Adopting a Fully Single-Use Process to Improve Speed to Clinic

A Leachables Case Study

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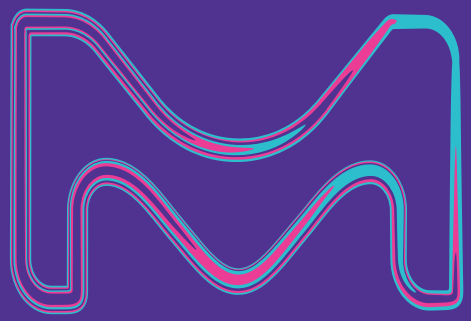
Asia Seminar Series, December 2015



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Overview

1. E&L Definitions, Concepts, Regulations
2. Study Motivation, Design and Execution
3. Analysis of Results and Risk Assessment
4. Conclusions

Extractables & Leachables (E&L): PDA Definitions

Extractables

"Any chemical component that is removed from a material by the application of an artificial or exaggerated force (e.g., solvent, temperature or time)."

Determined under "worst-case" conditions following the Model Stream approach.

Extractables Study:
To identify and quantify as many compounds as possible that have the potential to become leachables

Leachables

"A chemical component that migrates from a contact surface into a drug product or process fluid during storage or normal use conditions."

Determined with the product under normal processing/storage conditions.

Leachables Study:
To identify and quantify as many compounds as possible that migrate from the filtration process or storage systems into the actual drug product

PDA® Technical report N°26, 2008
PDA® Technical report N°66, 2014

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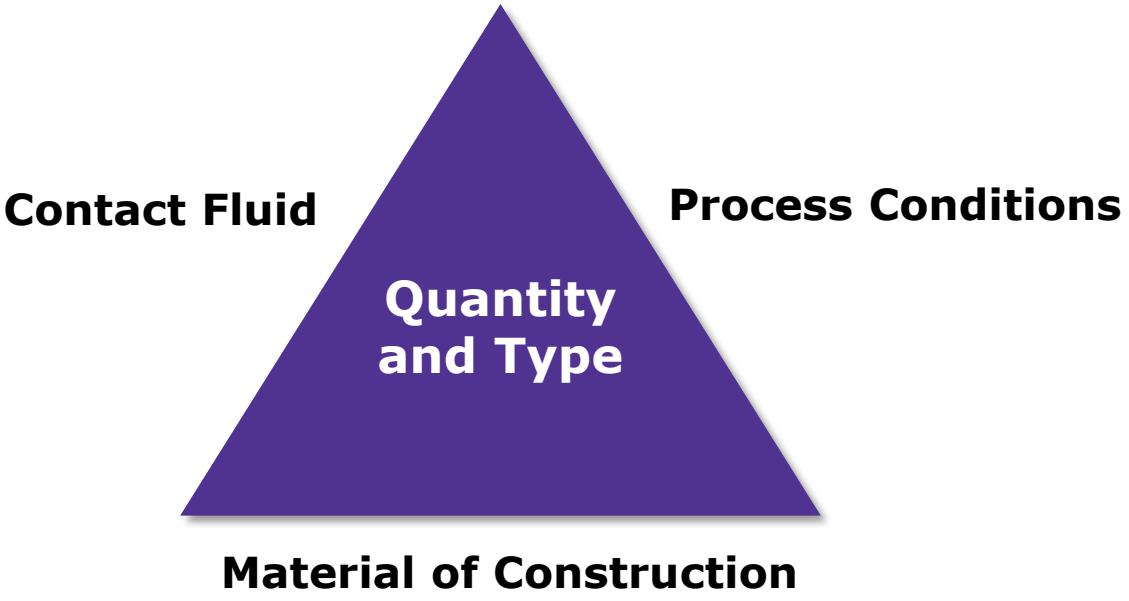
What are Extractables & Leachables?

Oligomers
PVDF, PP, PE
Etc.

Additives and Degradants
Antioxidants, UV stabilizers,
Slip agents, etc.

Residual Solvents



FDA/EU General GMP Guidelines

FDA

FDA, Code of Federal Regulations, Part 211, "Current Good Manufacturing Practice for Finished Pharmaceuticals", Part 211.65, "Equipment Construction", 2005

"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."

EU

European Commission, EUDRALEX Volume 4, "Good Manufacturing Practices, Medicinal Products for Human and Veterinary Use", Chapter 3, "Premise and Equipment", 2003

"Production equipment shall not present any hazard to the products. The parts of the 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."

