The Use of BPOG Generated Extractables Data for Toxicological Assessment

Sade Mokuolu, Ph.D Group Product Compliance Manager, WMFTG

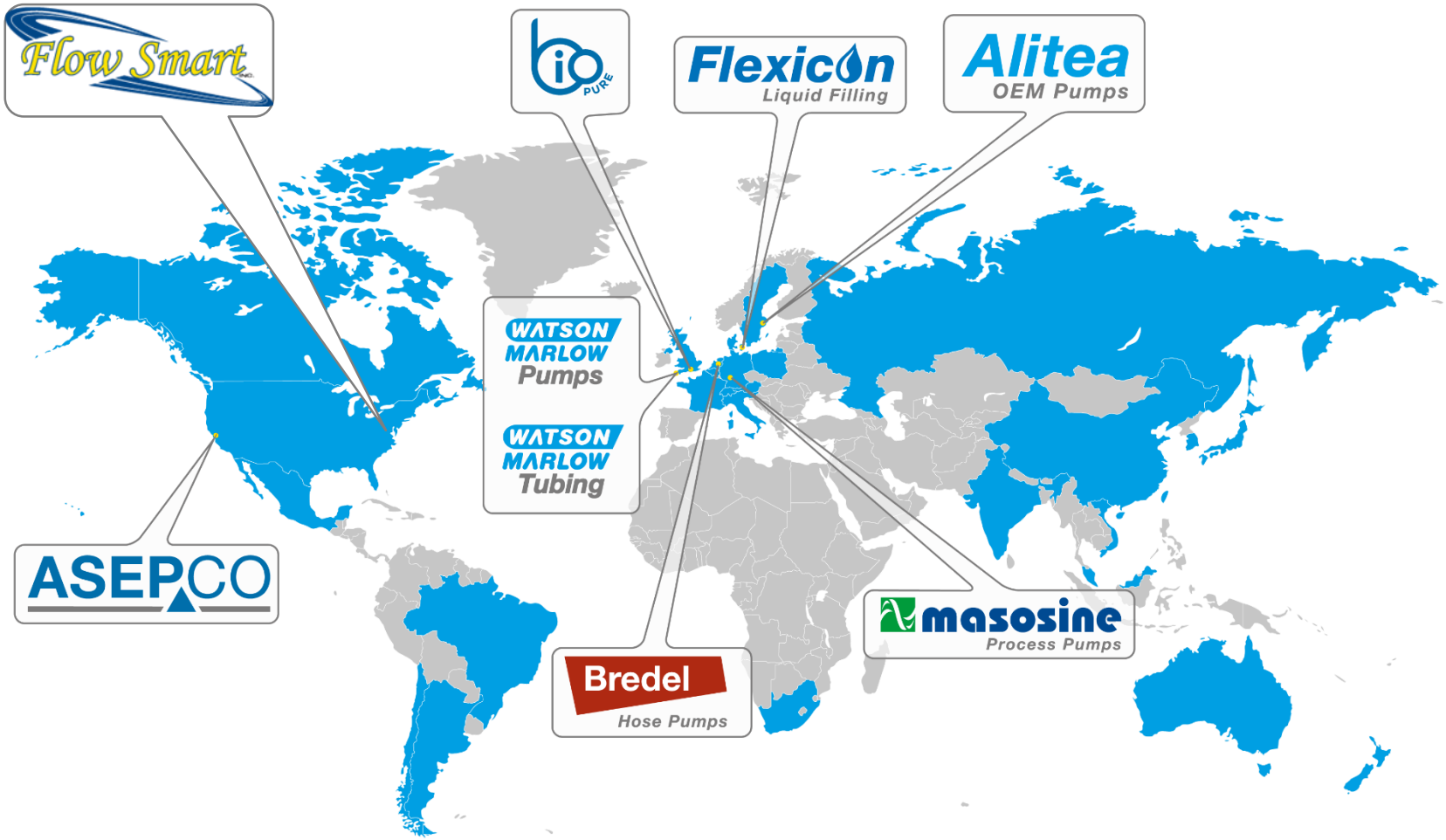
PDA Brazil 2017

Disclaimer

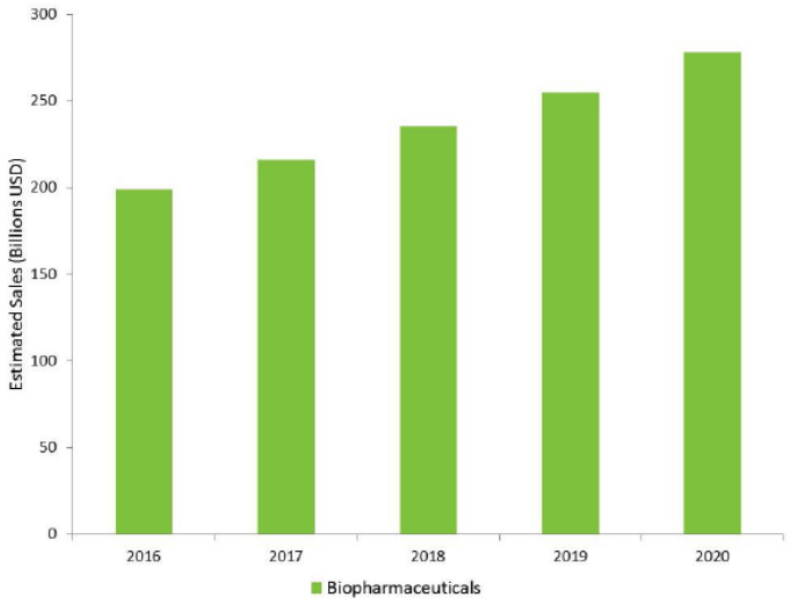
Overview

- Polymers used in SUS
- Extractables
- BPOG test Protocol
- Testing of WMFTG products to BPOG
- Results
- Risk assessment
- Toxicological evaluations
- Recommendations

Watson Marlow Fluid Technology Group



Biopharmaceutical Manufacturing



- Biopharm sales reached $154B in 2015 (projected to keep increasing)
