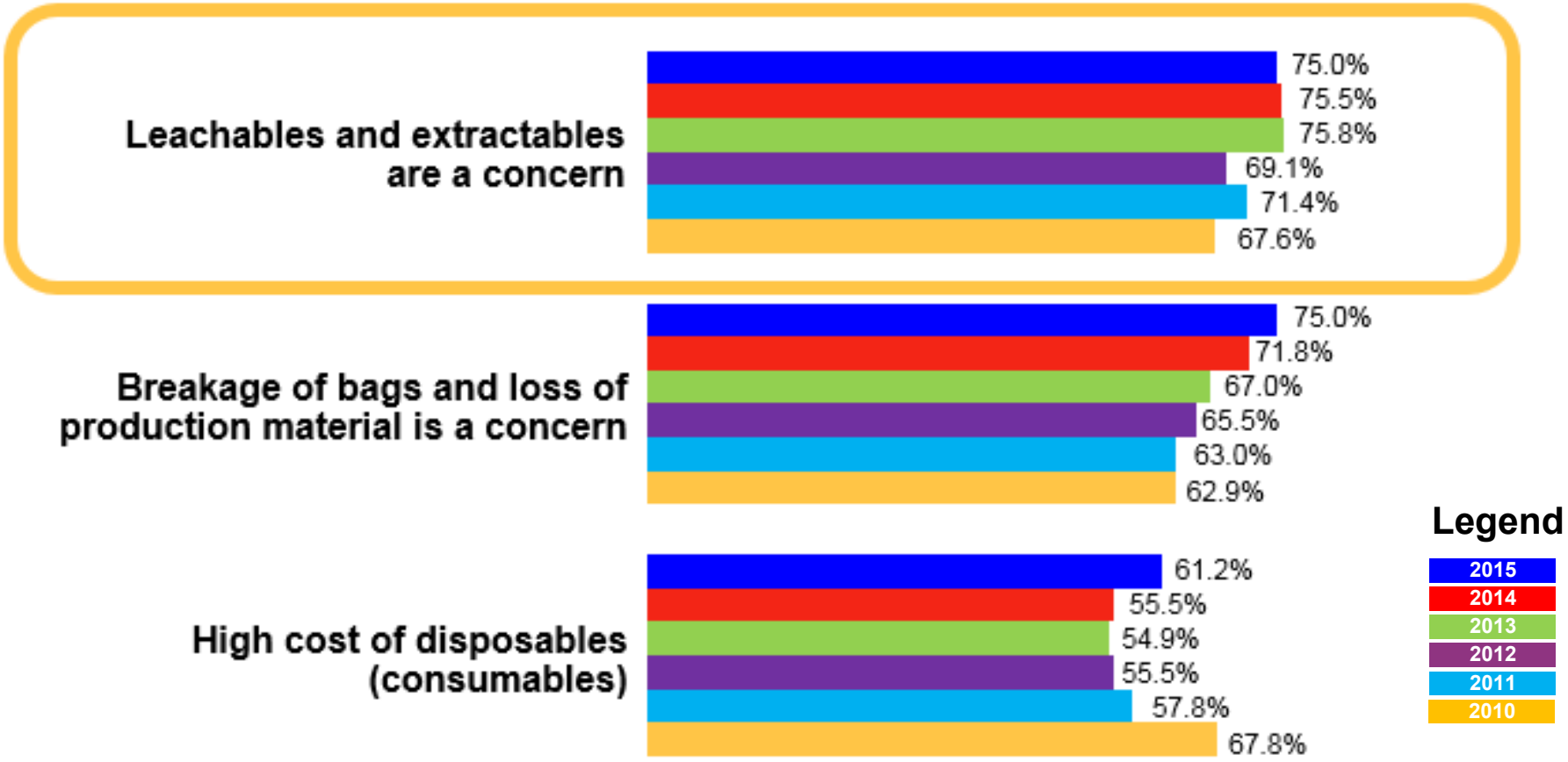
Standardized Extractables testing of polymeric materials enabling effective safety Risk Assessment

Patrick EVRARD, Sr Director SLS Single-use Technologies, Pall Corp.

AGENDA

- Introduction and Regulatory expectations
- BPOG standard proposal
- BPOG vs USP <665>
- Risk Assessment using single-use supplier's Datasets
- Conclusions