These regulations drive the need for evaluation of Extractable & Leachable substances

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Protect The Patient and Be in Compliance

Risk Based Approach

"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, and stability profile).

"**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 no additional testing should be submitted,"

Where there is relevant risk, the drug sponsor may have to **determine toxicity based on maximum dosage** of potential leachables based on extractables data.

If the maximum dosage of potential leachables presents a **safety risk, leachable evaluation and testing may be necessary**.

Additionally, if **product quality could be affected** by potential leachables, studies may need to be performed to **assess the effect** on product quality, including efficacy."

Destry M. Sillivan - Senior Regulatory Review Officer, CBER

IBC's 7th International Single Use Applications for Biopharmaceutical Manufacturing Conference, la Jolla, CA, June 14, 2010

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Evaluate High Risk Unit Operations

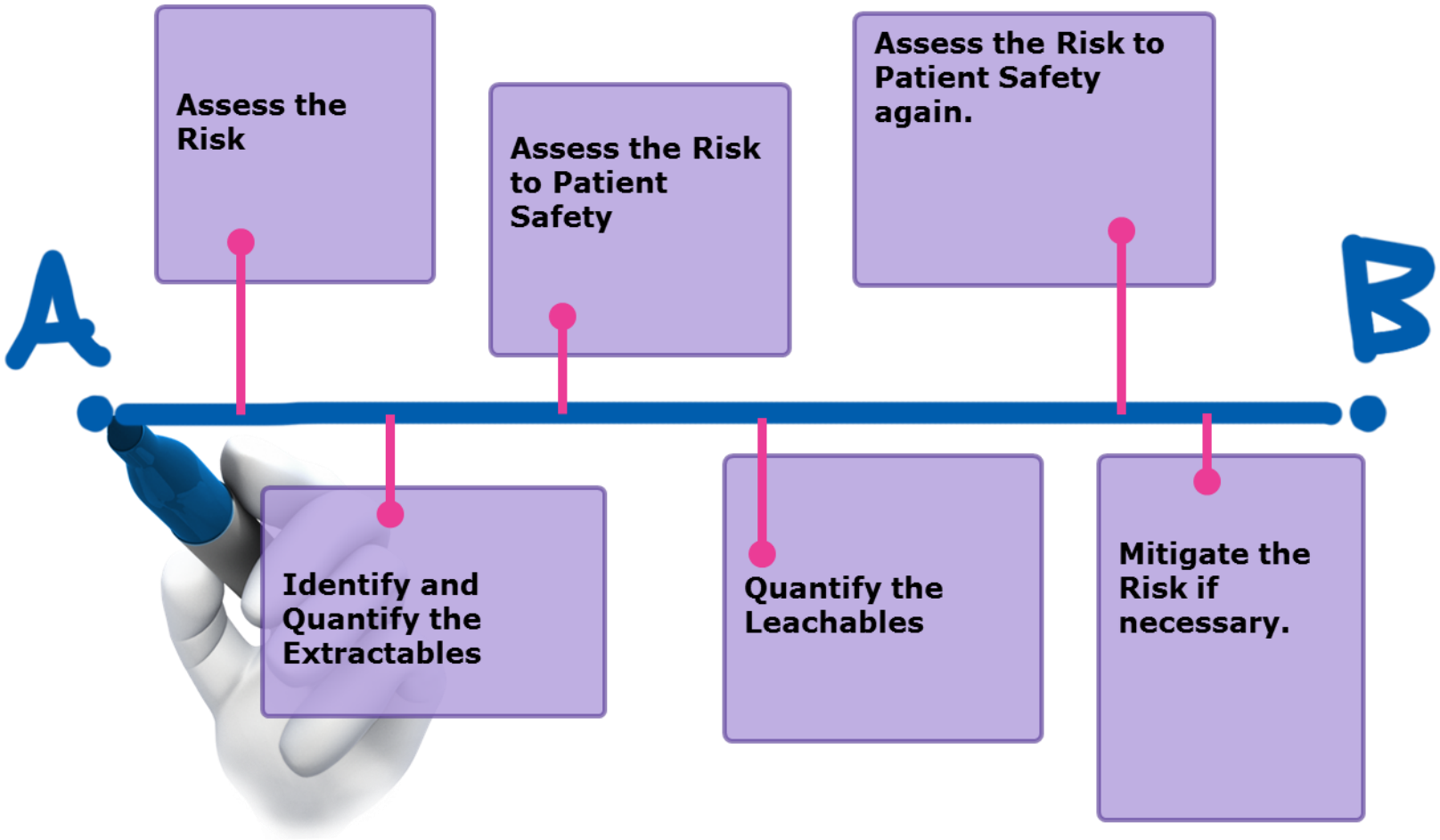
Table 5.2-1 Risk Complexities of SUS Items and Applications