- Approximately 80% of biopharma products are produced in mammalian cell cultures
- Smaller batch sizes and ambient processing conditions has facilitated the use of SUS
- SUS technologies has acted as an ‘enabler’ for the manufacture of therapeutics, which are helping patients to live longer and disease free

Stainless Steel – Legacy manufacturing model

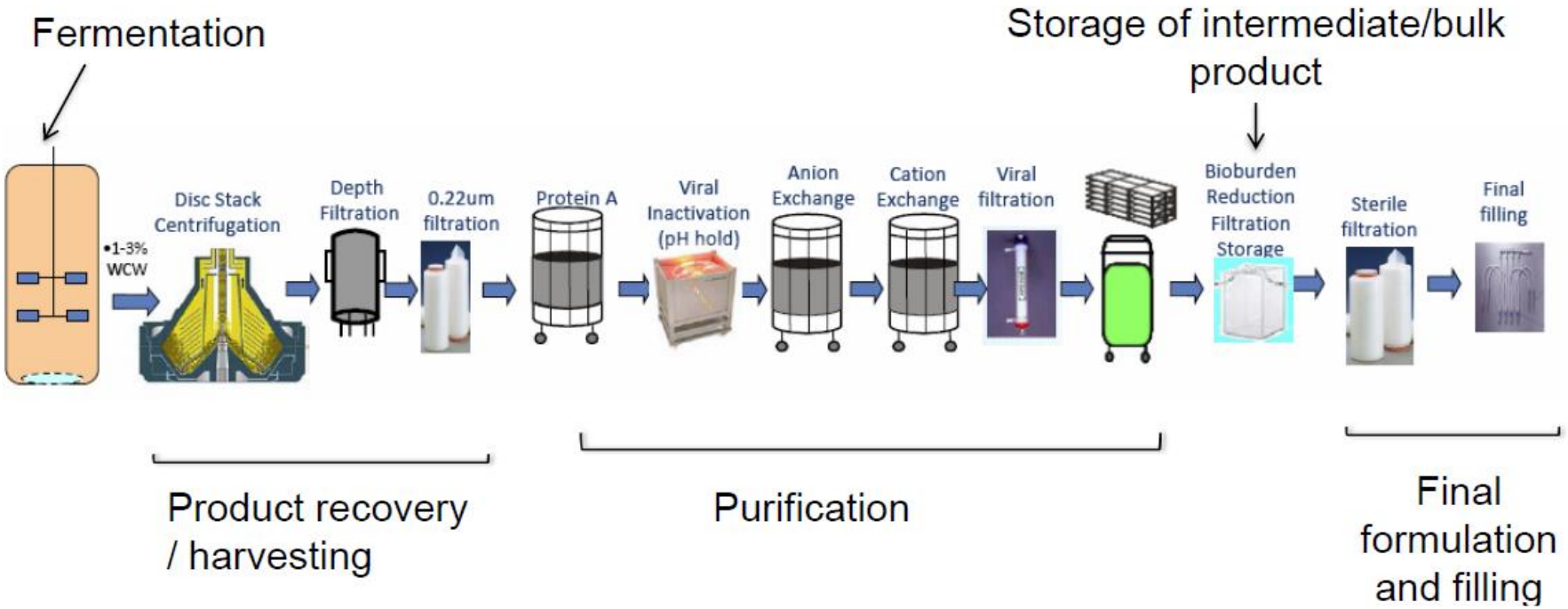
- Historically, processing equipment for drug products (particularly small molecule APIs) consists
  - Hastelalloy
  - Stainless steel
  - Silicon from tubing
  - Filter – polyester :drainage layers
  - Filter - PVDF, PES, nylon: membrane