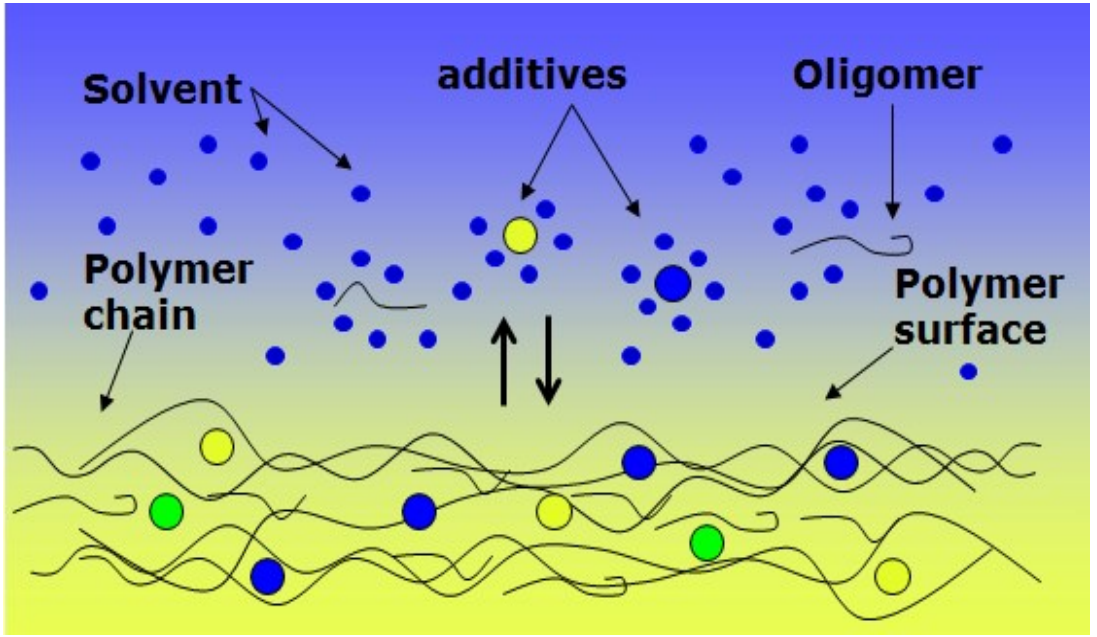
REASONS FOR RESTRICTING USE OF SUT



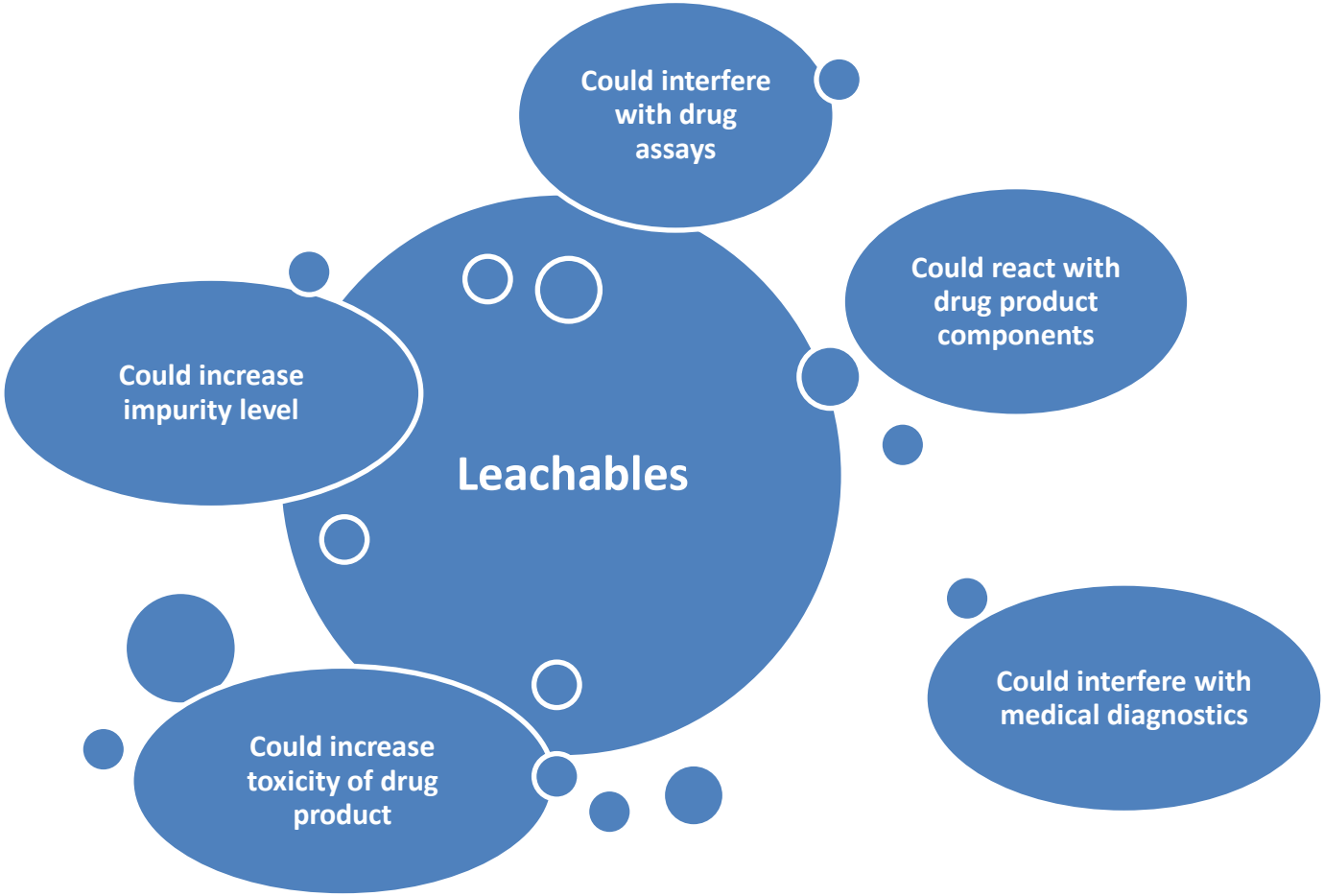
Source: 12th Annual Report and Survey of Biopharmaceutical Manufacturing, April 2015, preliminary data, www.bioplanassociates.com/11th

SOURCES OF E&L

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



WHY ARE LEACHABLES A CONCERN?



REGULATORY EXPECTATIONS

- US CFR 211.65[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."

- EC Eudralex[b]

  § 3.39: "Production equipment should not present any hazard to products. Parts of production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard"

a. US Code of Federal Regulations, Part 211, "Current Good Manufacturing Practice for Finished Pharmaceuticals", Sec. 211.65, "Equipment Construction", 2015

b. European Commission, EUDRALEX Volume 4, "Good Manufacturing Practices, Medicinal Products for Human and Veterinary Use", Vol 4, Chapter 3, "Premises and Equipment", 2014

KEY GUIDELINES

- *FDA - Guidance for Industry*
  Container Closure Systems for Packaging Human Drugs and Biologics, U.S. Department of Health and Human Services, FDA, May 1999

- *EMA - Guideline on plastic immediate packaging materials,*
  CPMP/QWP/4359/03, May 2005

KEY GUIDELINES

- *FDA - Guidance for Industry*
  Container Closure Systems for Packaging Human Drugs and Biologics, U.S. Department of Health and Human Services, FDA, May 1999
  - Attachment C – "E*xtraction studies may be conducted …"*
    - *s on plastics (USP <661>) or elastomers (USP <381>)*
    - *ogical Reactivity Tests (USP <87> and <88>)*
    - *ive extraction profiles of plastics or elastomers*
    - *ative extraction profiles of plastics or elastomers*

GENERIC EXTRACTABLES

EXTRACTABLES PROFILES

- *EMA - Guideline on plastic immediate packaging materials*, CPMP/QWP/4359/03, May 2005

REGULATORY EXPECTATIONS

"…with respect to extractable and leachable data … it is ultimately your responsibility to assess this data and its applicability to your products and process. CBER recommends a risk-based approach be taken in evaluating extractables and leachables where you take multiple aspects into account (e.g., indication, safety issues, product characteristics, dosage, formulation, stability profile, etc.)."

"If there is no relevant risk associated with the (material in question), vendor data can be cross-referenced and a detailed justification for the applicability of these data and a justification for additional testing should be submitted."

