BPSA 2020 Speaker Series

Wednesday, September 23, 2020
10:30-11:15 AM EDT

Overview of BPSA's Technical Guide, *Extractables/Leachables Considerations for Cell & Gene Therapy Drug Product Development*

BPSA Speaker Series Brought To You By…

BPSA Sustaining Sponsors

AdvantaPURE
Broadley James
bürkert FLUID CONTROL SYSTEMS
CHEMIC LABORATORIES, INC.
CPC
cytiva
Entegris
MilliporeSigma
Nordson MEDICAL
PALL Biotech
PENDOTECH Adding Value To Your Process
RENOLIT Rely on it.
SAINT-GOBAIN
SaniSure Be sure.
SARTORIUS
Savillex
ThermoFisher SCIENTIFIC

Created in Cooperation With…

socma
SOLUTIONS FOR SPECIALTIES

BAHP
CENTER FOR BABY AND ADULT HYGIENE PRODUCTS

BPSA
Bio-Process Systems Alliance
Advancing Single-Use Worldwide

CPMA
Color Pigments Manufacturers Association

INFORM · ADVOCATE · ACT
Flexible Vinyl Alliance

IPA

Ott Consulting Group LLC

Webinar Speakers

Dr. Armin Hauk
Sartorius Stedim Biotech

Joseph St. Laurent
Chemic Laboratories

Brendan Lucey
Gemini BioProducts

BPSA White Paper Authors

Published by:

Bio-Process Systems Alliance (BPSA)
1400 Crystal Drive
Arlington, VA 22202

www.bpsalliance.org

AUTHORS

Manjula Aysola, MilliporeSigma

Dominic Clarke, PhD, Charter Medical

Ray Colton, VR Analytical

Paul Cummings, Smithers MDT

Jayanthi Grebin, Colder Products Company

Armin Hauk, Sartorius-Stedim Biotech

Eva Heintz, Solvay

Todd Kapp, Entegris

Brendan Lucey, Gemini Bio

Ruth McDermott, Sartorius-Stedim

Hernán Parma, American RENOLIT

Joseph P. St. Laurent, Chemic Laboratories Inc.

Three terms that require understanding

- The U.S. FDA released its first Guidance for Industry related to CGT in March 1998. This Guidance defined "somatic-cell therapy" as *"…the administration to humans of autologous, allogeneic, or xenogeneic living cells which have been manipulated ex vivo."*

- Extractables: Organic and inorganic chemical entities that are released from a pharmaceutical packaging/delivery system, packaging component, or packaging material of construction and into an extraction solvent under laboratory conditions. *(www.usp.org)*

- Leachables: Foreign organic and inorganic chemical entities that are present in a packaged drug product because they have leached into the packaged drug product from a packaging/delivery system, packaging component, or packaging material of construction under normal conditions of storage and use or during accelerated drug product stability studies. *(www.usp.org)*

Contrast Traditional E&L with Unique Requirements of CGT

In cell and gene therapy, cells are the Drug product (DP) and there is little opportunity to separate impurities from the product.

Standardized protocols, such as USP <665> draft and/or the BioPhorum Operations Group (BPOG) extractables protocol, are available and may be applied for CGT products as well as all biological and biotechnology-based pharmaceutical products.

In classical biopharmaceutical manufacturing, the cells are utilized in the production of the Drug substance (DS) (e.g., a protein, an antibody or an enzyme).

From Charter Medical presentation at 2017 BPSA International Single-Use Summit

Single-Use	Intended Purpose	Material (common)
Collection bags	Starting materials	PVC (polyvinyl chloride)
Transfer/processing bags	Wash; manipulation	PVC
Transfer (tubing) sets	Fluid transfer; sample removal; reagent addition	PVC, ABS (acrylonitrile butadiene styrene), thermoplastic elastomer, silicone
Cell expansion containers	Cell culture or expansion	Polyolefin, EVA (ethylene vinyl acetate), FEP (fluorinated ethylene propylene), PE (polyethylene)
Media containers	Culture media; cryomedia; buffer storage	PVC, polyolefin, EVA, FEP, PE, PETG (polyethylene terephthalate glycol), LDPE (low density polyethylene)
Cryopreservation containers	Final fill; in-process frozen storage	Polyolefin, EVA, FEP, PP (polypropylene), COC (cyclic olefin co-polymer)

- Given the extensive use of SUT for CGT manufacturing, the cell-based product and the variety of possible contact surfaces and contact time, it is reasonable to believe that CGT products could be impacted by leachable compounds.