Deemed safe – based on knowledge and previous experience

Benefits to using Single Use Systems

- Cost Effectiveness and Economic Advantages
  - Reduction in Capital Expenditure
  - Reduction in Facility Footprint
- Safety and Quality
  - Reduction in Cross Contamination
  - Less Cleaning Validation
  - Improved Aseptic containment
- Operating Efficiencies
  - Faster Batch turn-around
- Sustainability
  - Reduction in use of water, energy and chemicals

Typical Biopharmaceutical manufacturing



Polymers used in SUS

Even in simple SUS assemblies, there may be numerous different types of materials present

They include

- Silicone
- Polypropylene
- EPDM
- Nylon
- Polycarbonate
- Polyethylene

There is a potential for leaching when these materials are in contact with fluids

Compounds used in polymer manufacturing

- Antioxidants
- Lubricants
- Acid Scavengers
- Peroxides
- Cross linking agents
- Adhesives
- Colourants
- Antistatics
- Monomers
- Pigments

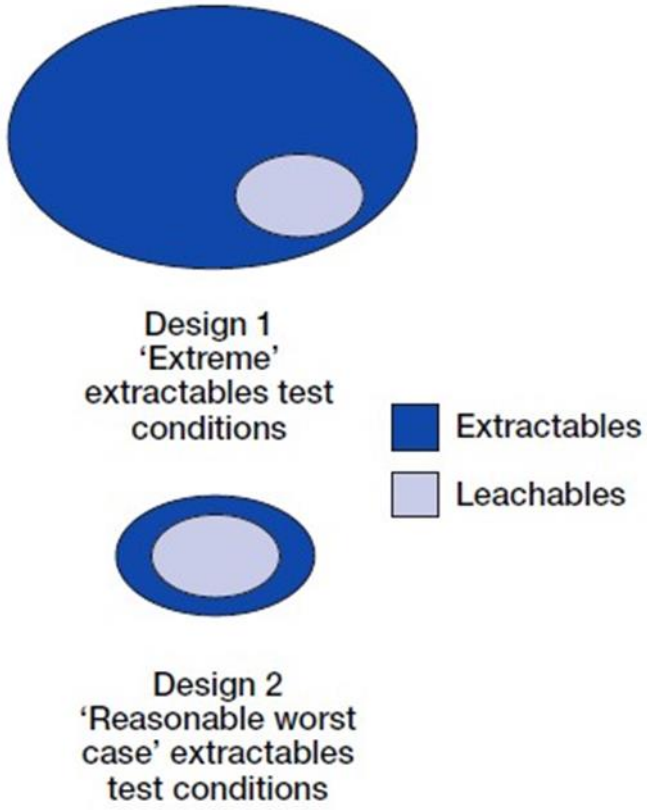
Definitions

Extractables

Chemical compounds that migrate from any product contact material, when exposed to an appropriate solvent under exaggerated conditions of time and temperature.

Leachables

Chemical compounds, typically a subset of extractables, that migrate into the drug formulation from any product contact material, as a result of direct contact with the drug formulation under normal process conditions or accelerated storage conditions and are found in the final drug product.



Regulatory Guidance

U.S.

Title 21 of the Code of Federal Regulations (CFR) 211.65 (1)

"...Equipment shall be constructed so *that* ***surfaces*** *that contact components*, in-process materials or drug products ***shall not be reactive, additive or adsorptive so as to alter safety, identity, strength, quality or purity*** *of the drug product beyond the official or other established requirements*..."

