

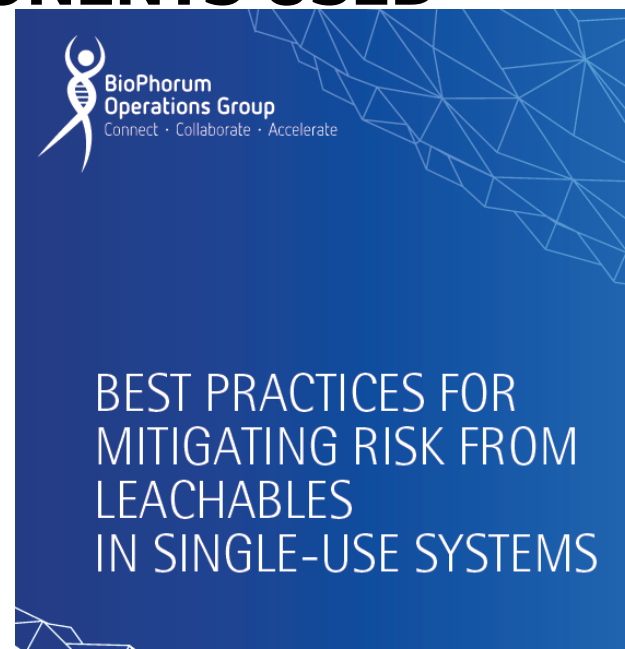


BPOG'S BEST PRACTICES GUIDELINE FOR MITIGATING RISK FROM LEACHABLES IN POLYMERIC SINGLE-USE COMPONENTS USED IN BIOMANUFACTURING

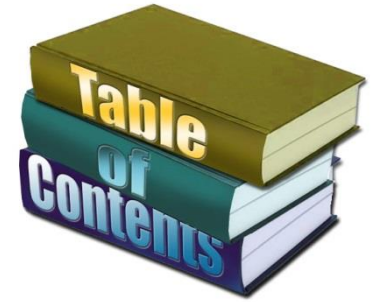
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BioProduction, Dublin
19-20 Oct 2016



Outline



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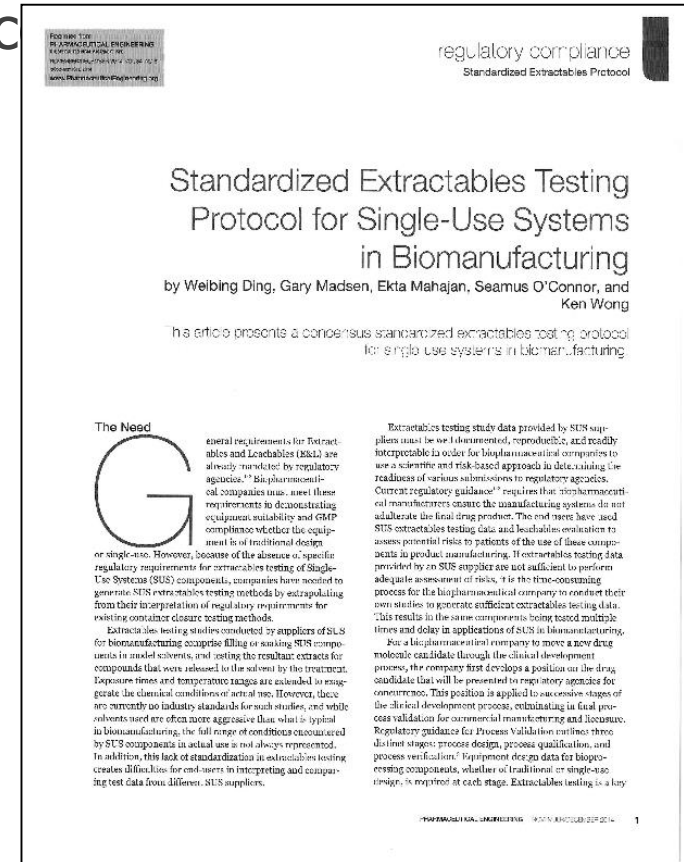
Acknowledgement:

Disposables L2 Leadership Team Members

BPOG Program Directors

BPOG's Disposable Working Group - E&L Subteams

- BPOG's extractable protocol as a user requirement:
 - Title "Standardized Extractables Testing Protocol for Single-Use Systems in Biomanufacturing"
 - Published in Nov 2014 Pharmaceutical Engineering Journal (ISPE)
 - Implemented by 18 companies as SUR
- BPOG's Leachable Study Best Practices
 - Risk assessment - using a standard model approach
 - Leachable study design for Single-Use components
 - Leachable test method(s) – analytical considerations



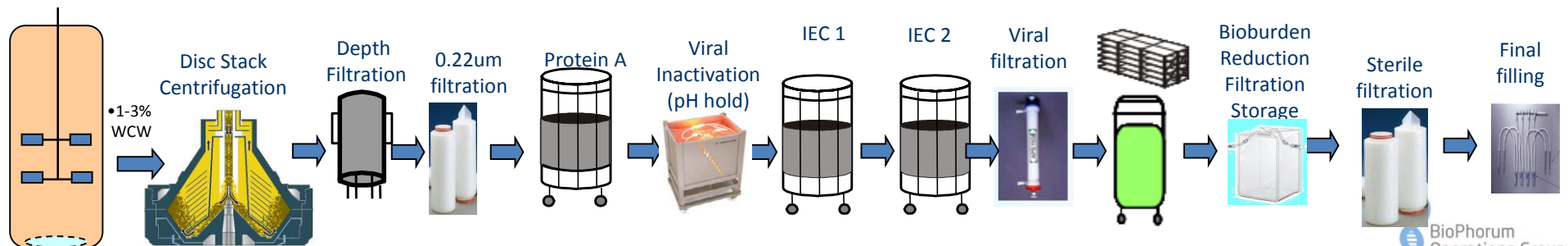
Introduction - Key Definitions: Extractable & Leachable (E&L)

- Extractables
 - Chemical entities that are able to be extracted from a component of a process system into a solvent under controlled conditions that are usually more aggressive than normal operating conditions.