- While manufacturing of CGT products is highly reliant upon SUT, the conditions experienced during manufacturing (e.g., length of contact material exposure time, solvent/ solutions) are typically less invasive in comparison to those in the biopharma industry.

- Although additives in the formulation may protect the polymer from oxidation, a variety of molecules may be created during this degradation/stabilization process.

Therefore….The principal difference is that the cells are the product, and apart from a few washing steps, there is no opportunity to separate the impurities from the product

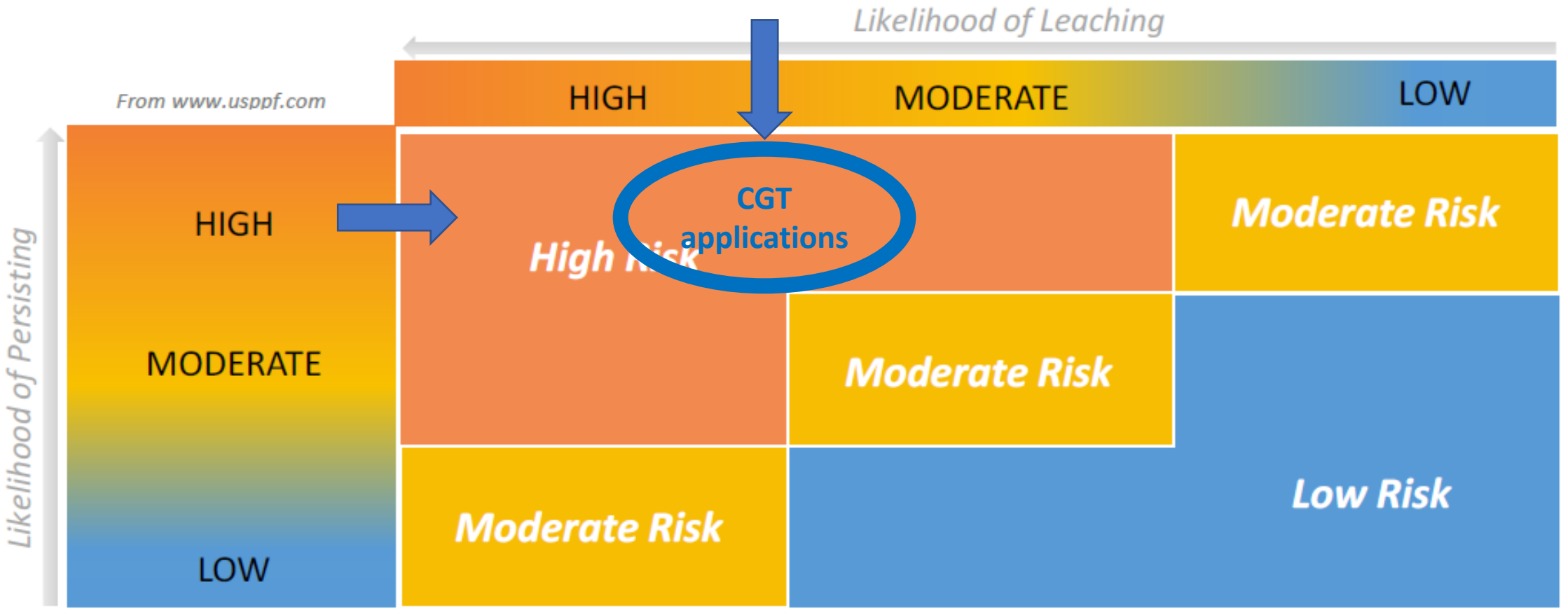
Risk Assessment

A risk analysis of each product contact material used in a process should be conducted. Some of the variables to consider include:

	Typical conditions in CGT applications
• Proximity to the final product	close to product and patient
• Extraction capability of the solution	aqueous conditions but storage in DMSO/water
• Contact time	medium in production and during storage
• Contact temperature	ambient and low temperature
• Product contact surface area	medium to high
• Pre-treatment of the material	sterilization methods
• Material compatibility/resistance	
• Supporting extractable testing provided by supplier	

Available compatibility information and extractables documentation e.g. for SUS/SUT, requires transfer to CGT application (“read-across”)

