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Extractables and Leachables in a Continuous Processing System

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BACKGROUND

- Single-use systems (SUS) and continuous processing are two significant trends in biopharmaceutical production. The two techniques are complementary to each other. Together, they can provide significant improvement in drug manufacturing efficiency and consistency of quality. While single-use systems had been widely implemented for decades, adoption of continuous processing in pharmaceutical production is still in its early stages. The rapid adoption of single-use technologies complements the implementation of a continuous bioprocess, providing flexible and enclosed systems for bioprocess manufacturing. A new generation of single-use systems have been developed to fit in a continuous processing platform.
- Since extractables and leachables remain a major concern for single-use systems adoption, each individual key component of the continuous processing system was evaluated for extractables following BioPhorum Operations Group (BPOG) protocol. The robust nature of these studies coupled with high surface to volume ratios may exaggerate the number and level of compounds expected to leach and persist throughout the bioprocess. From a risk assessment perspective, many of these compounds may be expected to be diluted or readily cleared during typical continuous bioprocess application steps. To evaluate the capability of the downstream purification steps to remove extractables from upstream components, samples were collected after each step in continuous processing for extractables studies.

Figure 1

Single-use adoption involves shared risks

Current regulatory guidance requires biopharmaceutical manufacturers to ensure the manufacturing systems do not adulterate the final drug product. The end users have used SUS extractables testing data and leachables evaluation to assess potential risks to patients of the use of these components in product manufacturing.