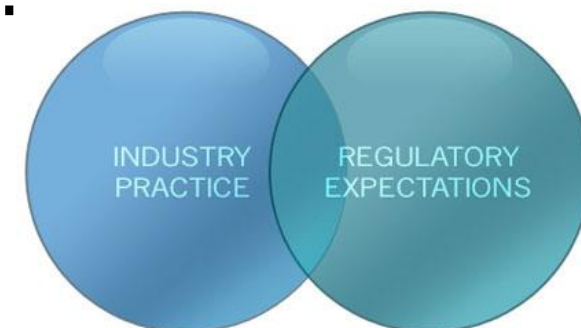
- Leachables
 - Chemical entities which come from SUS components during normal use

Typical bioprocess – cell culture to final filling



Introduction - Regulatory Expectation: Extractable & Leachable (E&L)

- E&L data for BLA submission is a MUST have
- Past regulatory requests: FDA, EMEA, TGA, CFDA, Malaysia and Thailand authorities
- Ingrid Markovic (CBER) presentation at May 2014 ASTM workshop, Boston, MA – Keys Take Away:
 - E&L are required by law:
 - **21CFR600.11(b) Equipment**
 - 21CFR600.11(h) Containers and Closures
 - E&L Risks: Product Quality, Safety and Efficacy
 - E&L studies are required to support the overall Product Quality
 - Leachable studies must be incorporated into stability program and considered when establishing product expiry



Introduction - Regulatory Expectation: Extractable & Leachable (E&L)...cont.

- **Destry M. Sullivan, FDA CBER**

CBER/DMPQ Communication to Regulated Industry

IBC Single Use Conference 2010

- *...with respect to extractable and leachable data...It is ultimately your (end users) 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.).*

- **CBER Agents**

SUS Cross Organizational Meeting, PDA headquarter, Washington DC, May 2014

- *... end users are required to demonstrate how the suppliers' extractable data relate to their intended use and specifically show the relevancy to their process conditions...*

Introduction - Regulatory Expectation: Extractable & Leachable (E&L)...cont.

- **21 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.” Non-reactive and non-absorbing properties of materials are usually controlled by process design and by the selection of raw materials and manufacturing components.*



- **EMA 2016 guideline on process validation for the manufacture of biotechnology-derived active substances**

- *When single use equipment is used in evaluation studies, consideration should be given to leachables and extractables. Information should be provided on the nature and amount of potential leachables, and the removal of such impurities. Besides data, this normally includes a risk assessment.*

Introduction - Regulatory Expectation: Extractable & Leachable (E&L)...cont.

- **ICH Q9 guideline on Quality Risk Management**

It is important to understand that product quality should be maintained throughout the product lifecycle such that the attributes that are important to the quality of the drug (medicinal) product remain consistent with those used in the clinical studies.