Risk Assessment



From USP ⟨1665⟩ Characterization of Plastic Materials, Components, and Systems Used in the Manufacturing of Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products, PF 43(3) [May–June 2017]

Risk Assessment

It is the responsibility of the industry to recognize that the presence and persistence of **P**rocess **E**quipment **R**elated **L**eachables (**PERL**s) directly result in relative risk, e.g., the presence of leachables

Three areas concerns associated with PERLs and Leachables:[1]

- **Process-performance**
- **Product quality**
- **Patient safety**

This means, translated into in the CGT area:

1. PERLs may be detrimental to cell growth and viability, along with undesired stimulation effects
2. PERLs may remain in the product due to absorption on and/or adsorption by the cells and therefore influence product quality and patient safety
3. The manipulation of the cells may result in degenerative cells. Degenerated cells can be a product quality issue but also a critical patient safety issue

[1] Li, K. et al. Creating a Holistic Extractables and Leachables (E&L) Program for Biotechnology Products. PDA J. Pharm. Sci. Technol. 69, 590–619 (2015).

Risk Assessment

ad 1) PERLs may be detrimental to cell growth and viability, along with undesired stimulation effects

What do we know from SUS used in classical bio-pharma:

- The bDtBPP case[1,2]
- The nitro-BPA-case[3]
- The Phthalate case[4]
- Issues often associated with serum free media

Classification of the issues

- Among the thousands of SUS applications, only a few cases, where extractables were identified to be detrimental to cells
- Even structural similar extractables show lower/no effects[5]
- Industry could develop materials, which did not show the undesired effects[6]

Consequences for CGT applications:

- We have – at least - strong evidence that most extractables are not detrimental to cell viability and growth (stimulation effect?)
- Risk mitigation possible by use of materials, for which successful cytotoxicity studies were conducted
- We need to develop biological tests to check compatibility of materials and extractables with cell-models, which fit to CGT

[1] Hammond, M. et al. Identification of a leachable compound detrimental to cell growth in single-use bioprocess containers. PDA J. Pharm. Sci. Technol. 67, 123–34 (2013)
[2] Hammond, M. et al. A cytotoxic leachable compound from single-use bioprocess equipment that causes poor cell growth performance. Biotechnol. Prog. 30, 332–337 (2014)
[3] Peng, J. et al. Chemical Identity and Mechanism of Action and Formation of a Cell Growth Inhibitory Compound from Polycarbonate Flasks. Anal. Chem. 90, 4603–4610 (2018)
[4] Ekwall B., et al. Toxicity of 29 Plasticizers to HeLa Cells in the MIT-24 System; Toxicology, 24 (1982), 199-210
[5] Budde D. et al. Identification and evaluation of cell- growth-inhibiting bDtBPP-analogue degradation products from phosphite antioxidants used in polyolefin bioprocessing materials; Analytical Bioanalytical Chem (2020)
[6] Blaschczok, K. et al. Evaluating New Film for Single-Use Bags: Growth Performance Studies with Animal and Human Cells. Bioprocess Int. 14, (2016).

Risk Assessment

ad 2) PERLs may remain in the product due to absorption on and/or adsorption by the cells and therefore influence product quality and patient safety

What do we know from SUS used in classical bio-pharma:

- Modern Extractables methodologies allow to comprehensively analyze extractables profiles
- SUS are sources of PERLs, but downstream operations are reducing PERL[1]
- Host cells can adsorb PERLs[2]

Classification of the issues

- Extractables methods are well suited to analyze *releasable* extractables from materials
- Extractables data give no answer
  - **on adsorption behaviors of PERLs**
  - **on direct transfer to adherent cells**
- CGT application do not include extensive purification steps, with the potential to remove PERLs

Consequences for CGT applications:

- Extractables assessment need to be re-considered, as only the sum of dissolved and adsorbed leachables gives the patient exposure
- We need a better knowledge of PERL adsorption on cells surfaces
- We need models to calculate PERL adsorption and transfer to adherent cells

[1] Hauk, A., et al. On the 'Fate of Leachables' in biopharmaceutical up-stream and down-stream processes. In: Single-use Technologies II: Bridging Polymer Science to Biotechnology Applications (2017)
[2] Paudel K, et al. Quantitative characterization of leachables sinks in biopharmaceutical downstream processing. Eur J Pharm Sci. 2020;143