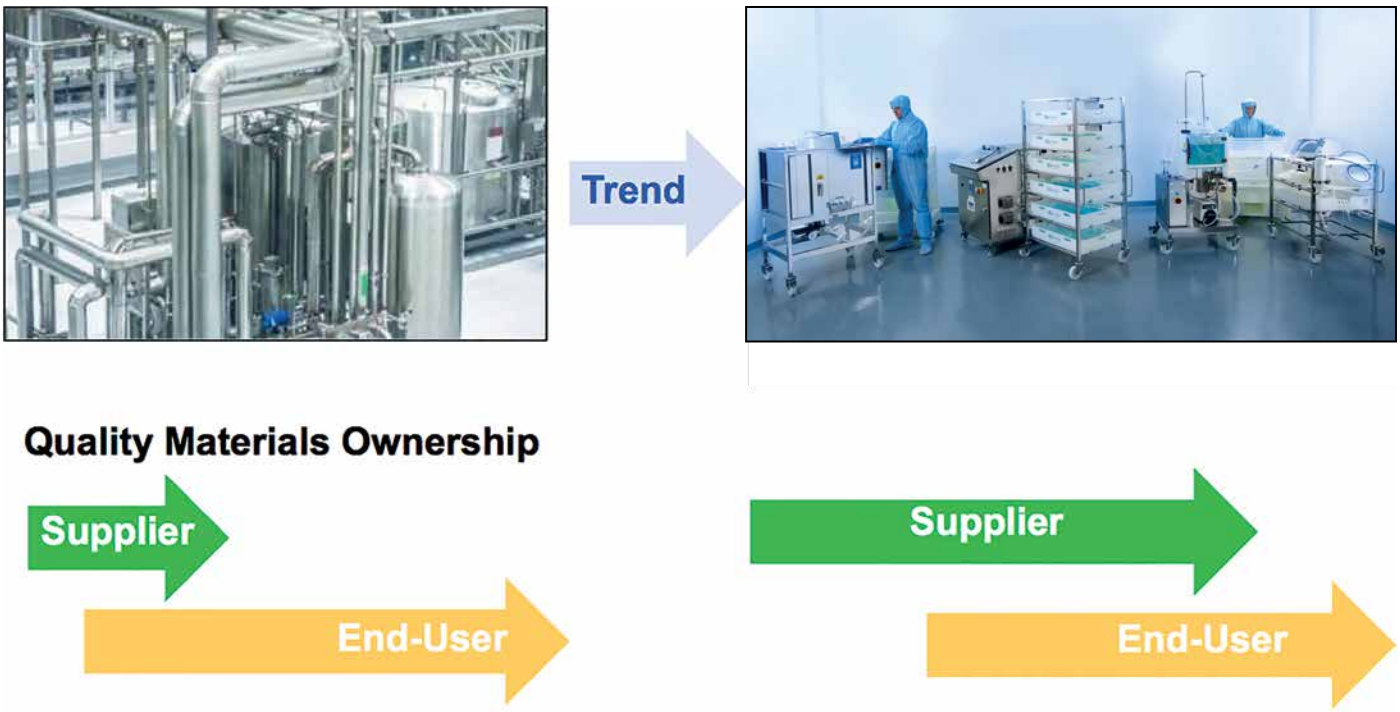
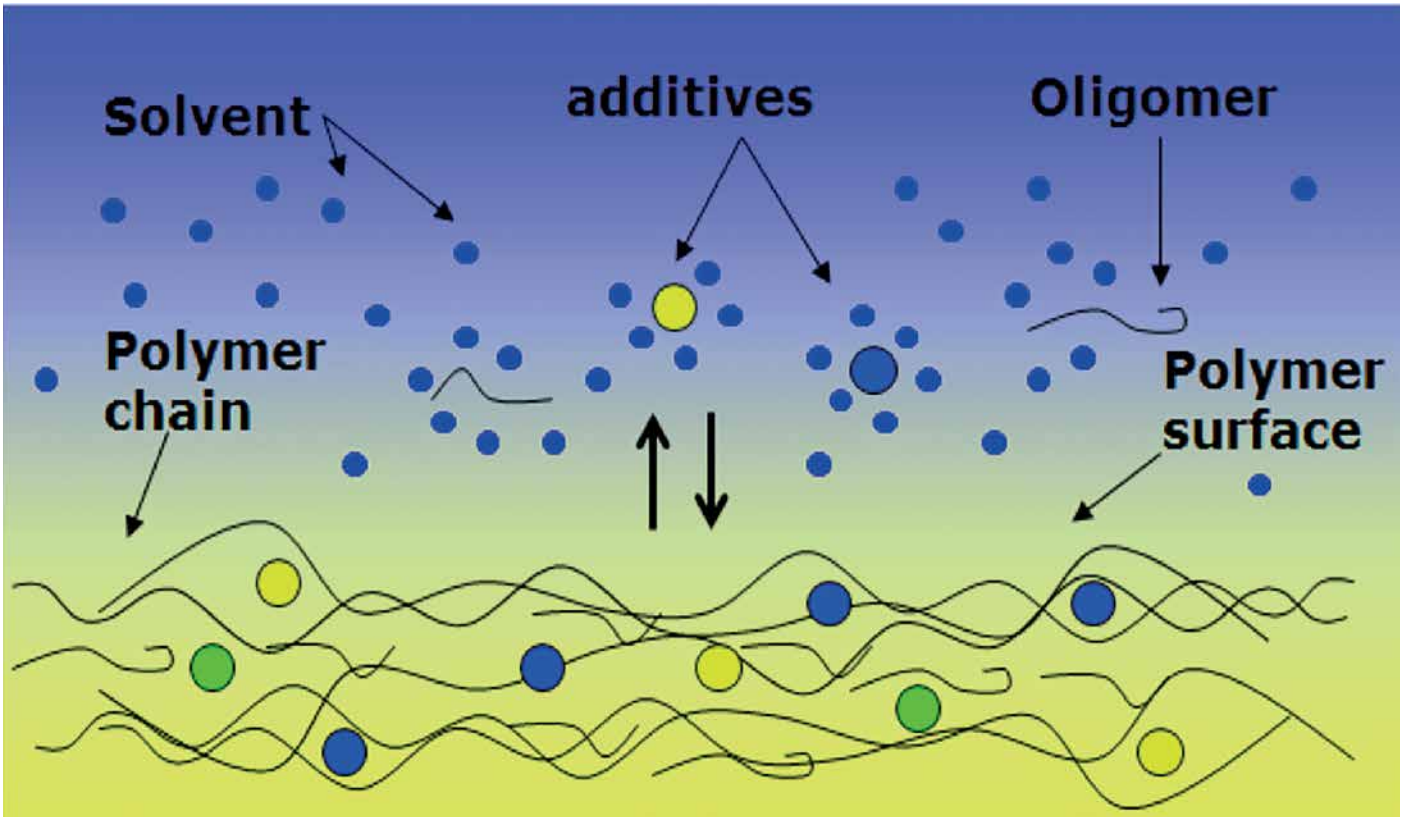