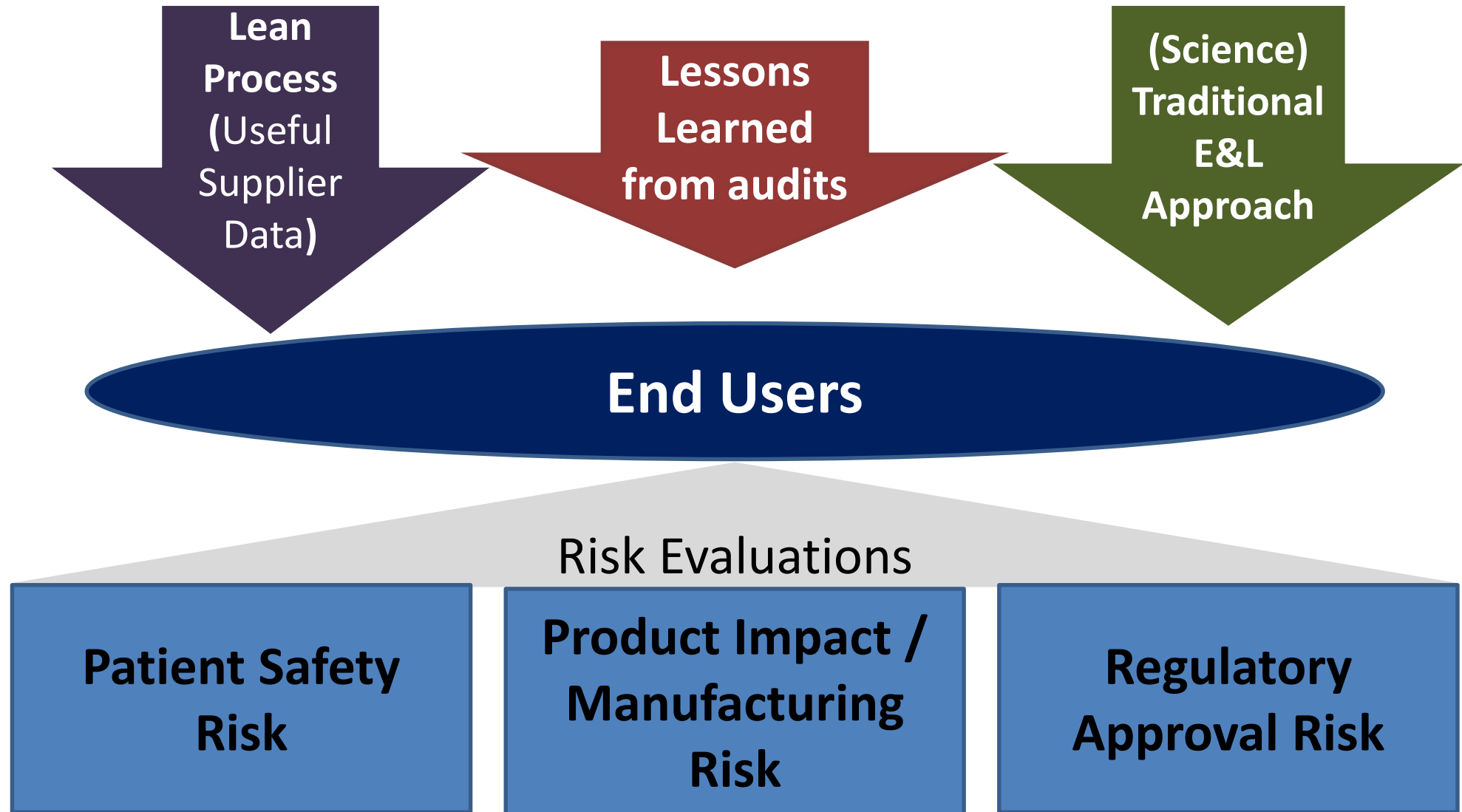


Introduction - Regulatory Expectation: Extractable & Leachable (E&L)...cont.

- **Biopharmaceutical manufacturer is responsible for examining various materials used in the manufacture of a biological drug substance (DS) to ensure that the materials are appropriate and meet defined specifications for:**
 - Process performance: Impact on process performance, (i.e., cell growth, etc.)
 - Product quality: Impact on final drug product quality (i.e. stability, activity, etc.)
 - Toxicological risk: Final Drug Product (FDP) safety



End Users Challenges (External and Internal)



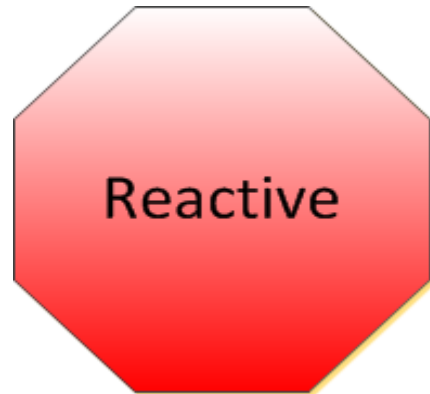
BPOG's Leachables Best Practices Guideline - Purpose

- Present a practical and adaptable approach for assessing SUS for the risks they present to biopharmaceutical patient safety.
- Where necessary, for designing studies to assess polymeric SUS components, using appropriate analytical methodologies for detection of potential leachable compounds.
- The methodology presented is intended to be robust and yet also sufficiently flexible to be adapted appropriately to each company's needs.



BPOG E/L Risk Assessment Regulatory Requirement - CFR 211.65a

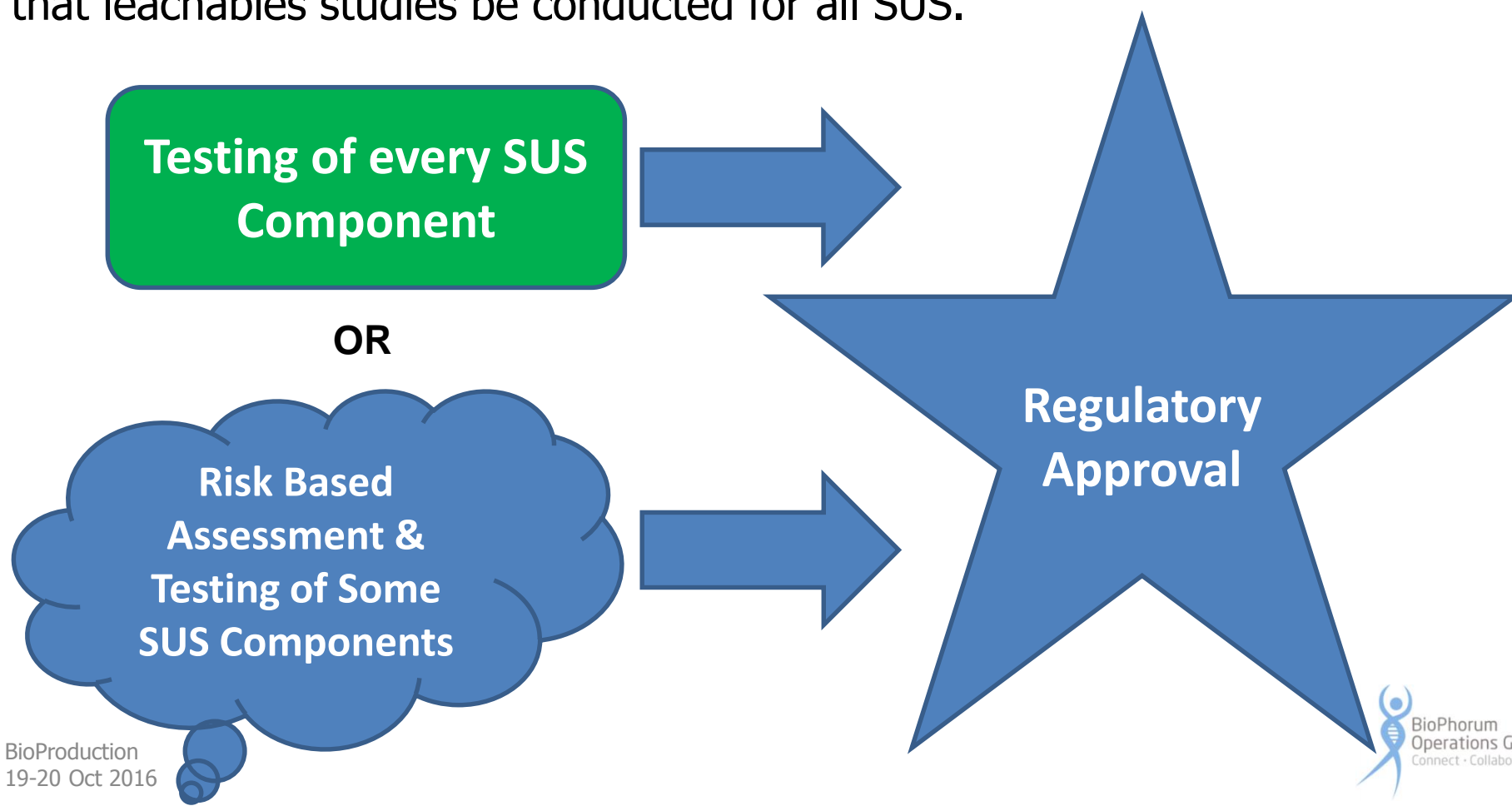
- Equipment used in the manufacture of drug substance shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be:



Single-use systems, also referred to as processing materials, must be evaluated for their propensity to contribute leachables to the drug substance / final drug product.

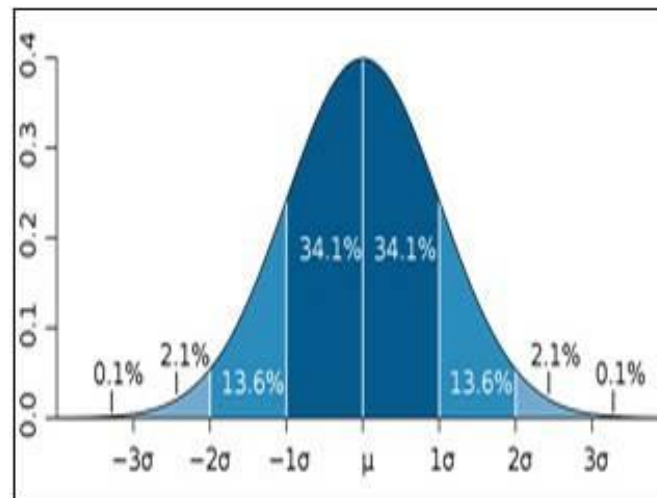
BPOG Leachables Risk Assessment Benefits

- Use of this guide will help to determine where there are significant risks that may require additional studies to better understand patient risk, if any, relating to the polymeric SUS components used in the drug manufacturing process and the conditions under which the SUS is used within that process.
- It is important to note a risk-based approach does not automatically require that leachables studies be conducted for all SUS.



BPOG Leachables Risk Assessment Challenge

- Efficiently design studies that support a full range of manufacturing process conditions and that will provide a thorough understanding of leachables that may be present within products and in process streams.
- Analytical techniques and considerations to help end users effectively detect and identify leachable compounds occurring within products or in process streams that have resulted from contact with SUS under conditions potentially experienced in actual manufacturing processes.
- Best practices will help to standardize approaches to identifying leachables risks, from a patient safety point of view, that warrant further study.

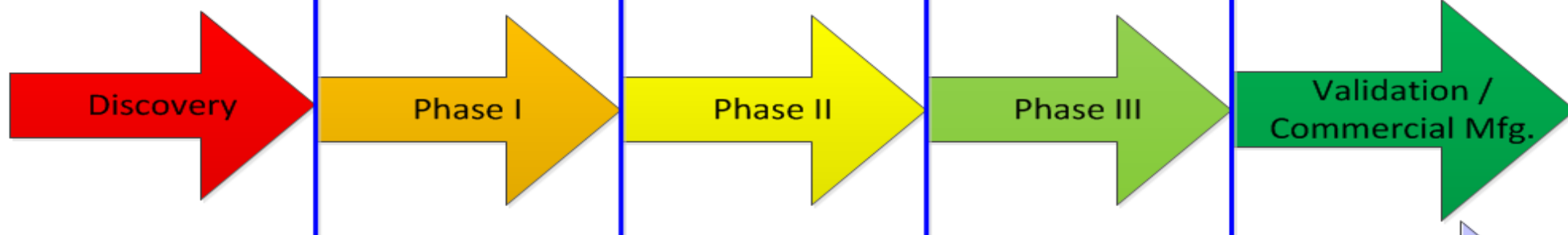


BPOG Leachables Risk Assessment

- BPOGs recommendations on key attributes to be considered for Leachables Risk Assessment
 - Comes from a collaboration across member companies.
 - Provides recommendations that also provide flexibility to allow appropriate adapted to each company's needs.