EUROPE

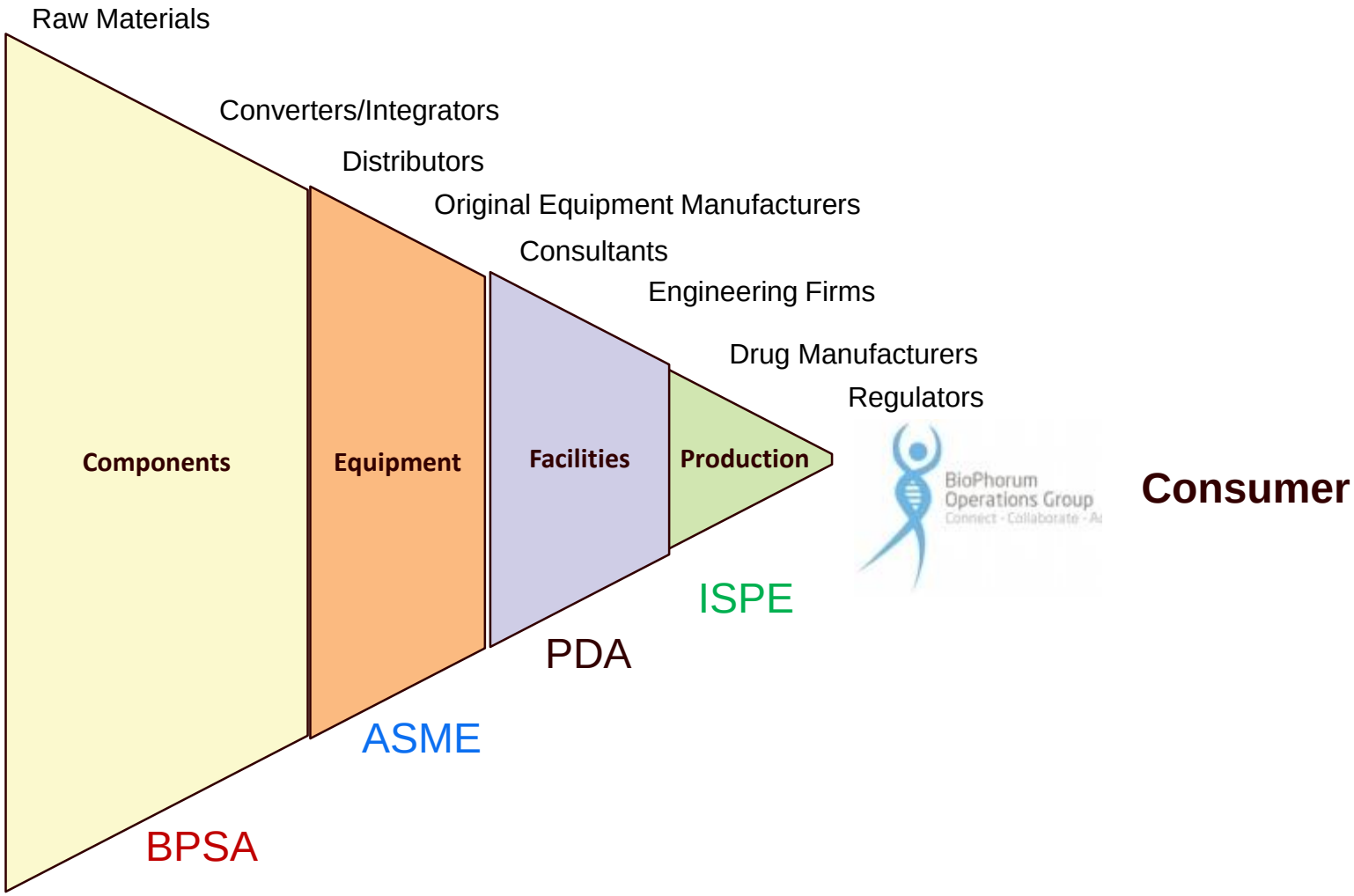
ICH Q7 – GMP Practice Guide

"...Equipment should not be constructed so that *surfaces that contact raw materials, intermediates or API's* ***do not alter the quality of the intermediates and API's*** *beyond the official or other established specifications..."*

EU – Good Manufacturing Practices

"...Production Equipment should 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... That it will affect the Quality of the Product..."