Impact to Process		System Complexity: Low	System Complexity: Moderate	System Complexity: High	Impact to Process	
	Low	Buffer/Storage	UF*/DF†/ Concentration	Clarification/ Recovery	Low	
	Moderate	Transport/ Shipping	Connectors/Mixing/ Medium Storage	Cell Culture/ Fermentation	Moderate	
	High	Freeze/Thaw	Purification/ Product Storage	Fill and Finish	High	

*UF – ultrafiltration †DF – diafiltration

Source: PDA TR 66: Single Use Systems 2014

Use a Stepwise Approach



Assess the Risk

Applications	Degree of severity		
	Low	**Intermediate**	**High**
Chemical compatibility	Compatible	Limited	Incompatible
Toxicity of extractables	Non-toxic	Toxic at high levels	Toxic at low levels
Contact time	Short	Moderate	Long
Contact Temperature	Ambient or below	Elevated	High
Surface area-to-volume	Low	Medium	Large
Proximity	Upstream	Downstream	Final fill/Storage
Dosage form	Solid	Liquid	Vapour
Route of administration	Topical, Oral	Ophthalmic, Transdermal	Inhalation, Injections

Assess the Risk of the Formulation

IV Drug Formulation

Active	10 mg/mL
Polysorbate 80	0.2 mg/mL
Sodium Chloride	9 mg/mL
WFI	QS

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Assess the Risk of the Process

IV Drug Formulation

Active	10 mg/mL
Polysorbate 80	0.2 mg/mL
Sodium Chloride	9 mg/mL
WFI	QS

Conditions

pH	6.5-7.5
Filtration Temp	5-30 ºC
Filtration time	8 hours
Gamma Irradiation	25-40 kGy

Applications	Degree of severity		
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Assess Risk to Patient Safety

"Alle Dinge sind Gift und nichts ist ohne Gift; allein die Dosis macht, dass ein Ding kein Gift ist."

"All things are poison and nothing is without poison; only the dose makes a thing not a poison."

Source: Paracelsus, Renaissance academic

Factors for Determination of Extractable Substances Toxicity:

- Toxicological data on compounds
- Concentration in final dosage
- Dose size, regimen, dose delivery
- Patient population

Protect The Patient and Be in Compliance

Minimum:

- Assess worst case extractables to evaluate potential compounds

High Risk Applications:

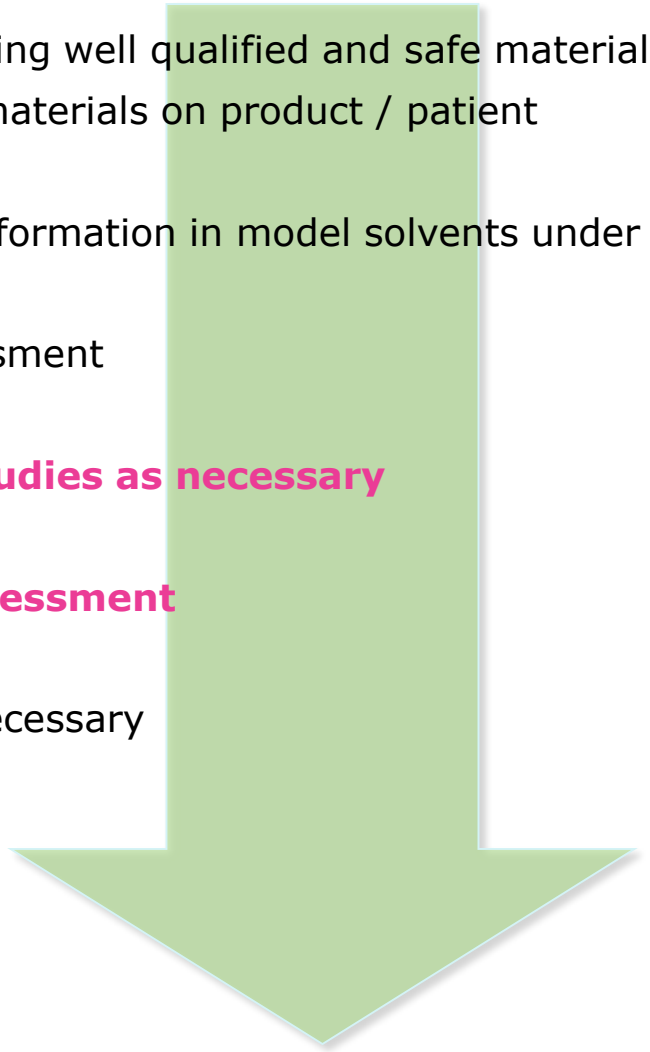
- Identify and quantify the impurities.
- Relate the impurities to a patient and dose. Assess the risk to patient safety.
- Mitigate the leachables if necessary.