BPOG E/L Risk Assessment - Proposed Phased Approach

DRUG DEVELOPMENT PHASES



Knowledge / Experience Gained

Considerations during Discovery, Phase I & II

1. Material of construction
2. Origin of material, potential for transmittable pathological agents
3. Product storage and shipping conditions, expiration dating
4. Manufacturer (site, licensing, quality history, etc.)
5. Assembly and packaging conditions, distributor (site, licensing, quality history, etc.)
6. Sterilization requirements and methods used
7. Physical and Chemical Compatibility with manufacturing conditions
8. USP Class VI compliance, CFR Part 21, Subpart 177, 178, 179 & 182; EP 3.1.1, EP 3.1.9, as applicable for tubing, ISO 10993
9. Extractables Profile (vendor provided, historical database or combination of both)

Extractable / Leachables Assessment

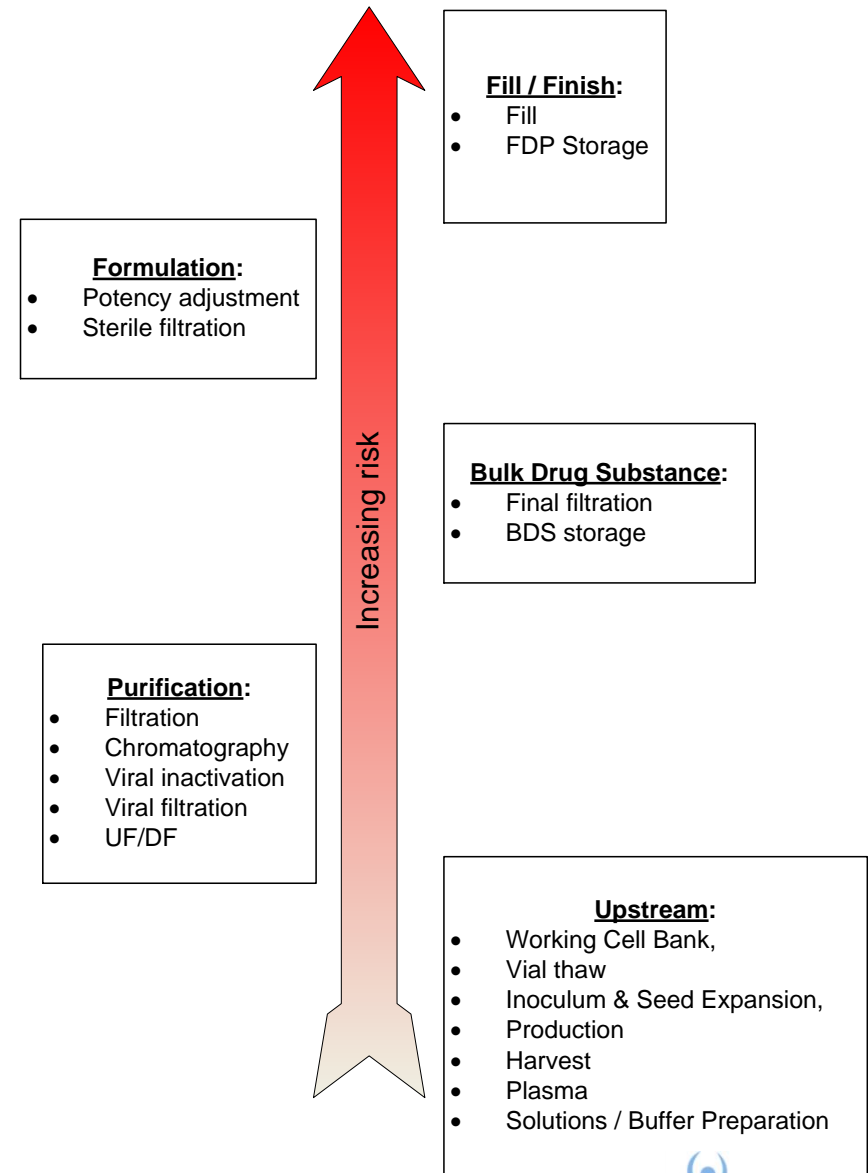
1. Extractables Profile
2. Risk Assessment / Evaluation
3. Toxicological Assessment
4. Leachables Study / Report

Regulatory Filing

BPOG Leachables Risk Assessment - 5 Key Attributes to Consider

1. Distance along production stream (DAS) or Proximity to API

- Any material, leaching into an intermediate, e.g. buffer used in process steps ($> n-2$) prior to clearance steps is less likely to end up in the API production stream



BPOG E/L Risk Assessment - 5 Key Attributes to Consider (ctd).

2. Exposure Temperature (ET)

- Higher operating temperatures increase the possibility of leachables.

3. Exposure Duration (ED)

- Longer exposure durations increase the possibility of leaching impurities

4. Process Fluid Interaction (PFI)

- **Material Compatibility**
- Increasing solvation power of the process fluid to organic increases penetration into the polymer thereby increasing the possibility of leaching

5. Dilution Ratio (DR)

- **(Exposure Surface Area (ESA) to process liquid Volume (V) Ratio)**
- Any extractables & leachables will be diluted by the process fluid. A higher dilution ratio increases the concentration of any extractables & leachables representing a higher risk

■ Pre-Treatment Steps

- Any pre-treatment steps like autoclaving or gamma irradiation, WFI flushes, etc., may result in a change in the extractables and leachables from that material.

■ Process Performance

- Any extractables / leachables may potential to impact not just product quality but also process performance.
- Ex: leachables impacting cell growth of certain cell lines (Irgafos antioxidant degradation to bis-(2,4-di-tert-butylphenyl)phosphate (bDtBPP)).