Organisations working to SUS implementation



BPSA (Bioprocess Systems Alliance)

Aim: To facilitate the implementation of single use systems into biopharmaceutical manufacturing

- Formed in 2004
- Trade association of suppliers and some end-users
- Primarily single use component suppliers, integrators, polymer manufacturers and some end user groups
- Safe harbour for dialogue between suppliers
- End-user/ supplier forums
- Best practice guides

BPSA
Bio-Process Systems Alliance

BPOG (Biophorum Operations Group)

Value Add – win win situation

- **Suppliers**
  - Consensus End User Requirement for Extractables – one Voice of The Customer (BPOG companies represent more than 80% of the global commercial biopharmaceutical capacity)
  - Know what extractable protocol to follow – clear, common reporting format
  - Solid starting point for the creation of future Standards

- **End Users**
  - Consensus Extractables Protocol – enables users to screen and select SUS products efficiently and effectively
  - Solid starting point for risk based decisions around further testing
  - Know exactly what will be available from suppliers
  - Reliable, consistent extractable data
  - Able to make rapid early decisions to move SUS forward along the developmental path
  - Fewer regulatory questions by having a consistent data package from all suppliers

- **Regulators**
  - Informs the development of standards
  - Gives confidence in the industry Supply Chain and helps to manage regulatory expectations

The journey to the solvent selection

- Model Solvents
  - WFI pH 11-12
  - 5M NaCl
  - PBS
  - 50% Ethanol
  - WFI pH 2
  - 20% Polysorbate 20
  - WFI neutral

We started here and moved on to ....

- Model Solvents
  - WFI pH 11-12 (0.5N NaOH)
  - 5M NaCl
  - PBS
  - 50% Ethanol
  - WFI pH 2 (0.1M Phosphoric acid)
  - **10%** Polysorbate 20
  - **10% Polysorbate 80**
  - WFI neutral

Current position .... note that we are still considering that certain solvents may be skipped:
1.If material is incompatible;
2.If the intended use of the component will not be exposed to such extreme

- Model Solvents
  - **0.5N NaOH**
  - 5M NaCl
  - 50% Ethanol
  - **0.1M Phosphoric acid**
  - **1% Polysorbate 80**
  - WFI neutral

Disposable Solutions

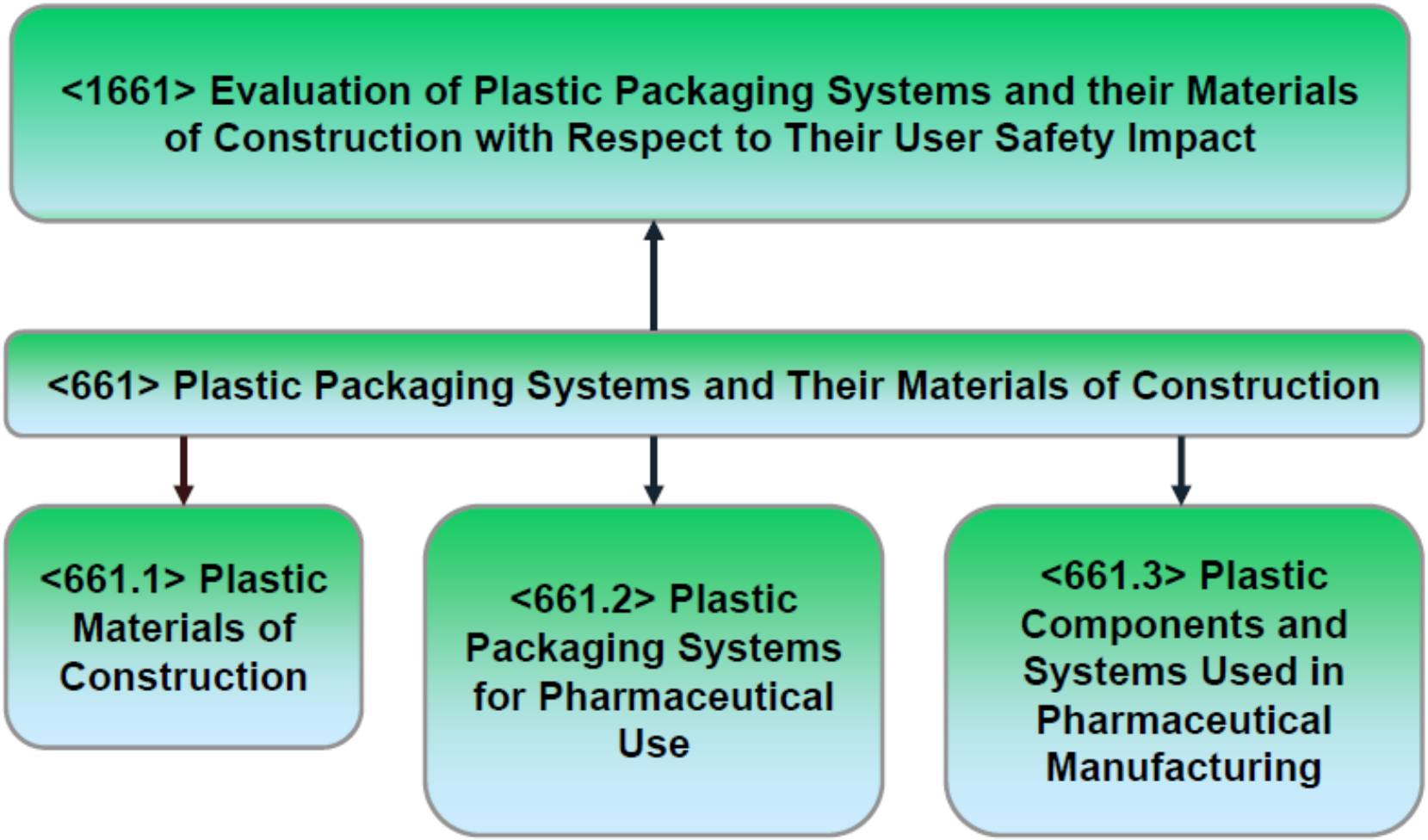
BioPhorum Operations Group
Connect • Collaborate • Accelerate