Destry M. Sillivan, FDA CBER
IBC Single Use Conference, June, 2010

SUPPORTIVE DATA

GENERIC

NVR

TOC

PROFILES

Direct Inj. GC\MS

Headspace GC\MS

LC\UV\MS

ICP\MS

BPOG

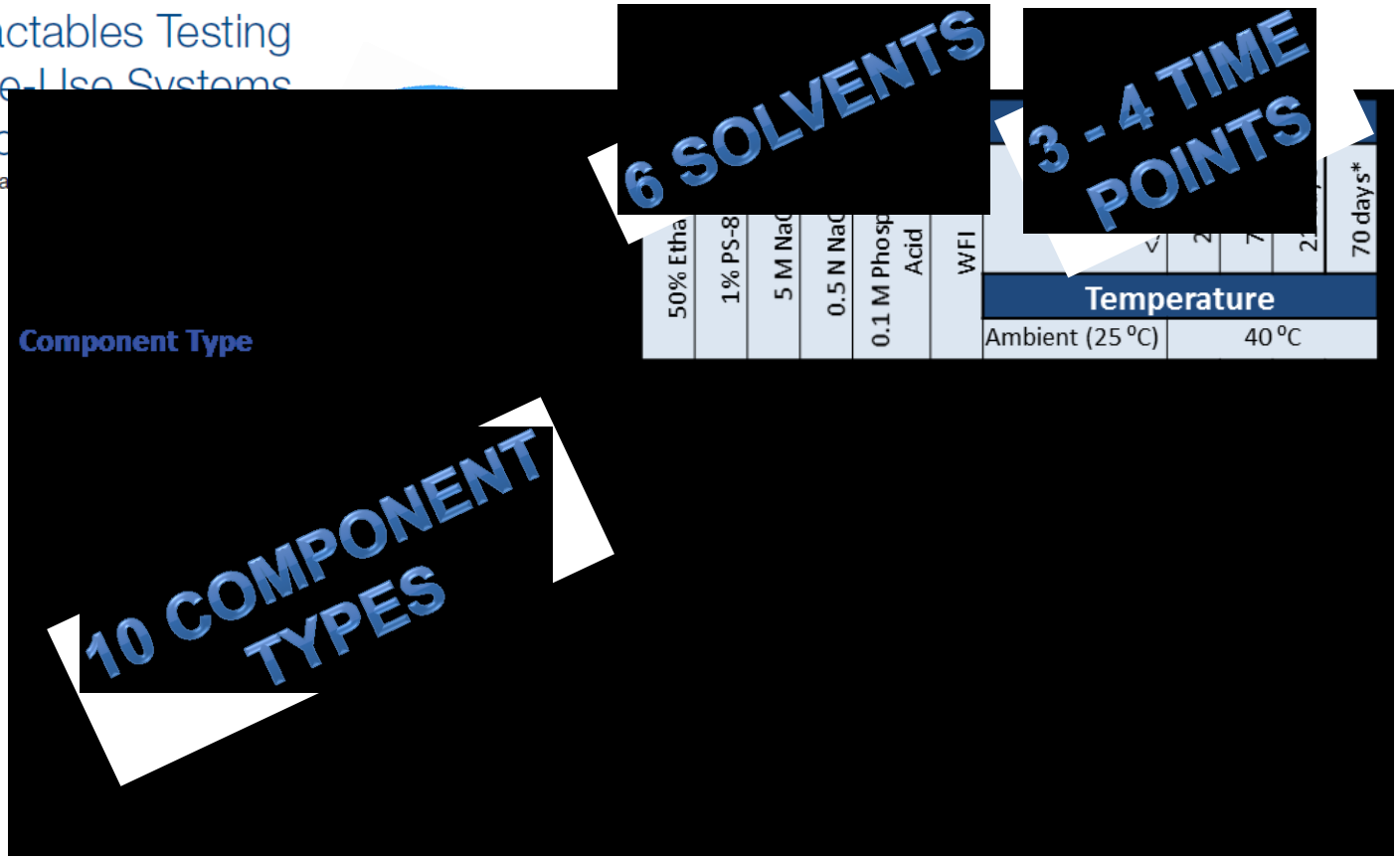
- Industry group
- Issue guidance documents to facilitate industry's topics of concern

STANDARDIZED EXTRACTABLES DATA

Aimed to bracket >80% Biologics Applications

Standardized Extractables Testing Protocol for Single-Use Systems in Bio

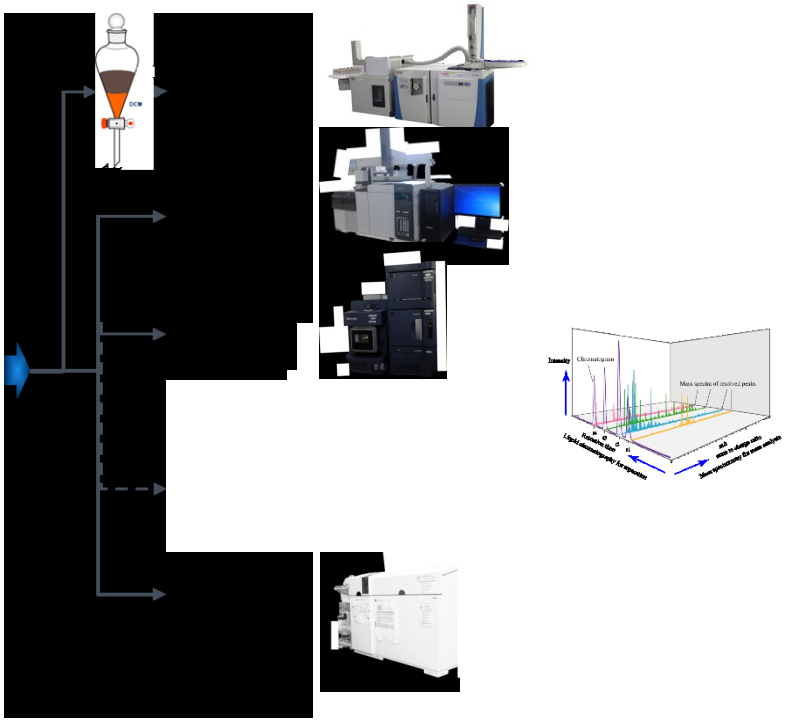
by Weibing Ding, Gary Madsen, Ekta Ma



** Duration for testing storage bags necessary to support 3-year storage at 0 °C (Q_{10}=2.0)*

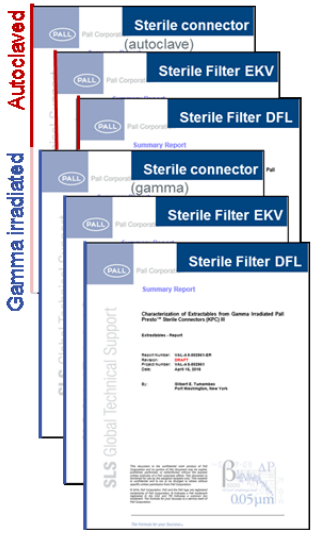
IMPLEMENTATION OF BPOG PROTOCOL

Component Manufacture → **Extraction** → **Analytical Testing** → **Reporting**

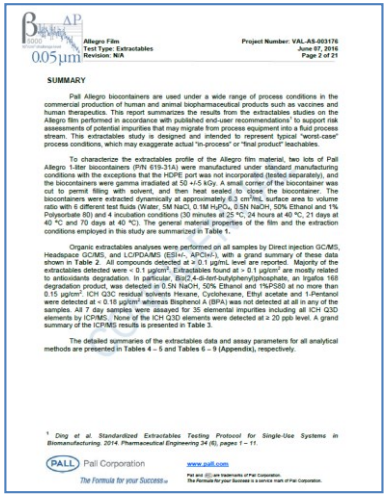


PALL BPOG REPORTS

Technical Report



Descriptive Summary



SUMMARY

Pall Allegro biocontainers are used under a wide range of process conditions in the commercial production of human and animal biopharmaceutical products such as vaccines and human therapeutics. This report summarizes the results from the extractables studies on the Allegro film performed in accordance with published end-user recommendations[1] to support risk assessments of potential impurities that may migrate from process equipment into a fluid process stream. This extractables study is designed and intended to represent typical "worst-case" process conditions, which may exaggerate actual "in-process" or "final product" leachables.

