

Extractables and Leachables in Single-Use Systems

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Why this Training Program

- Required by Good Manufacturing Practices
- 21CFR Part 211.25 Personnel qualifications.
- (a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions... Training in current good manufacturing practices shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.



What are Extractables?

- Extractables are components that have the potential to be removed by extremes of force, e.g., high temperatures and long exposures.
- For polymeric devices these may be:
 - A component of the polymer – monomer, oligomer
 - A solvent used in manufacturing of the polymer
 - An additive to the polymer
 - A metal, catalyst, or other non-organic component



What are Leachables?

- Leachables are extractables that migrate from the polymer into the drug product or solvent under normal operating parameters, time, temperature, and pressure.
- Leachables considered a subset of extractables



Regulatory Guidance

- Multiple guidance documents world-wide.
- Many are vague and contradictory.
- Compendial tests (USP <87,88, 381, 661, 1031>) required.
 - The biological tests <87,88> are acceptable predictors of toxicological activity but do not identify extractables or leachables.
 - USP section <381> physicochemical tests are typically done in water or, possibly the solvent vehicle. They are nonspecific and have no limits. Since they are gross measures, they provide minimal information as to which chemical species may migrate into the dosage form and at what concentration.



Review of the Regulations

- FDA Guidance for Industry – Container Closure System for Packaging Human Drugs and Biologics (1999)
 - CDER and CBER guidance document details QC expected of a container closure system to be used in the packaging of drugs and biologics
 - Outlines a risk based approach
- FDA Guidance for Industry – Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products (1998)
 - CDER guidance document detailing testing and documentation required of in NDA's and ANDA's.



21 CFR 211.65 Equipment construction

(a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.



21 CFR 211.94 Drug product containers and closures

(a) Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity or the drug beyond the official or established requirements.



ICH Q7A Guidance for Industry

- Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (8-2001)
- Section V. Process Equipment (5)
 - Design and Construction (5.1): Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.
- Section IX. Packaging...of APIs and Intermediates (9)
 - B. Packaging Materials (9.2): ...These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.



PDA Technical Report 26

- “Testing for leachables is critical for sterilizing grade filtration applications since the final step in the production process is typically sterile filtration prior to filling...Extractables can be classified as toxic or nontoxic, and should be demonstrated to be nontoxic at the levels observed in the final product.
- The end user must carefully evaluate the filtration process and demonstrate that these processes do not contribute extractables at levels that affect final product quality and safety.”
- PDA Journal of Pharmaceutical Science & Technology
- Technical Report No. 26 (revised 2007)



Where are Leachables Most Likely Be a Concern?

- Higher Risk Administration Routes
 - Injectables, Inhalants, Ophthalmic Solutions
- Long Exposure Times
 - Containers and closures
 - Intermediate Process Storage Containers
- High Surface Area Components
 - Filters
 - Small volume polymeric ampoules
- Certain Materials
 - Rubbers
 - phthalate-plasticized PVC



1999 FDA Packaging Guidance

Degree of Concern Associated with Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	Medium	Low
Highest	<ul style="list-style-type: none"> • Inhalation Aerosols and Solutions • Injections and Injectables Suspensions 	<ul style="list-style-type: none"> • Sterile Powders and Powders for Injection • Inhalation Powders 	
High	<ul style="list-style-type: none"> • Ophthalmic Solutions and Suspensions • Transdermal Ointments and Patches • Nasal Aerosols and Sprays 		
Low	<ul style="list-style-type: none"> • Topical Solutions and Suspensions • Topical and Lingual Aerosols • Oral Solutions and Suspensions 	<ul style="list-style-type: none"> • Topical Powders; Oral Powders 	<ul style="list-style-type: none"> • Oral Tablets • Oral Capsules



BioPharm Risk Assessment Table*

Risk Variable	Qualifier	Risk Value	Risk of Material
Proximity to API			
Final formulation		10	
Purification		6	
Fermentation		2	
Extraction capability of Solvent			
High	Organic	10	
Medium	Water/organic	Ratio	
Low	Water	4	
Length of Contact			
High	>30 days	10	
Medium	> 24 hours to 30 days	6	
Low	< 24 hours	2	
Product Contact Surface Area			
High	> 6,000 cm ²	10	
Medium	500 to 6,000 cm ²	6	
Low	5 to 500 cm ²	2	

* BioPharm International, December 2002, page 28.



BioPharm Risk Assessment Table*

Risk Variable	Qualifier	Risk Value	Risk of Material
Cytotoxicity of Extractables			
High	100% cell death	10	
Medium	50% cell death	4	
Low	0% cell death	0	
Temperature			
High	>70 °C	10	
Medium	37 °C to 70 °C	6	
Low	2 °C to 37 °C	2	
Inherent Material Resistance to Extraction			
High	Elastomer/plasticized polymers	10	
Medium	Rigid plastic and Type II and III glass	4	
Low	Metals and Type I glass	1	
Total Risk (Sum)			

* BioPharm International, December 2002, page 28.



Extractable & Leachable Studies

- What testing is appropriate?
- When should you perform testing?
- Is manufacturer's test date sufficient?
- Which lab should one use for testing?



What Testing Is Appropriate?

- How close is it to the final sterile fill?
 - All product contact surfaces can be a source of leachables
 - Many impurities may be removed by subsequent purification steps (e.g. diafiltration, chromatography)
 - Final choice is responsibility of the user based on regulatory needs and company risk assessment



When Should You Address Leachables?

- Determination of potential leachables
- Obtain extraction data to assess potential for chemical incompatibilities with drug formulation, buffers, processes.
- Extractable testing data (with standard solvents) should be obtained in Phase I Trials
- Leachable testing should be completed in Phase II.
- Drug manufacturers may not address until Phase III – higher risk to make a change in the process requiring revalidation, added costs and time to market delays.