Risk Assessment

ad 3) The manipulation of the cells may result in degenerative cells. Degenerated cells can be a product quality issue but also a critical patient safety issue

What do we know from SUS and CCS used in pharma applications

- Back in the 1990th PAHs, Nitrosamines and MBT were found in rubber parts of pMDI dosing heads[1]
- CMRs are commonly not part of SUS extractables profiles

Classification of the issues

- Modern Extractables methods allow to detect known CMRs
- Thousands of safe SUS applications, with no evidence that CMRs occur as PERLs
- Only one historic case is documented (pMDI case); issue is today solved by applying suitable rubber-materials
- Knowledge about CMRs is based on systemic effects (i.e. entire organisms)
- Isolated cells are more sensitive to degeneration than cells embedded into an entire organism

Consequences for CGT applications:

- Extractables analysis can be improved, that all known/anticipated CMRs can be detected
- There is low evidence that PERLs are CMRs[2,3]
- CGT cells as isolated cells (e.g. stem cells) may be more sensitive to CMRs
- Risk mitigation possible by use of materials, for which successful CMR-studies were conducted
- We need to develop biological tests to check materials and extractables with cell-models from the CGT area

[1] Ball, D.J., Norwood, D.L., Stults, C.L.M., Nagao, L.M., 2012. Leachables and Extractables Handbook: Safety Evaluation, Qualification, and Best Practices Applied to Inhalation Drug Products. Wiley
[2] Li, K. et al. Creating a Holistic Extractables and Leachables (E&L) Program for Biotechnology Products. PDA J. Pharm. Sci. Technol. 69, 590–619 (2015)
[3] D. Jenke, Safety risk categorization of organic extractables associated with polymers used in packaging, delivery and manufacturing systems for parenteral drug products, Pharm. Res. 32 (3) (2015) 1105e1127

Risk Assessment

Summary on E&L risk and risk mitigation for CGT applications:

- There is a low evidence that the standard plastics, which are used in the CGT area can be detrimental to the cell growth and viability
- Extractables methodologies are powerful tools to establish comprehensive extractables profiles and to detect critical compounds
- Extractables assessment need to include interaction with cells (adsorption-effects, direct transfer of PERLs to cells) to estimate a reasonable patient exposure
- Low evidence that PERLs are CMRs $\rightarrow$ low evidence that PERLs can induce the formation of degenerative cells
- Extractables methodologies can be enhanced to detect more/any CMR

- Low risk is associated with materials, which are established as safe materials in the SUS area or the medical device area
- It is desirable that bio-test-systems are developed, which allow to check cells used in the CGT area for their viability and integrity

Regulatory Considerations

- Strict regulatory guidance supporting and governing CGT product manufacturing where single-use and multi-use systems are used is ABSENT. The regulatory implications require the acknowledgement that ALL polymeric and elastomeric materials are the source of extractable analytes, which may result in potential product adulteration as leachables.

- The USP chapter <665> (Pharmacopeia Forum 43 (3), May 5, 2019) and chapter <1665> are the current benchmark documents providing regulatory direction surrounding the conduct of a SUT-CGT extractable investigation.

    - It should be noted that although USP chapter <665> is currently not officially promulgated and <1663 & 1665> are considered informational chapters, they can provide a basis for the design, justification, and execution of an extractables investigation supporting CGT.

USP <665> describes the following parameters that may be considered:

- 1) The chemical and physical nature of the contacted material/component, establishing the material's/component's 'propensity to be leached'
- 2) The chemical nature of the contacting process stream, establishing the process stream's 'leaching power'
- 3) The conditions of contact, addressing the 'driving force' for leaching
- 4) The ability of upstream process operations to eliminate the PERLs from the process stream or to dilute the PERLs to such an extent that an adverse effect is unlikely
- 5) The inherent risk associated with the manufactured drug product, considering such factors as the nature of the manufactured dosage form".