To characterize the extractables profile of the Allegro film material, two lots of Pall Allegro 1-liter biocontainers (P/N 619-31A) were manufactured under standard manufacturing conditions with the exceptions that the HDPE port was not incorporated (tested separately), and the biocontainers were gamma irradiated at 50 +/-5 kGy. A small corner of the biocontainer was cut to permit filling with solvent, and then heat sealed to 'close' the biocontainer. The biocontainers were extracted dynamically at approximately 6.3 cm²/mL surface area to volume ratio with 6 different test fluids (Water, 5M NaCl, 0.1M H_3PO_4, 0.5N NaOH, 50% Ethanol and 1% Polysorbate 80) and 4 incubation conditions (30 minutes at 25 °C, 24 hours at 40 °C, 21 days at 40 °C and 70 days at 40 °C). The general material properties of the film and the extraction conditions employed in this study are summarized in Table 1.

Organic extractables analyses were performed on all samples by Direct injection GC/MS, Headspace GC/MS, and LC/PDA/MS (ESI+/-, APCI+/-), with a grand summary of these data shown in Table 2. All compounds detected at ≥ 0.1 µg/mL level are reported. Majority of the extractables detected were < 0.1 µg/cm². Extractables found at > 0.1 µg/cm² are mostly related to antioxidants degradation. In particular, Bis(2,4-di-tert-butylphenyl)phosphate, an Irgafos 168 degradation product, was detected in 0.5N NaOH, 50% Ethanol and 1%PS80 at no more than 0.15 µg/cm². ICH Q3C residual solvents Hexane, Cyclohexane, Ethyl acetate and 1-Pentanol were detected at < 0.16 µg/cm² whereas Bisphenol A (BPA) was not detected at all in any of the samples. All 7 day samples were assayed for 35 elemental impurities including all ICH Q3D elements by ICP/MS. None of the ICH Q3D elements were detected at ≥ 20 ppb level. A grand summary of the ICP/MS results is presented in Table 3.

The detailed summaries of the extractables data and assay parameters for all analytical methods are presented in Tables 4 – 5 and Tables 6 – 9 (Appendix), respectively.

[1] *Ding et al. Standardized Extractables Testing Protocol for Single-Use Systems in Biomanufacturing. 2014. Pharmaceutical Engineering 34 (6), pages 1 – 11.*

Pall Corporation www.pall.com

The Formula for your Success

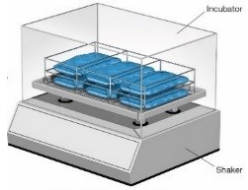
Extraction Parameters

Test Article	Allegro Biocontainer		
Number of Test Articles	48		
Part Number	619-31A (manufactured without HDPE port)		
Lot Numbers	6010363, 6010435		
Pretreatment	Variable(s)	Units	Values
Gamma Irradiation	Dose	kGy	50 ± 5
Autoclave	Time, temperature, number of cycles	minutes, °C, #	N/A
Pre-flush	Fluid identity, duration, temperature, volume	Name, minutes, °C, L	None
Test Article Extraction Conditions	Variable	Units	Values
	Temperature	°C	25, 40, 40, 40
	Duration	minutes, hours, days	30 minutes, 24 hours, 21 days, 70 days
	Solvent contact surface area	sq.cm. (cm^2)	613
	Solvent volume	mL	130
	Surface area to volume ratio	ratio	6.3
	Solvent Loss (or pre- and post- weight)	% loss	< 15 %
Supporting Information			
Bags	Film thickness	mm	0.325
	Volume (capacity)	L	1
Tubing	Wall thickness	mm	N/A
	Internal diameter	mm	N/A
	Length	mm	N/A
Tubing connectors and aseptic connectors	Internal diameter	mm	N/A
	Length	mm	N/A
Filters and TFF cassettes	EFA	sq.m (m^2)	N/A
Filling Needles	Internal diameter	mm	N/A
2D and 3D bags	Time between film manufacturing and gamma irradiation	Days	~ 60
All gamma-irradiated components	Time between gamma irradiation and extraction	days	< 35
	Typical dose range during normal manufacturing	kGy	27 - 37

Analytical Method Details

Standards	2-Propanol and Methyl ethyl ketone (MEK)		
Limit of Detection	Signal-to-noise ratio ≥ 3 (all standards)		
Limit of Quantitation	Signal-to-noise ratio ≥ 10 (all standards)		
Internal Standard	None		
Precision	RSD ≤ 2 % (Retention Time) and ≤ 20% (Area Counts) (n = 6), 1 - 10 ppm (all standards in all solvents)		
Spike Recovery	80 - 120%, 1 - 8 ppm (all standards in all solvents)		
Sample Bracketing	Every 10 sample injections (all standards), % Difference ≤ 20%		
Column	Agilent DB-624 MS, 60m x 0.25 mm, 1.4 µm		
Injection Port Temperature	250 °C		
Headspace Vial Temperature	70 °C		
Injection Volume	1.0 µL		
GC Temperature Program	Rate (°C/min)	Temperature (°C)	Hold Time (min)
	N/A	40.0	4.00
	5.0	50.0	5.00
	5.0	65.0	5.00
	15.0	200.0	5.00
m/z range, amu	35 - 650		

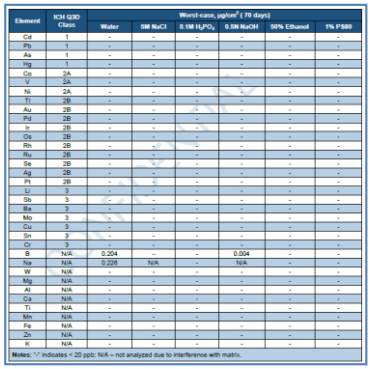
Images of Extraction Process



Summarized Organic Extractables Data (µg/cm²)