Study Motivation

- Increased availability of single-use components in downstream arena enables 100% single-use clinical-scale operations
- Traditional vendor focus has been on extractables
- Capability of purification unit operations to remove leachables throughout the process
- Templated downstream process for mAbs offers unique opportunity

E&L Evaluation Process

- Build in quality by selecting well qualified and safe materials
  - assess overall risk of materials on product / patient
- Generate extractables information in model solvents under worst-case conditions
- Patient safety risk assessment
- **Conduct leachables studies as necessary**
- **Patient safety risk assessment**
- Mitigate patient risk if necessary



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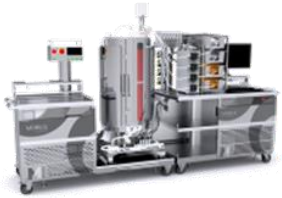
Blank Run on Complete Process

200L SU Bioreactor batched with Cell Culture Media	▪ No inoculation ▪ 13 days at process temperature & agitation, with feeds ▪ Sampled at t=0, t=13 days ▪ Day 13 harvest followed by full DSP
Downstream Processing	▪ Full-scale operations with all devices/resins ▪ All unit operations utilized single-use systems & flowpaths ▪ All process buffers prepped & stored in SU bags ▪ Sampling from each buffer bag and from each process intermediate pool
Sample Analysis Methods	▪ GC-MS (VOC and sVOC) ▪ LC-MS (non VOC) ▪ ICP (Metals)