Figure 2

Sources of extractables and leachables



- Antioxidants
- Stabilizers
- Molding agents
- Extrusion agents
- Polymerization aids
- Pore formers
- Colorants
- Lubricants
- Residual solvents
- Unreacted monomers
- Oligomers
- Degradation products

Figure 3

Implementation of BPOG protocol

Method Optimization

- More than 2000 single-use components
- Grouping into families based on materials of construction (MOC)

Initial Profiling & Building Library

- Ensuring availability of at least two lots
- Specificity, sensitivity, precision, accuracy/recovery, robustness
- Establish system suitability requirements
- Sample pre-treatment
- Extraction set-up
- Lessons learned (PS80, salts)

Actual Testing

- Extraction of representative components and/or MOC
- Qualitative profiling using Quadruple-Time of flight mass spectrometer (Qtof)
- Retention time (RT), mass/charge ratio (m/z) ions, accurate mass, chemical formula

Figure 4

Benefits of standardized data

- Exposure times and temperature ranges are extended to exaggerate the chemical conditions of the actual use.
- Solvents used are often more aggressive than what is typical in biomanufacturing.
- A standardized extractables testing protocol with an agreed-upon set of testing methods to generate and analyze extracts to establish common expectations among suppliers, end-users, and regulators.

Brackets >80% biologics applications

Standardized Extractables Testing Protocol for Single-Use Systems in Biomanufacturing

	Solvents						Time				
	50% Ethanol	1% PS-80	5 M NaCl	0.5 N NaOH	0.1 M Phosphoric Acid	WFI	<30 min	24 hrs	7 days	21 days	70 days*
							Temperature				
Component Type							Ambient (25 °C)	40 °C			
Storage, Mixing, and Bioreactor Biocontainers	X	X	X	X	X	X	X	X		X	X
Tubing	X	X	X	X	X	X	X	X		X	X
Tubing Connectors and Disconnectors	X	X	X	X	X	X	X	X		X	
Aseptic Connectors and Disconnectors	X	X	X	X	X	X	X	X	X		
Sterilizing-grade Filters/Process Filters	X	X	X	X	X	X	X	X	X		
Tangential-flow Filtration Cassettes	X	X	X	X	X	X	X	X		X	
Sensors and Valves	X	X	X	X	X	X	X	X		X	
Chromatography Columns, Elastomeric Parts; Wetted Polymeric Surfaces of Positive Displacement Pumps	X	X	X	X	X	X	X	X			
Molded Parts of Mixers	X	X	X	X	X	X	X	X		X	
Filling Needles	X	X	X	X	X	X	X	X			

