenic toxic effects.

➔ The Working Group proposes a SCT of 0.15 µg per day for an individual leachable in an OINDP (Orally Inhaled and Nasal Drug product).

The threshold below which a given non-carcinogenic leachable is not considered for safety qualification (toxicological assessments) unless the leachable presents structure-activity relationship (SAR) concerns.

 The Working Group proposes QT of 5 µg per day for an individual leachable in an OINDP.

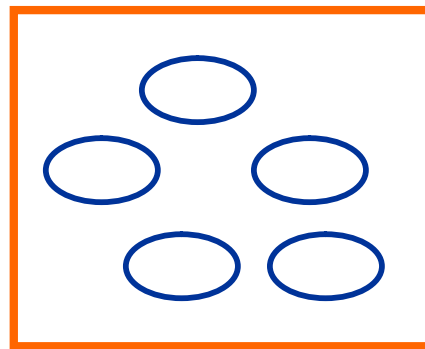


Certain compound classes of potential extractables and leachables with special safety concerns may require lower thresholds. Such extractables (PAHs, Nitrosamines, 2-mercaptobenzothiazole) should be considered on a case-by-case basis.

Threshold at or above which a chemist should begin to identify a particular leachable and/or extractable and report it for potential toxicological assessment

➔ SCT must be converted into relative amounts.

- Use information on drug product configuration (e.g. number of actuations, number of doses, etc.)



SCT 0.15µg/day

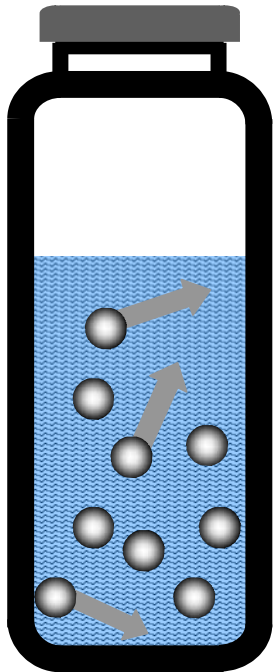
Tablet = 300mg



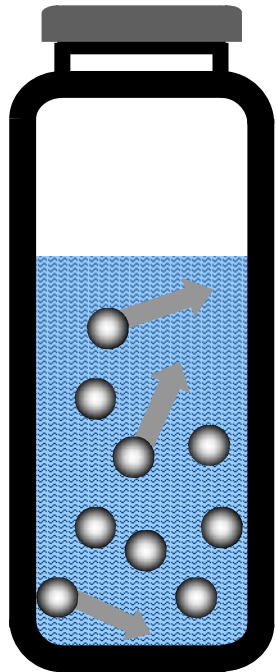
0.03µg/tablet



AET 0.10µg/g



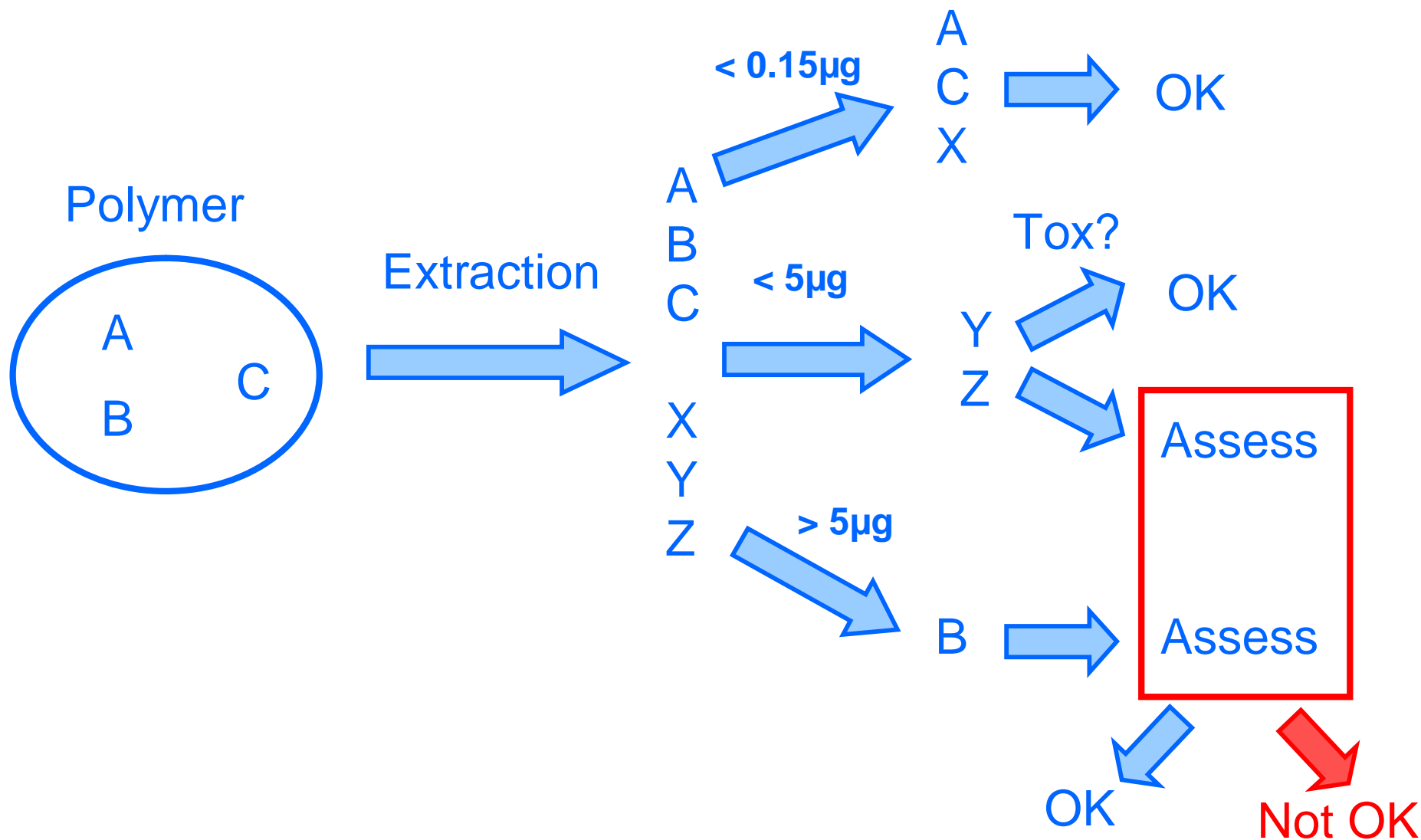
- Extraction with most suitable solvent (optimized for polymer)
- Vigorous extraction technique(s)
- Asymptotic levels for extractables
- Potentially multiple analytical techniques, e.g. GC, LC
- Identify and quantify extractables greater than or equal to the AET
- AET based on SCT