Solvent	Method	Mode	RT (min)	Compound	CAS No.	ID Level	ICH Q3C Class	Standard Used for Semi-Quantification	LOD (µg/mL)	LOQ (µg/mL)	Worst-case, µg/cm²			
											½ hr	24 hrs	21 days	70 days
Water	HS GC/MS	TIC	8.77	2-Methyl-2-propanol	75-65-0	Confirmed	N/A	2-Methyl-2-propanol	0.205	0.685	<LOD	<LOQ	<LOQ	<LOQ
	HS GC/MS	TIC	27.43	3,4-Dimethyl-3-hexanol	19550-08-4	Tentative	N/A	2-Methyl-2-propanol	0.205	0.685	<LOD	<LOD	<LOD	<LOQ
	LC/PDA/MS	ES+, TIC	8.99	Unknown (mass ion 587.6)	N/A	Unknown	N/A	Erucamide	0.090	0.301	<LOQ	<LOD	<LOQ	<LOQ
	HS GC/MS	TIC	12.86	Ethyl Acetate	141-78-6	Confirmed	3	Ethyl acetate	0.041	0.138	<LOD	<LOQ	<LOD	<LOD
	HS GC/MS	TIC	19.64	Pentanal	110-62-3	Confirmed	N/A	Pentanal	0.032	0.107	<LOD	<LOQ	<LOQ	<LOQ
	DI GC/MS	TIC	N/A	None Detected	N/A	N/A	N/A	*n*-Decane, 2,4-Di-*tert*-butylphenol	0.032, 0.022	0.106, 0.074	<LOD	<LOD	<LOD	<LOD
5M NaCl	HS GC/MS	TIC	8.74	2-Methyl-2-propanol	75-65-0	Confirmed	N/A	2-Methyl-2-propanol	0.017	0.057	<LOQ	0.0362	0.0378	0.0530
	HS GC/MS	TIC	12.76	Ethyl acetate	141-78-6	Confirmed	3	Ethyl Acetate	0.026	0.088	<LOD	0.0168	<LOD	<LOD
	LC/PDA/MS	PDA (210-400 nm), ES+/-, APCI +/-	N/A	None Detected	N/A	N/A	N/A	BPA (PDA), DEHP (PDA), Erucamide (ES+), Irganox 1010 (ES-), Irganox 1010 (APCI+,APCI-)	0.036, 0.211, 0.014, 0.018, 0.489, 1.79	0.120, 0.703, 0.047, 0.060, 1.63, 5.98	<LOD	<LOD	<LOD	<LOD
	DI GC/MS	TIC	N/A	None Detected	N/A	N/A	N/A	*n*-Decane, 2,4-Di-*tert*-butylphenol	0.039, 0.025	0.132, 0.084	<LOD	<LOD	<LOD	<LOD
0.1M H_3PO_4	HS GC/MS	TIC	8.79	2-Methyl-2-Propanol	75-65-0	Confirmed	N/A	2-Methyl-2-propanol	0.147	0.490	<LOD	<LOQ	<LOQ	0.0811
	DI GC/MS	TIC	6.87	Hexanoic acid	142-62-1	Confident	N/A	2-Octanone	0.001	0.002	<LOD	0.00829	0.0185	0.0191
	HS GC/MS	TIC	19.63	Pentanal	110-62-3	Confirmed	N/A	Pentanal	0.050	0.166	<LOD	<LOD	<LOQ	<LOQ
	LC/PDA/MS	PDA (210-400 nm), ES+/-, APCI +/-	N/A	None Detected	N/A	N/A	N/A	BPA (PDA), DEHP (PDA), Erucamide (ES+), Irganox 1010 (ES-) Irganox 1010 (APCI+,APCI-)	0.161, 0.389, 0.077, 0.062, 4.68, 8.69	0.536, 1.30, 0.256, 0.207, 15.6, 29.0	<LOD	<LOD	<LOD	<LOD

Summarized Inorganic Extractables Data



Element	ICH Q3D Class	Worst-case, µg/cm² (70 days)					
		Water	5M NaCl	0.1M H_3PO_4	0.5N NaOH	50% Ethanol	1% PS80
Cd	1	-	-	-	-	-	-
Pb	1	-	-	-	-	-	-
As	1	-	-	-	-	-	-
Hg	1	-	-	-	-	-	-
Co	2A	-	-	-	-	-	-
V	2A	-	-	-	-	-	-
Ni	2A	-	-	-	-	-	-
Tl	2B	-	-	-	-	-	-
Au	2B	-	-	-	-	-	-
Pd	2B	-	-	-	-	-	-
Ir	2B	-	-	-	-	-	-
Os	2B	-	-	-	-	-	-
Rh	2B	-	-	-	-	-	-
Ru	2B	-	-	-	-	-	-
Se	2B	-	-	-	-	-	-
Ag	2B	-	-	-	-	-	-
Pt	2B	-	-	-	-	-	-
Li	3	-	-	-	-	-	-
Sb	3	-	-	-	-	-	-
Ba	3	-	-	-	-	-	-
Mo	3	-	-	-	-	-	-
Cu	3	-	-	-	-	-	-
Sn	3	-	-	-	-	-	-
Cr	3	-	-	-	-	-	-
B	N/A	0.204	-	-	0.004	-	-
Na	N/A	0.228	N/A	-	N/A	-	-
W	N/A	-	-	-	-	-	-
Mg	N/A	-	-	-	-	-	-
Al	N/A	-	-	-	-	-	-
Ca	N/A	-	-	-	-	-	-
Ti	N/A	-	-	-	-	-	-
Mn	N/A	-	-	-	-	-	-
Fe	N/A	-	-	-	-	-	-
Zn	N/A	-	-	-	-	-	-
K	N/A	-	-	-	-	-	-

Notes: "-" indicates < 20 ppb; N/A – not analyzed due to interference with matrix.