Unique Challenge of CGT & Responsibilities for E&L Testing

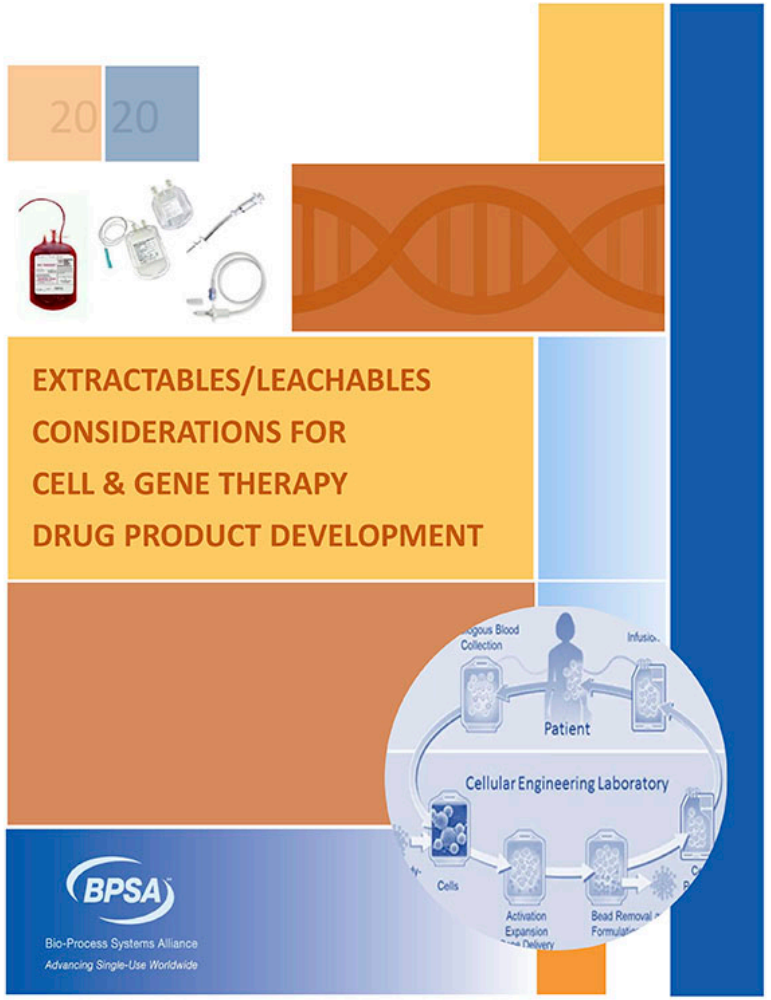
Currently, an overarching issue associated with E&L studies supporting CGT is the study designs largely investigate the contacting liquid phase (e.g. extractable[s]), as this information can provide a direct correlation to the degree of absorption of said analytes to the cells (e.g., leachables). However, one must consider the adherent cells where a direct transfer of PERLs from the contact material into the cells may occur.

With the increasing usage of single-use components, specialty packaging devices, unique drug delivery platforms and novel container closure systems E&L study design has become increasingly complex requiring highly technical skills and unique Analytical instrumentation.

Conclusions

- E & L Studies are a regulatory requirement for DP submission and approval
- All Polymers and Plastics can be a source of Extractables and Product Adulterating Leachables
- E & L studies should be designed in line with promulgated parameters with patient and product RISKS being considered
- Study design should consider liquid phase absorption AND direct transfer of extractables
- E&L study design has become increasingly complex and require highly skilled and technical teams to conduct the investigations.

E&L White Paper Available Now



The full document can be found on the BPSA website, along with over a dozen additional white papers and technical documents

https://bpsalliance.org/technical-guides/

Questions?

Thank You

BPSA Speaker Series Brought To You By…

BPSA Sustaining Sponsors

AdvantaPURE
Broadley James
bürkert FLUID CONTROL SYSTEMS
CHEMIC LABORATORIES, INC.
CPC
cytiva
Entegris
MilliporeSigma
Nordson MEDICAL
PALL Biotech
PENDOTECH Adding Value To Your Process
RENOLIT Rely on it.
SAINT-GOBAIN
SaniSure Be sure.
SARTORIUS
Savillex
ThermoFisher SCIENTIFIC

Created in Cooperation With…

socma
SOLUTIONS FOR SPECIALTIES

BAHP
CENTER FOR BABY AND ADULT HYGIENE PRODUCTS

BPSA
Bio-Process Systems Alliance
Advancing Single-Use Worldwide

CPMA
Color Pigments Manufacturers Association

INFORM · ADVOCATE · ACT
Flexible Vinyl Alliance

IPA

Ott Consulting Group LLC

BPSA 2020 Speaker Series

Wednesday, October 21, 2020
10:00-11:15 AM EDT

Building an Integrity Assurance Approach in Single-Use Processing through the SUS Whole Life Cycle