Example Leachable Risk Scoring – Distance Along Production Stream (DAS) & Exposure Temperature (ET)

Consideration	Ratings		Weight
Distance along production stream (DAS)	1	Synthesis: Vial thaw, inoculum, expansion, production, harvest, plasma	0.4
	3	Purification: Affinity chromatography, viral inactivation, ion exchange chromatography, viral filtration, UF/DF	
	5	Bulk Drug Substance: Formulation, Filtration, BDS storage	
	9	Final formulation, fill/finish Potency adjustment, sterile filtration, filling	
Exposure Temperature (ET)	1	Frozen	0.15
	3	0 – 8 °C	
	5	> 8°C to < 30°C	
	9	≥ 30°C	

Example Leachable Risk Scoring – Exposure Duration (ED) & Process Fluid Interaction (PFI)

Consideration	Ratings		Weight
Exposure Duration (ED)	1	Transient (≤ 60 minutes)	0.15
	3	Short (≤ 24 hours)	
	5	Medium (≤ 7 days)	
	9	Long (> 1 week)	
Process-Fluid Interaction (PFI)	1	Limited penetration into polymeric component (i.e., Water)	0.15
	3	Low solvation power or low penetration of polymeric component (e.g., neutral pH without organics, surfactants, etc.)	
	5	Medium solvation power or medium penetration of polymeric component (e.g., surfactant low concentration organics, high/low pH solutions without organics/detergents)	
	9	High solvation power or high penetration of polymeric component	

Example Leachable Risk Scoring – Dilution Ratio (DR)

Consideration	Ratings		Weight
Dilution Ratio (DR)	1	$< 1 \times 10^{-03} \text{ m}^2/\text{L}$	0.15
	3	$1 \times 10^{-02} \text{ to } 1 \times 10^{-03} \text{ m}^2/\text{L}$	
	5	$1 \times 10^{-01} \text{ to } 1 \times 10^{-02} \text{ m}^2/\text{L}$	
	9	$> 1 \times 10^{-01} \text{ m}^2/\text{L}$	

BPOG E/L Risk Assessment

Example of Proposed Leachables Risk Scoring

Leachables Propensity Rating (LPR)	Calculated by the following equation: $LPR = DAS * Weight (0.4) + ET * Weight (0.15) + ED * Weight (0.15) + PFI * Weight (0.15) + DR * Weight (0.15)$ Possible range: 1.0 to 9.0
Suggested Leachables Risk Rating	6.3 to 9.0: High 3.7 to 6.2: Medium 1.0 to 3.6: Low

Abbreviations: DAS = distance along the production stream; DR = dilution ratio; ED = exposure duration; ET = exposure temperature; LPR = Leachables Propensity Ratio; PFI = process fluid interaction.

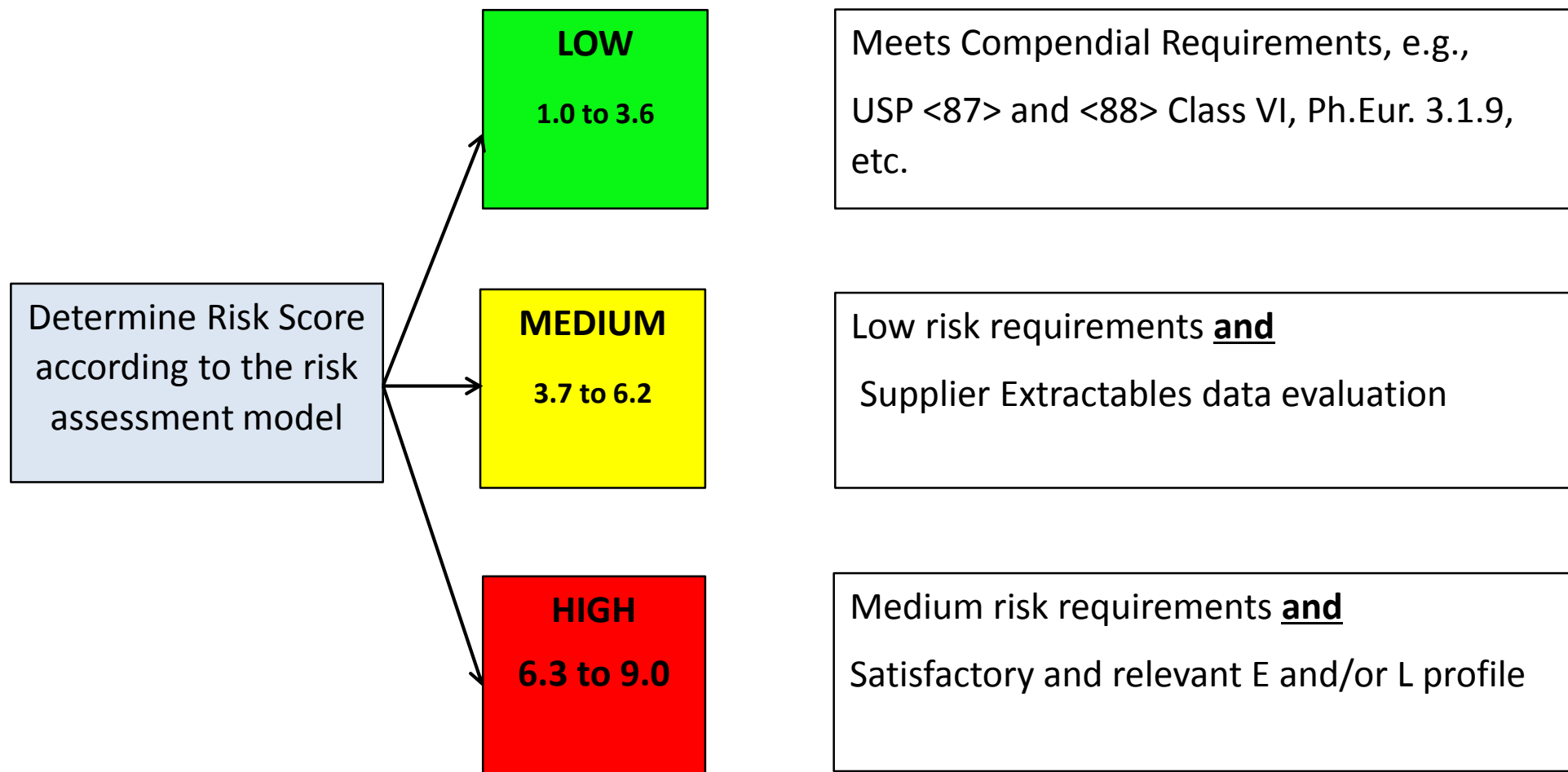
Road Test of Risk Assessment Model

- Compared model with the member companies' internal approaches.