Includes all ICH Q3D plus additional elements

IMPACT OF PRE-TREATMENT

Study	Sterilization	Total Compounds
Sterile connector (24 hr)	Autoclaved	
	Gamma irradiated	
PES filter (24 hr)	Autoclaved	
	Gamma irradiated	

| Common compound

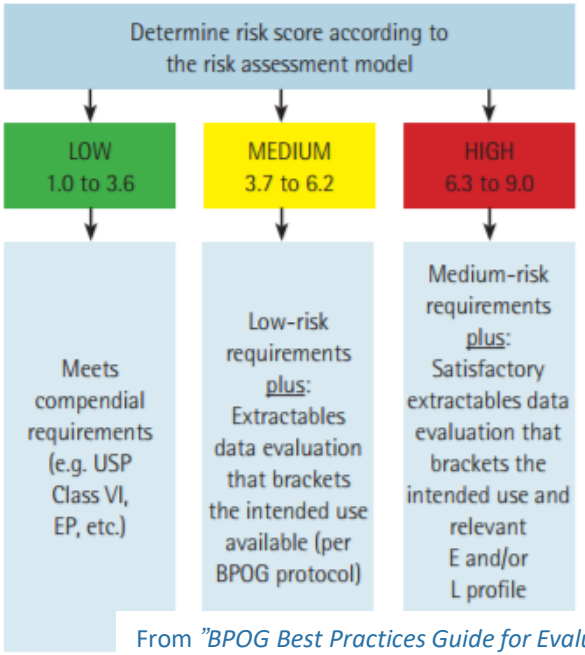
| Unique compound

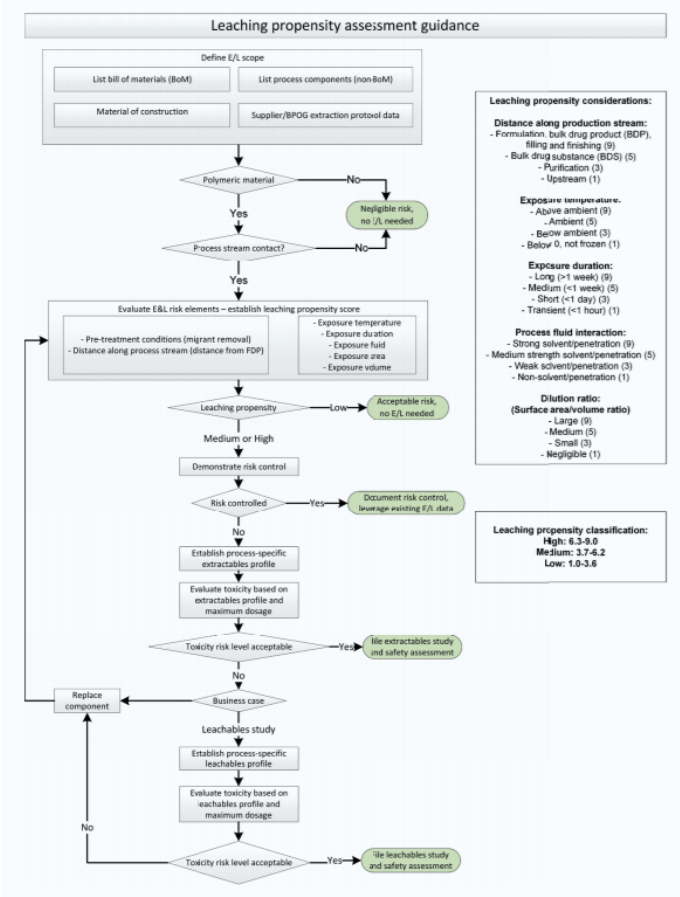
BPOG RISK ASSESSMENT GUIDANCE

BioPhorum Operations Group
Connect · Collaborate · Accelerate

- Risk Assessment model
  - Distance along production stream
  - Exposure temperature
  - Exposure duration
  - Process Fluid Interaction
  - Dilution ratio

⇨ Risk Level



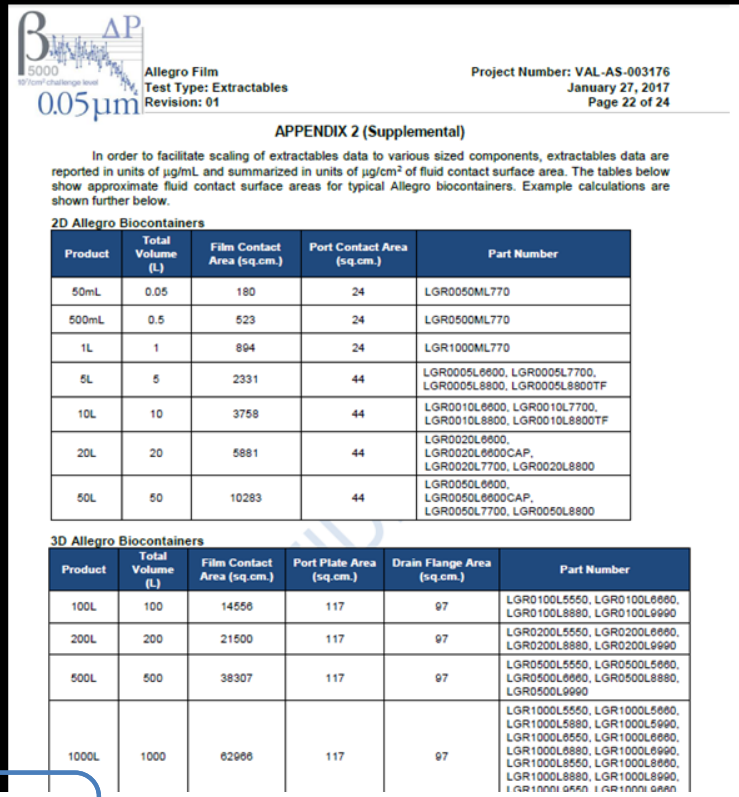


From *"BPOG Best Practices Guide for Evaluating Leachables Risk in Biopharmaceutical Single-Use Systems"*

SCALING DATA FOR E/L EVALUATION

Technical Report

Scaling to Different Size Biocontainers



Allegro Film
Test Type: Extractables
Revision: 01

Project Number: VAL-AS-003176
January 27, 2017
Page 22 of 24

APPENDIX 2 (Supplemental)

In order to facilitate scaling of extractables data to various sized components, extractables data are reported in units of µg/mL and summarized in units of µg/cm² of fluid contact surface area. The tables below show approximate fluid contact surface areas for typical Allegro biocontainers. Example calculations are shown further below.

2D Allegro Biocontainers

Product	Total Volume (L)	Film Contact Area (sq.cm.)	Port Contact Area (sq.cm.)	Part Number
50mL	0.05	180	24	LGR0050ML770
500mL	0.5	523	24	LGR0500ML770
1L	1	894	24	LGR1000ML770
5L	5	2331	44	LGR0005L6600, LGR0005L7700, LGR0005L8800, LGR0005L8800TF
10L	10	3758	44	LGR0010L6600, LGR0010L7700, LGR0010L8800, LGR0010L8800TF
20L	20	5881	44	LGR0020L6600, LGR0020L6600CAP, LGR0020L7700, LGR0020L8800
50L	50	10283	44	LGR0050L6600, LGR0050L6600CAP, LGR0050L7700, LGR0050L8800