Fully Single-Use MAb Process

t=0 Culture Fluid

= Analysis Samples



13-day Culture Fluid

Bioreactor
Mobius® Single-use 200 L Bioreactor

Clarified Harvest Pool

Depth Filtration
Millistak+® D0HC and X0HC POD filters

Post Capture Pool

Capture Step
ProSep® Ultra Plus resin

Post VI Pool

Virus Inactivation
Mobius® Mix system with Millipore Express® SHC filter

Bulk Drug Substance

t=0
t=7 days

Express® SHC filter

UF/DF
Pellicon® 3 Ultracel 30kD cassette

Post VF Pool

Viral Filtration
Viresolve® Pro+ solution

Post AEX Pool

AEX Step
Membrane Adsorber

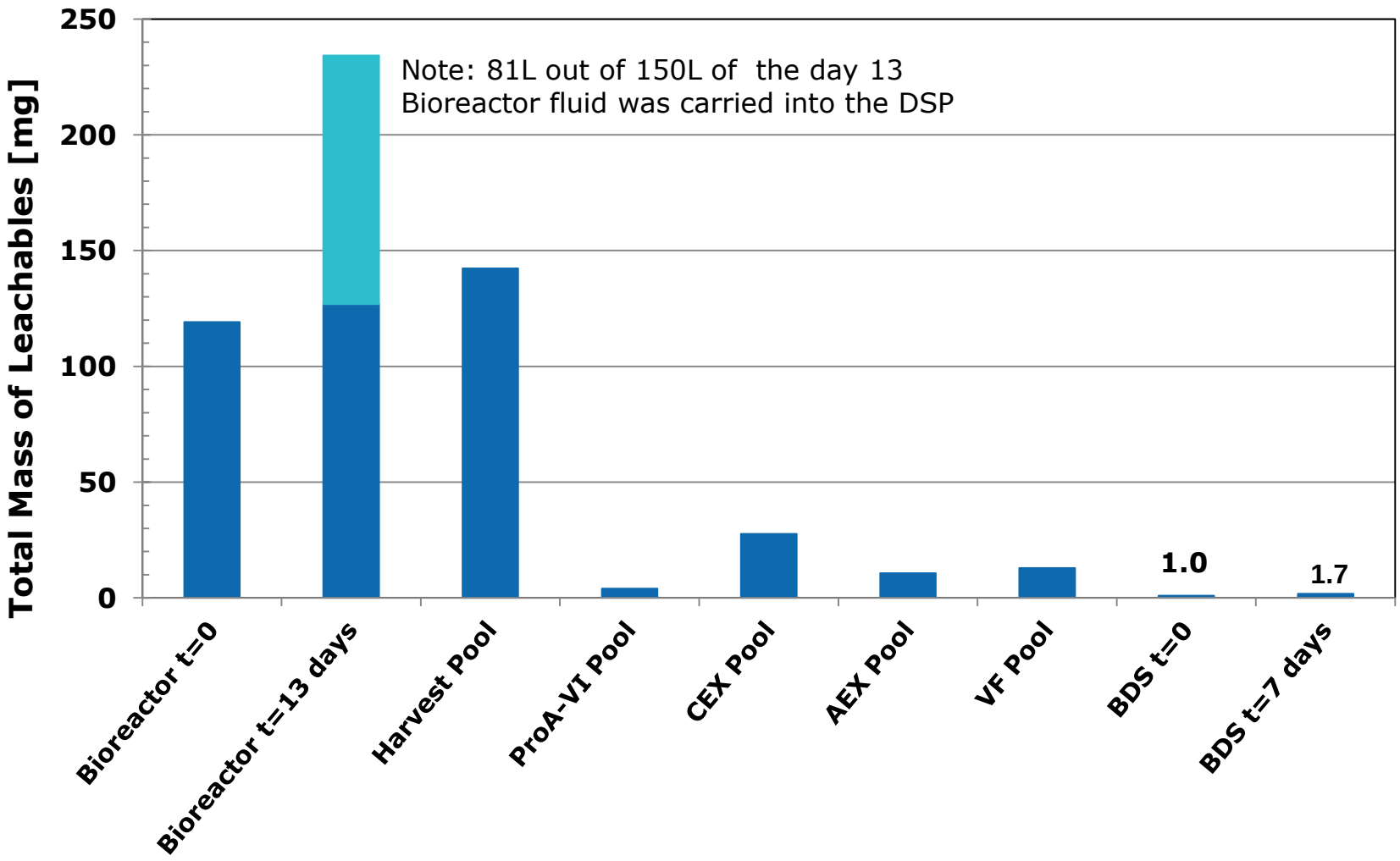
Post CEX Pool

CEX Step
Fractogel® SO_3 resin

Summary of Total Material Exposures

Unit Operation	Devices	# Sterile Filters	# System Flowpaths	# Product Bags	# Buffer Bags
Bioreactor	n/a	2	1	1	2
Harvest	2.64 m^2	2	2	1	2
Capture Chrom	1.6 L	5	3	5	8
CEX Chrom	1.6 L	2	2	1	6
AEX Chrom	50 mL	2	2	3	4
Virus Filtration	0.14 m^2	2	2	1	3
TFF-UFDF	0.5 m^2	1	2	1	4
BDS Filtration	0.029 m^2	0	1	1	0

Total Mass of Leachables through Process



Summary of Bioreactor Samples

Day 0

- **<0.1 ppm** in total **VOC** leachables
  - All compounds are products of gamma irradiation
  - alkanes, aldehydes, ketones
- **0.95 ppm** in total **SVOC** leachables
  - All compounds are products of gamma irradiation.
  - branched alkenes, long chain alcohols, ketones, siloxanes.
- **ICP** and **LCMS** did not observe any compounds except those which are part of the media formulation.

Day 13

- **0.22 ppm** in total **VOC** leachables
  - All products of gamma irradiation
  - alkanes, aldehydes, ketones, 2,4-di-tert-butyl phenol
- **1.34 ppm** in total **SVOC** leachables.
  - All compounds are products of gamma irradiation
  - branched alkenes, aldehydes, and siloxanes
- **ICP** did not observe any compounds except those which are part of the media formulation.
- **LCMS** detected trace (<20 ppb) amount of bis-di-tert-butyl phenol phosphate (bis-DtBPP).