On the horizon

USP

- To improve Global Health through public standards and related programs that help to ensure the quality, safety and benefit of medicines and foods.
- Achieved by publishing monographs and referenced general chapters
- Official purpose – to provide standards for plastic materials /components for medical devices (pharma, biologics, etc)

Plastic packaging materials/ components

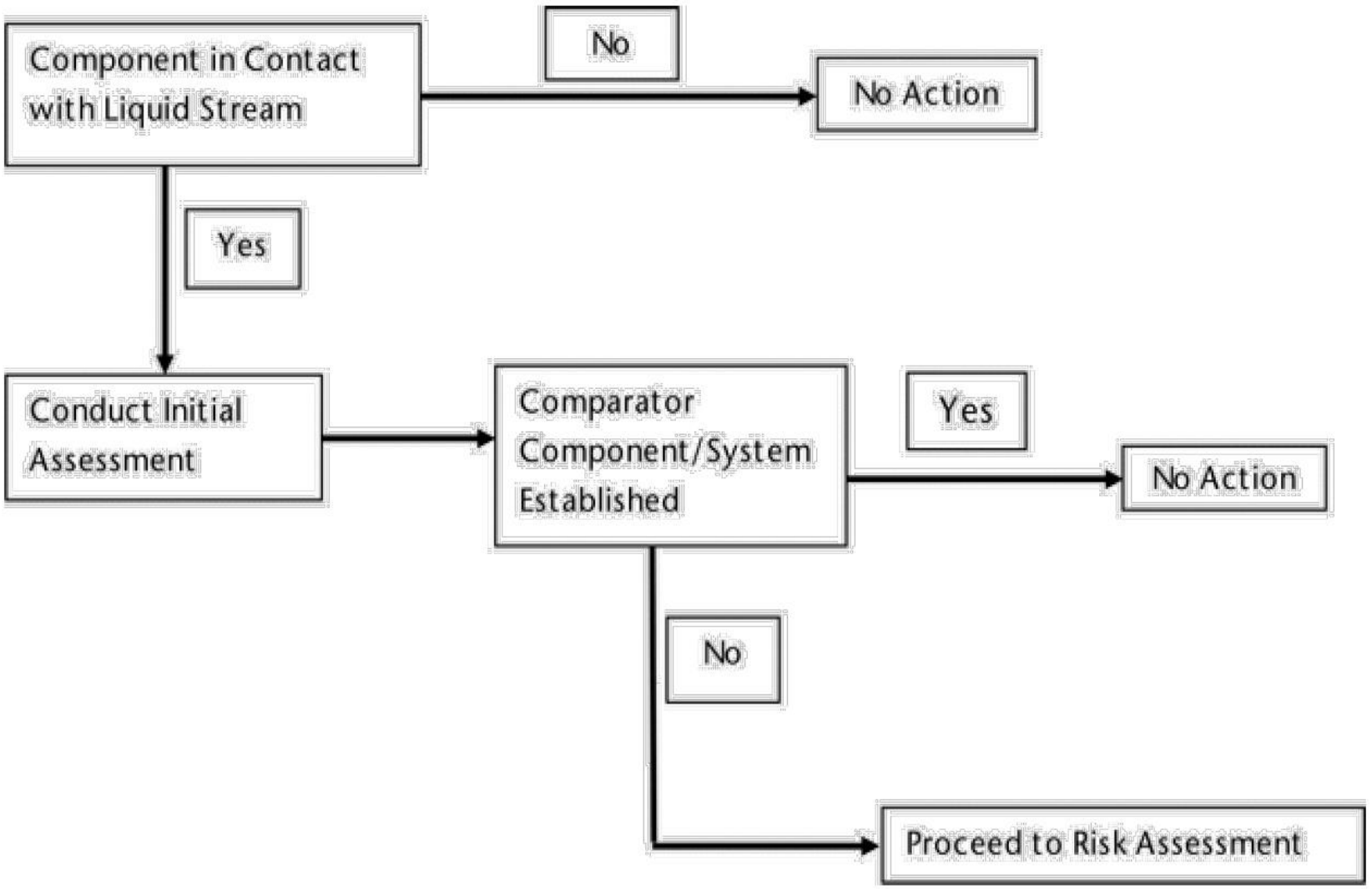


USP 665 - Pending

USP 665 – Guideline for Plastics used in single use and multi use assemblies for pharmaceutical manufacturing

- Focusing on 80:20 philosophy
- For extractables don’t preclude additional testing with more solvents
- Set acceptable level of testing
- BPOG – industry end user consensus document
- USP 665 because it is a chapter less than 1000, enforceable by FDA

USP 665 - Pending



USP risk criteria based on dosage forms

USP have in chapter 665 developed a risk level table

Risk level	Dosage Forms	Characterisation level	Test requirements
A	Oral	Baseline assessment	<87> Physiochemical tests Extractables metals Additives (ref to 21 CFR)
B	Other dosages	Expanded baseline	Same but additives tested and <88>
C	Other dosages	Full assessment	<87> and <88> Extractables studies to identify organic compounds Physiochemical tests

USP solvents

Extraction	Solution composition	Test perfomed
Solution C1	Water	Absorbance, acidity or alkalinity, TOC
Solution C2	0.1 N HCl	Extractables metals
Solution C3	Acid/salt buffer, pH 3	Organic extractables
Solution C4	Phosphate buffer, pH 10	Organic extractables
Solution C5	Ethanol:water (50:50)	Organic extractables