Analytical methods must be capable of detecting and quantifying

- All extractables characterized in the Controlled Extraction Studies, e.g. oligomers and additives
- Identifying “unspecified” extractables (e.g. resulting from unanticipated changes or some external contamination)

Summary





Examples

Leachables	Solution Type	Container Size	Storage Conditions	Level (ppm)
DEHP	0.9% saline	500	2.5 years, RT	0.01
	5% glucose	500	3.5 years, RT	0.02
	Ringer's lactate	500	4.5 years, RT	0.01
	Cyclosporine (in Cremophore EL)	-	24h, RT	767
	Taxol (7.5% Cremophore/7.5% EtOH)	-	26h, RT	550
Cyclohexanone	0.9% saline	100	1 year, RT	35
	0.9% saline	500	-	3.3
	5% glucose	100	-	14.5

Analytical method	Leachable information (PVC)	
	ID	Source
GC (MS, FID, ECD)	Di-(2-ethylhexyl)Phthalate DEHP	Primary plasticiser
GC (MS, FID, ECD) HPLC (UV)	Mono-(ethylhexyl)phthalate MEHP	hydrolysis of DEHP
GC (MS, FID, ECD) HPLC (UV)	Phthalic acid	hydrolysis of DEHP
GC (MS, FID, ECD) HPLC (UV)	Phthalide	impurity in DEHP
GC/FID	Vinyl chloride (monomer)	base material
GC (MS, FID) HPLC (UV)	Cyclohexanone (carcinogenic)	processing agent (residual solvent)
GC (MS)	Caprolactam	product overwrap
GC (MS) HPLC (UV)	BHT	antioxidant
HPLC (MS)	...	oxidation product of BHT
GC (MS)	t-butyl cyclohexanone	printing inks
GC (MS)	Toluene sulfonamides	printing inks

- Coating to reduce extractables
 - Flurotec® : strong barrier, but not total
 - PTFE (not fully gamma irradiated.), ETFE = gamma irradiated.
 - Cross linked silicone.
- Newer formulations are much purer, contain no/much less natural origin materials (supply reliability)



Rubber formulation			
Before 1980		Today	
Halobutyl	40%	Halobutyl	51%
Crepe	16%	Mg Silicate	40%
Isobutene	2%	Mg Oxide	3%
Al Silicate	23%	TiO ₂	2%
Ca Carbonate	3%	Sulfur	<1%
Phenolic Resin	3%	Color	<1%
Silicone Oil	2%		
TiO ₂	1%		
ZnO	2%		
Antiox	1%		
Stearic acid	1%		
Color	<1%		



PolymerForum

- Members:
 - AstraZeneca
 - Bayer HealthCare
 - Boehringer Ingelheim
 - GSK
 - Ivax
 - Janssen Pharmaceutica N.V.
 - Novartis
 - Orion Pharma
 - Pfizer
 - Roche
 - Sanofi-Aventis
 - Vectura

- Changes in materials need to be qualified:
 - Can take up to 3 years

- Closer cooperation with resin suppliers
 - Minimum shelf life of 3 years
 - Three year rolling availability
 - 3 year notice period for changes
 - Last-call option to negotiate supply
 - Develop method for controlling changes

Aim:

- The PolymerForum wishes to develop generic method(s) for monitoring extractables from plastics for pharmaceutical products and devices for use by plastic suppliers.

Purpose:

- Provide to suppliers a method to monitor consistency in composition of the final plastic including control of unintended changes at the manufacturer

Long term vision:

- Provide to the plastic industry a range of harmonized methods for monitoring extractables from a broad range of plastic materials to design and maintain high quality products for our patients

Benefits:

- Partnership between Pharma industry and their suppliers based on a
 - Common understanding on the needs and requirements of the Pharma industry
 - Harmonized approach and common standard
 - Continued quality through periodic verification of composition



- By end of 2008:
 - Method for the first class of plastics, e.g. Polyolefins available

- Next step:
 - Method development for other plastic types

- Complex matter
- Knowledge of materials is crucial
- Dependent on application and material
- Key = simplicity of materials
 - “Less is more”
 - No changes