Summary of Bulk Drug Substance Samples

Day 0

- **<0.1 ppm** in total **VOC** leachables
  - All products of gamma irradiation
  - alkanes, aldehydes, ketones
  - No individual component present at >100 ppb
- **0.38 ppm** in total **SVOC** leachables
  - All products of gamma irradiation
  - branched alkene, long chain alcohol, siloxanes, 2,4-di-tert-butyl phenol
  - No individual component present at >100 ppb
- **ICP** and **LCMS** did not observe any compounds

Day 7

- **0.21 ppm** in total **VOC** leachables.
  - All products of gamma irradiation
  - alkanes, aldehydes, ketones
  - One component present at >100 ppb (hexanal)
- **0.67 ppm** in total **SVOC** leachables.
  - All products of gamma irradiation
  - branched alkene, long chain alcohol, siloxanes, 2,4-di-tert-butyl phenol
  - No individual component present at >100 ppb
- **ICP** and **LCMS** did not observe any compounds.

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Risk Assessment Strategy for BDS Leachables

Patient exposure depends on:

- Mass of leachables per dose
  - Total mass of leachables in BDS bag
  - Total volume of BDS in bag
  - Milliliters of BDS per patient dose (mg protein per dose / protein concentration in BDS)
- Consideration for how many doses are received over time

Updated ICH M7 guidelines published June 2014

- acceptable intake of impurities for intermittent dosing based on overall duration

Regulatory Guidance recommends …

Where a potential risk has been identified, risk assessments should be performed.

- For unknown impurity the Threshold for Toxicological Concern (TTC) is 1.5 ug/person/day
- For Less-Than-Lifetime (LTL) exposure the acceptable intake levels can be raised based on the duration of the treatment

New guidelines for multiple mutagenic impurities sets a limit on total impurities

Table 2: Acceptable Intakes for an Individual Impurity

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

ICH M7 ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) I.., June 2014

Patient Exposure to Leachable in BDS

Based on mAb **low-dosing regimen** of 50 mg API/1 week

- **Case 1:** Assume BDS API concentration = 100 g/L

BDS Leachables Concentration (µg/mL)	Dosage (mL)	Patient Exposure (Total µg/dose)	Exposure Assessment
0.9	0.5	0.4	**OK for lifetime dosing**

- **Case 2:** Assume BDS API concentration = 10 g/L

BDS Leachables Concentration (µg/mL)	Dosage (mL)	Patient Exposure (Total µg/dose)	Exposure Assessment
0.9	5.0	4.4	**OK up to 10 years dosing**

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Patient Exposure to Leachable in BDS

Based on mAb **high-dosing regimen** of 1050 mg API/2 weeks

- **Case 1:** Assume BDS API concentration = 100 g/L

BDS Leachables Concentration (µg/mL)	Dosage (mL)	Patient Exposure (Total µg/dose)	Exposure Assessment
0.9	10.5	9.2	**OK up to 10 years dosing**

- **Case 2:** Assume BDS API concentration = 10 g/L

BDS Leachables Concentration (µg/mL)	Dosage (mL)	Patient Exposure (Total µg/dose)	Exposure Assessment
0.9	105	91.6	**OK up to 1 month dosing**

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Evaluate Individual Compounds

- The leached compound identified in the greatest concentration within the BDS after 7 days storage was Hexanal (CAS 66-25-1)
  - VOC identified and quantified via HS GCMS at a concentration of 110 ppb or 0.11 µg/mL

- The concentration of this individual compound was placed into the **worst-case mAb model**: MAb high-dosing regime with assumed BDS conc. of 10g/L

BDS Leachables Concentration (µg/mL)	Dosage (mL)	Patient Exposure (Total µg/dose)	Permissable Daily Exposure Limit (µg/day)
0.11	105.0	11.6	**3750**

- Note: A PDE for Butanal/Pentanal has been established at 3.75 mg/person

Conclusions

1. Complete leachables blank run demonstrates that downstream purification unit operations provide a level of leachables removal throughout the process
2. Study confirms and supports direction of industry to focus on evaluating E&L from the bioreactor and from BDS storage through to drug product
3. Study brings confidence in patient safety in regard to leachables from single-use processes as demonstrated by toxicological threshold analysis
4. Final filling operation utilize primarily the same MoC's as evaluated here, providing confidence that leachables should not pose a safety hazard
5. Provides confidence that leachates from the Provantage ClinicReady template will not adversely impact the clinical studies vs. a traditional process and that the materials/media contained within the ClinicReady template are commercially viable from a material safety standpoint

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Thank you!

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