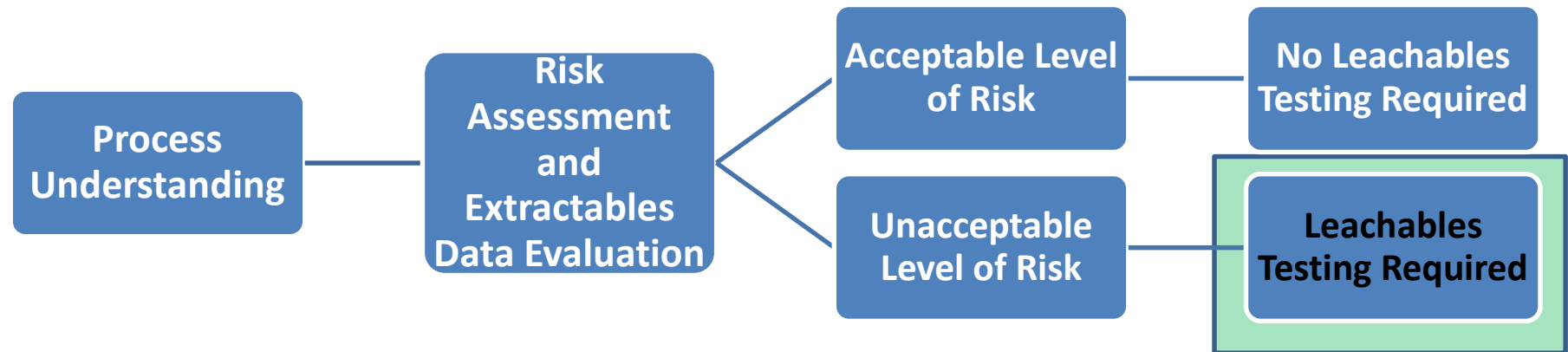


- The model aligns well with the current practices!

Suggested Requirements Based on Leachables Risk Categorization of Polymeric Components



- **Single Use System/Consumable Qualification Process**
 - Biopharmaceutical manufacturers must demonstrate that processing components do not impact the quality of the drug product.
 - Drug processing components must not be additive, reactive, or absorptive.



■ Study Design

• Robust

- Supports full range of possible manufacturing or storage conditions

• Efficient

• Appropriate for component type

○ Representative processing component samples

- Storage containers
- Filters
- Other processing components
- Appropriate pre-treatment used (e.g., steam sterilized or gamma-irradiated, flushes/rinses, etc.)
- Mimic process fluids where possible

- **Extraction Mode**

- Dynamic
 - Rocker table
- Static

- **Contact Duration**

- Must adequately cover the full range of potential time for in-process usage
- Exceed maximum process time for worst-case approach
- Long Term Studies (≥ 6 months)
 - Consider multiple time points over full course
 - Each time point with its own sample and control
 - Mitigates risks of contamination from aliquoting and changes in exposed surface area to volume ratio over the course of a study