** Duration for testing storage bags necessary to support 3-year storage at 0 oC (q10=2.0)*

METHODS

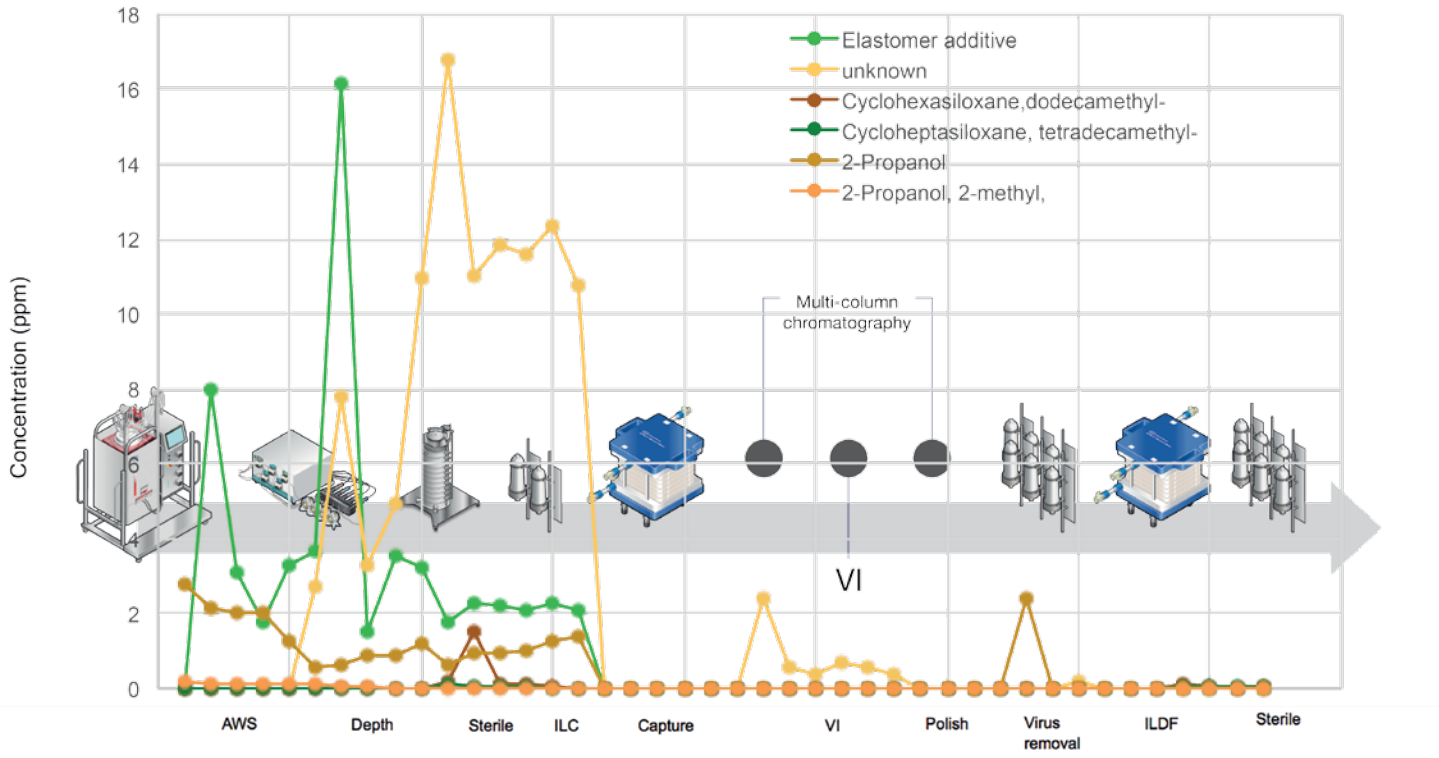
- Model fluid ran through continuous processing system
- Fluid samples were collected after each step
- Fluid samples were analyzed by headspace gas chromatography (GC) / mass spectrometry (MS), direct injection GC/MS, and liquid chromatography (LC) / photodiode array (PDA) / MS for extractables study

RESULTS

Figure 5

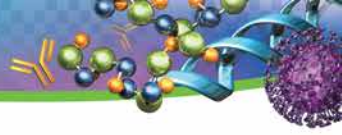
Extractables in continuous processing system

This study tracks the emergence and clearance of extractables in model fluids observed at various stages throughout a typical continuous bioprocess implementation. More than 99% of the extractables in model fluids from upstream components get cleared after downstream purification and diafiltration steps.



SUMMARY

- Extractables and leachables remain a major concern for single-use system adoption. Each individual key component of the continuous processing system was evaluated for extractables following BPOG protocol. Risk and toxicology assessment has been performed on the extractables from critical components particularly in downstream processing. Provision of comprehensive, BPOG aligned extractables packages for each single-use bioprocessing component helps frame what extrinsic compounds and degradants may potentially leach into the process flow.
- This study tracks the emergence and clearance of extractables in model fluids observed at various stages throughout a typical continuous bioprocess implementation. More than 99% of the extractables in model fluids from upstream components get cleared after downstream purification and diafiltration steps. Subsequent evaluation of extractables in drug product in continuous processing will be in future studies.



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