3D Allegro Biocontainers

Product	Total Volume (L)	Film Contact Area (sq.cm.)	Port Plate Area (sq.cm.)	Drain Flange Area (sq.cm.)	Part Number
100L	100	14556	117	97	LGR0100L5550, LGR0100L6660, LGR0100L8880, LGR0100L9990
200L	200	21500	117	97	LGR0200L5550, LGR0200L6660, LGR0200L8880, LGR0200L9990
500L	500	38307	117	97	LGR0500L5550, LGR0500L5660, LGR0500L6660, LGR0500L8880, LGR0500L9990
1000L	1000	62966	117	97	LGR1000L5550, LGR1000L5660, LGR1000L5880, LGR1000L5990, LGR1000L6550, LGR1000L6660, LGR1000L6880, LGR1000L6990, LGR1000L8550, LGR1000L8660, LGR1000L8880, LGR1000L8990, LGR1000L9550, LGR1000L9660

Scaling Examples

Example Calculation Showing Final Concentration of Port Extractables in Filled 1L and 20L Allegro 2D Biocontainers

Compound	Worst-case Amount (µg/cm²)	Port Contact Area in Biocontainer		Worst-case Amount in Filled Biocontainers (µg/mL)[a]	
		1L	20L	1L	20L
Palmitic acid	3.18	24	44	0.0763	0.0070
1,3-Di-tert-butylbenzene	2.89	24	44	0.0694	0.0064
2-Propanol	1.51	24	44	0.0362	0.0033
Stearic acid	1.44	24	44	0.0346	0.0032
2-(Formyloxy)-1-phenyl-ethanone	1.23	24	44	0.0295	0.0027
Ba	0.020	24	44	< 0.001	< 0.0001
Mo	0.018	24	44	< 0.001	< 0.0001

[a] Worst-case Amount in Filled Biocontainer = [Worst-case Amount (µg/cm²) x Port Contact Area] / Total Volume

Single-use system

µg/cm²

Surface/Volume ratio
Dilution factors

Drug Product

µg/ml

BPOG VS USP <665>

	BPOG
Scope	User requirement specification for single use components
Goal	Intended to standardize and expedite component qualification by bracketing worst case extractables for ~80% of bioprocess applications
Risk-based	No supplier risk assessment. End user responsibility
Time points	3 to 4
Solvents	6
Low pH	0.1 M H_3PO_4 (~pH 1.6)
High pH	0.5 N NaOH (pH 13.5)
Organic	50% EtOH
Aqueous	WFI
Salt	5 M NaCl
Surfactant	1% Polysorbate 80

BPOG VS USP <665>

	BPOG	USP <665> & <1665> (draft)
Scope	User requirement specification for single use components	Standard for extractables profiling of plastics used in pharmaceutical processing equipment
Goal	Intended to standardize and expedite component qualification by bracketing worst case extractables for ~80% of bioprocess applications	Intended to aid supplier selection through meaningful component profiling covering ~80% of applications
Risk-based	No supplier risk assessment. End user responsibility	Yes. Level of data based on risk matrix described in <1665>
Time points	3 to 4	1
Solvents	6	3
Low pH	0.1 M H_3PO_4 (~pH 1.6)	KCl/HCl (pH 3)
High pH	0.5 N NaOH (pH 13.5)	Phosphate (pH 10)
Organic	50% EtOH	50% EtOH
Aqueous	WFI	-
Salt	5 M NaCl	-
Surfactant	1% Polysorbate 80	-

RISK ASSESSMENT USING E&L DATASET

1. Product & Process map
2. Single-Use System
3. Component Quality Information
4. Aggregate and Scale Relevant Data
5. Application Information
6. Toxicological Risk Assessment