pH range may be adjusted depending on the compatibility of the component

WMFTG studies following principles from the BPOG protocol

BPOG extractables test protocol

Solvents	Temperature
WFI	25°C
1% Polysorbate 80	40 °C
50% Ethanol	
5M Sodium Chloride	
0.1 M Phosphoric acid	
0.5 N Sodium Hydroxide	

Time Points

- component dependent

Specific guidance

- Pre treatment,
- Surface Area to volume ratios
- Analysis of semi volatiles, non volatiles and elemental impurities

Elemental impurities
(as described in ICH Q3D and USP 232)

Single use components samples used for study

- Pumpsil tubing (Pt cured Silicone tubing)
- Biobarbs (polypropylene connectors)

puresu

Risk Assessment

- The evaluation of the risk to quality should be based on **scientific knowledge** and ultimately link to the **protection of the patient.** The level of effort, formality and documentation of the quality risk management process should be **commensurate with the level of risk**.
- Select most appropriate data for process conditions
- Evaluation of risk from extractables that could present a safety concern
- Use extractables data to know what to look for in future leachables studies

Recommendations

- YOU need a risk strategy for using extractables to determine if there are any compounds of a potential safety concern
- Evaluate using ‘worst case’ parameters
  - Solvent
  - Extraction Time
  - Extraction Temperature
  - Surface Area
- Use Supplier data to ensure appropriate level of information is available to perform risk assessment
- **Engage with a Supplier who understands your requirements**

Questions

Obrigado