Extractable / Leachable Studies

- Step 1 – Extractable In Standard Solvents
 - Accelerated extractions in water, ethanol, acidic and basic solutions and solvents.
 - Determine what could extract out of the polymer.
 - Manufacturers often have this information
- Step 2 – Leachables in Actual Drug Product
 - Test in formulation determines actual leachates
 - Test in reasonable operating conditions /parameter
 - Known materials of construction assist in identification



Leachable Testing

- Test using actual formulation
 - protocols to eliminate product interference
- Test normal storage temperature for duration of shelf-life
- And accelerated temperature for submission
- Compare any leachables with known extractables
- Identify any significant compounds not found during extractables mapping



Analytical Methods

- Non-specific analysis – measures total leachates
 - TOC – total organic carbon
 - NVR – non volatile residue – USP <661>
- Specific – detects/identifies specific leachables
 - HPLC – high performance liquid chromatography
 - GC – gas chromatography
 - FTIR – Fourier transform infrared
 - LC/MS – HPLC followed by mass spectroscopy
 - GC/MS – GC followed by mass spectroscopy



Specific and Non-specific Tests

- Non-specific tests (NVR, TOC) are helpful to determine total extractions. May not capture volatile compound
- Specific tests (LC, GC / MS) are needed for detection, identification and quantification of individual compounds.
- Perform extractions studies in different solvent systems and analyze by both specific and non-specific methods
 - NVR
 - TOC
 - HPLC-UV
 - GC/MS



Non-Specific Analytical Methods

- NVR – Non Volatile Residue – using water
 - Boil away water and measure weight of solid material that is remaining
 - Measure difference between sample and control to determine extractable weight.



Conclusions - NVR

- NVR can be used to measure by weight extractables / leachables
- NVR does not identify extractables / leachables
- GC, HPLC detect individual extractables & leachables by chromatographic separations.
- Polymeric components UV active



Extractables from Various Filters

Reif , Oscar W. et.al, PDA Journal, Vol. 50, No.6, pp 399-410, 1996

A	B	C	D
Identified Extractables of Different Membrane Filter Cartridges from Several Manufacturers			
Diethylphthalate	Cyclohexane	Propionic acid	Dibutyl-phthalate
Stearic acid	Ethoxy-benzoic acid	Diphenylether	12 oligo. aliphates
2,6,Di-tert-butyl-cresol	2,6,Di-tert-butyl-cresol	2,6,Di-tert-butyl-cresol	Hydroxy-benzoic acid
2,2-methylene bis-4-ethyle-6-tert butyl phenol	Cyclohexa-diene-1,4-dion	Dimethoxy-diphenyl-sulfone	Tert.-butyl-methyl 2,5-cyclo hexadi-ene-1-on
7 oligo -siloxanes	Phenyliso-cyanate	Palmitic acid	3 oligo. siloxane
Hydroxy-benzoic acid	Palmitic acid	Hydroxy-benzoic acid	polyether
Bis-(2-ethyl-hexyl)-phthalate	Stearic acid	11 oligo. aliphates	2,4-Bis(1,1-di methyl-ethyl)-phenol
12 oligo. aliphates	12 oligo. aliphates	Bis-(2-ethy hexyl)-phthalate	
4-methyl-2-5-cyclo-hexa-dience-1-on	11 oligo. siloxanes	4-methyl-2-5-cyclo-hexa-dience-1-on	



Test Approaches

- Modeling
 - Predict extractables by extraction with a solution of similar chemical nature to the product formulation
- Actual product testing
 - Test with actual product formulation in simulated filtration conditions



Modeling Studies

- Modeling – the model solvents are used to estimate the leachables from the actual formulation
- Use solvent systems that mimic the components of a drug formulation such as:
 - Water
 - Hydrochloric acid solution
 - Sodium hydroxide solution
 - 20% sodium chloride solution
 - 0.1% aqueous Tween (a surfactant)
 - Ethanol



When To Use Modeling

- Use when actual formulations interfering components can not be removed.
- Use when mimic solvent clearly brackets operating parameters /conditions.
 - Time, temperature, pressure, surface area
- Use as preliminary data for product /solvent.



Modeling Example

Component	Model Stream Characteristic	Expected Effect on Extractables	Model Stream Surrogate
Active Ingredient	Solute	None	Water
Disodium Phosphate	Solute	None	Water
Surfactant	Solvent	Increase	100% Ethanol
Preservative	Solute	None	Water
PEG	Solvent	Increase	100% Ethanol
pH 3	Acidic Conditions	Increase	pH 2 HCl

Stone et.al., Pharm. Tech., Sept. 1994 pp. 116



When to Test with Actual Formulations

- Greater compliance with regulatory guidelines
- For a more comprehensive study
- To capture synergistic effects, product /solvent
- To avoid multiple mimic solvent analysis



Detecting Leachables in Actual Formulations

- Proteins:
 - Selectively adsorb leachables
 - Size exclusion chromatography
 - Liquid / liquid separations, etc.
- Emulsions:
 - Centrifugation
- UV-Active Interfering Components
 - Extract into organic solvent
- Combinations of various analytical methods



Summary

- Study protocols for detecting and measuring extractables and leachables based on good science.
- Non-specific analytical techniques are used for measuring total extractables.
- Specific analytical techniques are for identification and quantification of leachables.
- Leachables from actual formulations can be detected and identified using specific analytical techniques
- Modeling studies appropriately used can provide data and analysis to meet industry and regulatory requirements.



Extractable / Leachable Presentation

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