- **Temperature**

- Bracket the high end of potential in-process exposure

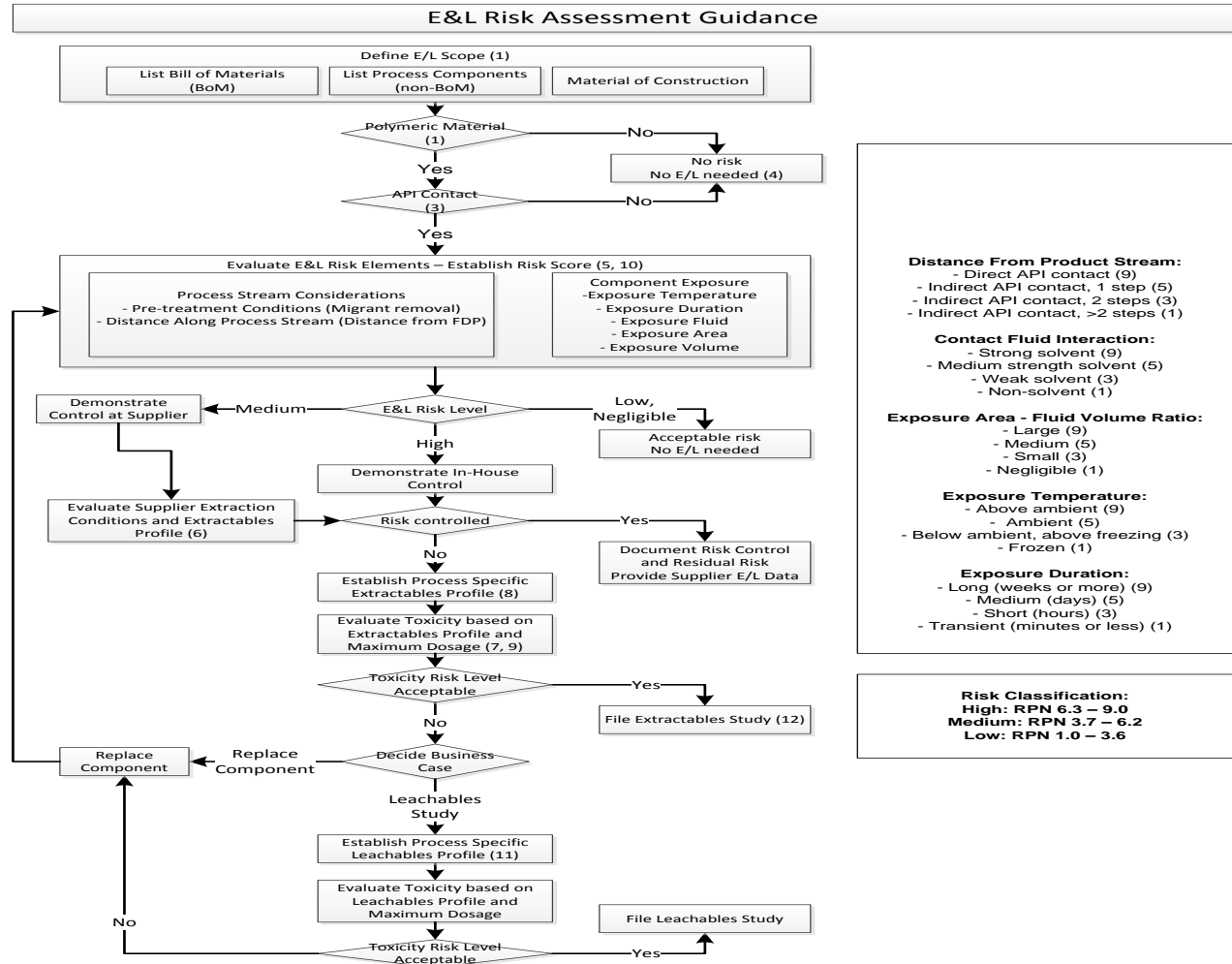
Recommended Analytical Techniques for Leachables Identification and Quantification

1. LC-UV-MS: HPLC with UV Photodiode Array Detection and Mass Spectrometry
2. GC-MS: Direct Injection Gas Chromatography with Mass Spectrometry
3. Inductively-Coupled Plasma with Mass Spectrometric Detection (ICP-MS) or with Optical Emission Spectrometric Detection (ICP-OES)
4. Ion Chromatography(IC)

Recommended operating parameters for each are provided in the guidance!

BPOG E/L Risk Evaluation PFD

There will be
a flowchart to
aid the
process!!!



Conclusion: Benefits of Best Practice Guide for Leachables Study Design

Benefits

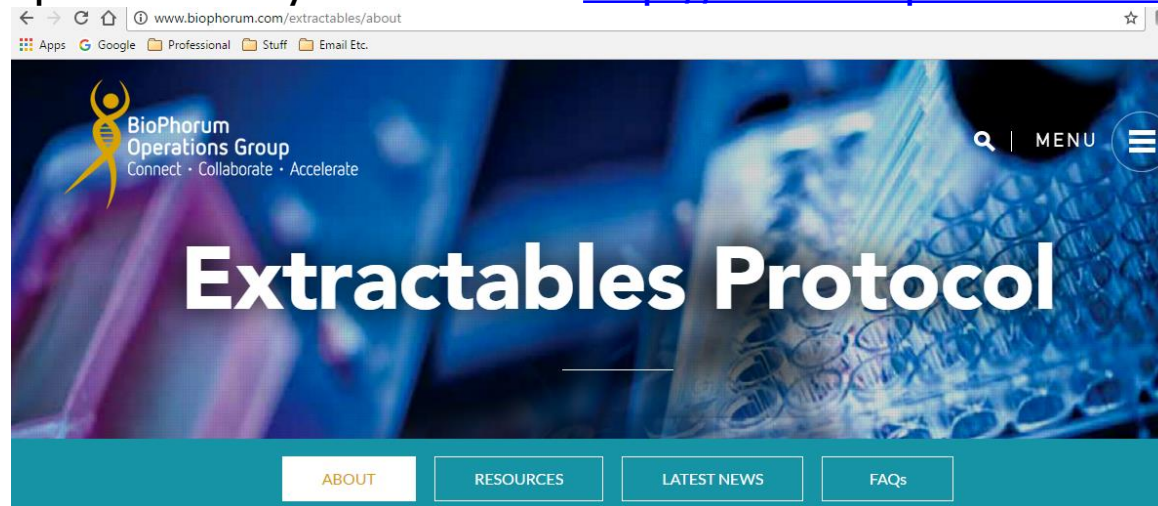
- Provides a standardised framework for industry
 - Adaptable: Can be modified to fit the needs of any company
 - Provides industry with key parameters to consider for an effective study design.
 - Increases study efficiency
 - Increase study robustness
 - Assists regulatory bodies in evaluating the strength of data packages presented by companies
 - Should reduce the need for leachables testing (i.e., overall number of specific studies – extractables data may suffice especially data provided in accordance with the BPOG extractables protocol!)

**Ultimately benefits patients through
increased assurance of safety**

BPOG Approach to Leachables

- BPOG will publish the finalized best practice guide in (Jan 2017) for **Mitigating Risk from Leachables in Polymeric Single Use Systems Used in Biopharmaceutical Manufacturing**
- See <http://www.biophorum.com/> for details.
- For further information contact Gerry McAuley – E&L Team Facilitator (gerry@biophorum.com)

The extractables protocol may be found at <http://www.biophorum.com/extractables/about>



THANKS!
a  bunch

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