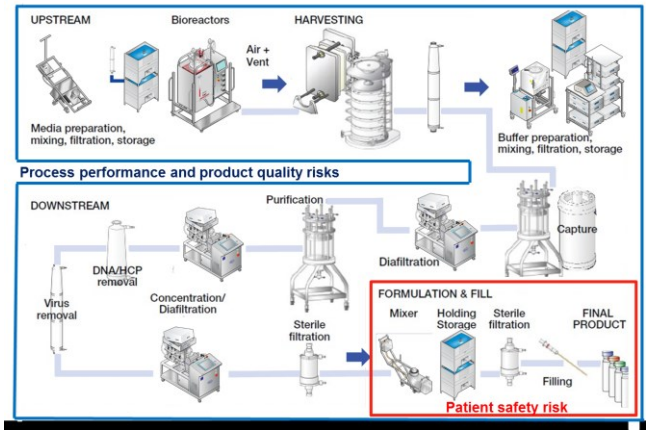
Product Map

- Delivery route
- Dose
- Dose regimen

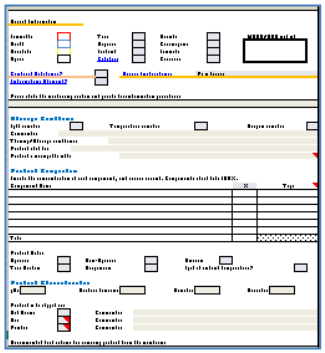
Product Description

- Organic content
- Surfactants
- pH

Process Map

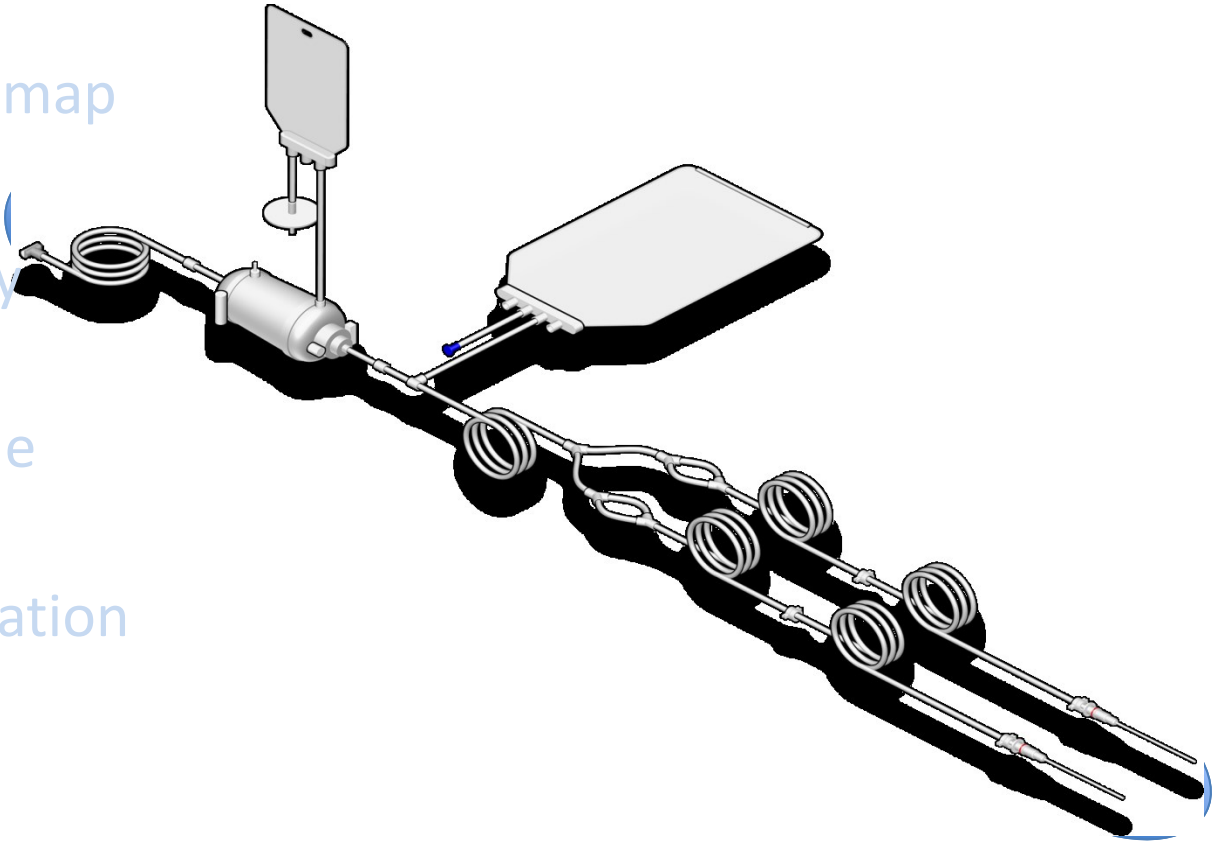


Process Description



RISK ASSESSMENT USING E&L DATASET

1. Product & Process map
2. Single-Use System
3. Component Quality Information
4. Aggregate and Scale Relevant Data
5. Application Information
6. Toxicological Risk Assessment



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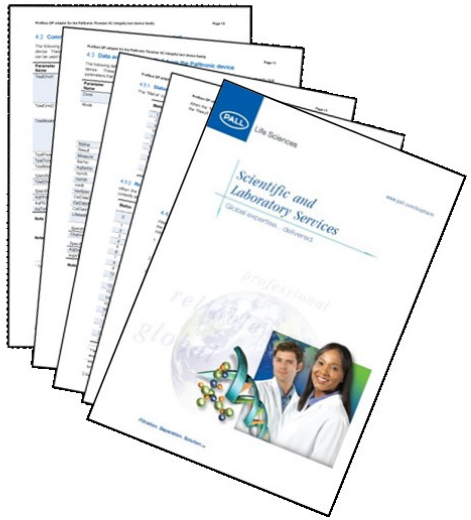
BPOG Component Extractables Data



Compendial Extractables Baseline Data

- USP <87>, <88>, <661>
- EP monographs

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			Standard Solvents Data Available (µg/cm²)							Action		Reported Compounds (µg)				
	Component	Surface Area	pH 1.6	WFI	pH 13.5	50% EtOH	5% PS80	5M NaCl	Other	Risk Assess	Test	Compound A	Compound B	Compound C	Compound D	Compound E
Component	PES Filter (KA3EKVP1G)	1530	●	●	●	●	●	●	○	●	○	0.1	0.1	0.1	12	1.4
	Allegro Biocontainer	225	●	●	●	●	●	●	○	●	○	0.6	0.6	12	3.1	1.1
	Tubing	122	○	●	○	●	○	○	●	●	○	0.1	1	0.4	0.5	0.6
	Kleenpak Presto Connector	44	●	●	●	●	●	●	○	●	○	-	0.1	0.1	-	-
	Fittings	34	○	●	○	●	○	○	●	○	●	0.2	-	-	0.1	-
	Filling Needle	6	○	●	○	●	○	○	○	●	○	-	-	-	-	-
	Total Extractable Levels per SUS											**0.9**	**1.8**	**13**	**16**	**3.2**

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	Filling Needle	6	○	●	○	●	○	○	○	●	○	-	-	-	-	-
	Total Extractable Levels per SUS											**0.9**	**1.8**	**13**	**16**	**3.2**

AET

	Total Daily Exposure (µg/day)	0.7	1.4	10	13	2.6
Application	Route of Administration	IV injection
	Final API Concentration	1 mg/mL
	Dosage Concentration	250 µg/mL
	Maximum Dosage per day	2 mg
	Duration of Exposure	Lifetime
	Patient Poplation	All

Threshold of Toxicological Concern (TTC) a level of exposure for all chemicals below which there would be no appreciable risk to human health

Analytical Evaluation Threshold (AET) threshold at or above which a leachable should be characterized and reported for toxicological assessment

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	Duration of Exposure	Lifetime					
	Patient Poplation	All					

Tox	Toxicology Cramer Class	II	I	I	I	I
	Genotoxicity (ICH M7)	N	N	N	N	N
	Protein or Cell Interactions	N	N	N	N	N
	ICH Q3C (Class)	III	-	-	-	-
	Permitted Daily Exposure (PDE)	✓	✓	✓	✓	-

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	Filling Needle	6	○	●	○	●	○	○	○	●	○	-	-	-	-	-
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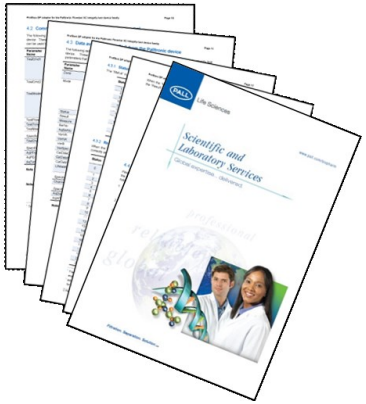
	Duration of Exposure	Lifetime					
	Patient Poplation	All					

Tox	Toxicology Cramer Class		II	I	I	I	I
	Genotoxicity (ICH M7)		N	N	N	N	N
	Protein or Cell Interactions		N	N	N	N	N
	ICH Q3C (Class)		III	-	-	-	-
	Permitted Daily Exposure (PDE)		✓	✓	✓	✓	-

☑ Component Safety Risk Assessment

SUPPORT LEVELS TO PHARMA END-USER



Standardized extractable data

Consulting services related to core data

Help to build Risk Assessment: identification of compounds to be evaluated, facilitation of Toxicological assessment, …

Laboratory Services for process specific data

e.g. specific Extractables

Suppliers can provide different levels of support to E&L topics depending on customer's needs

CONCLUSIONS

- Standardized extractable data facilitate adoption of SUT
- They enable **c**GMP extractable and toxicological risk assessment
- Extractable data can also be used as input (alert signal) for product impact risk assessment

- It becomes very important to have high impact components well characterized by standardized extractables protocols

ACKNOWLEDGMENT

- Special thanks to my colleagues James Hathcock for helping setting up this presentation