Connecting People, Science and Regulation

DISPOSABLE & SINGLE-USE SYSTEMS

PDA WORKSHOP
EXTRACTABLES – LEACHABLES
Brussels
13-14 March, 2014

Dr. Piet Christiaens

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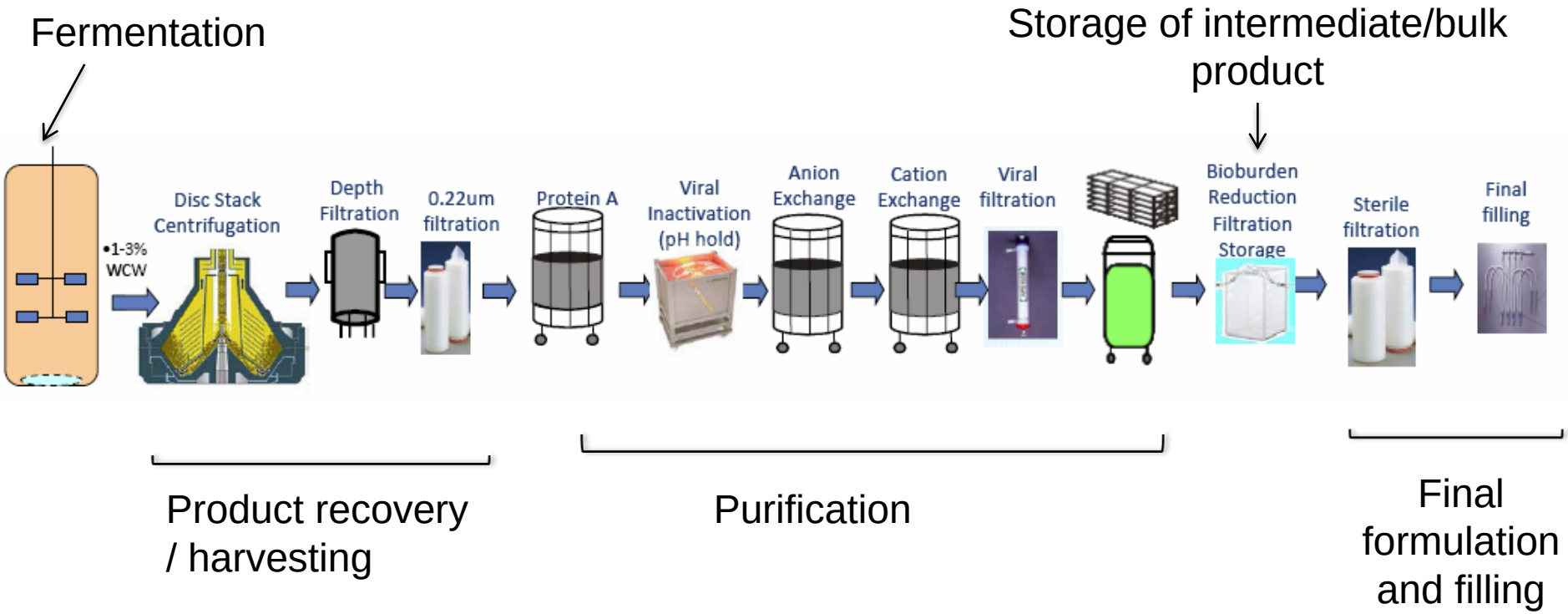
BIOPRODUCTION PROCESS

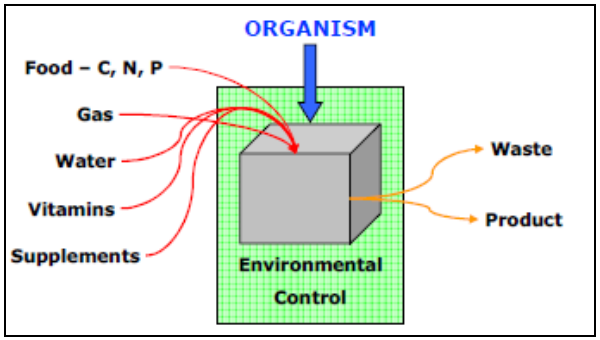
Bioproduction process



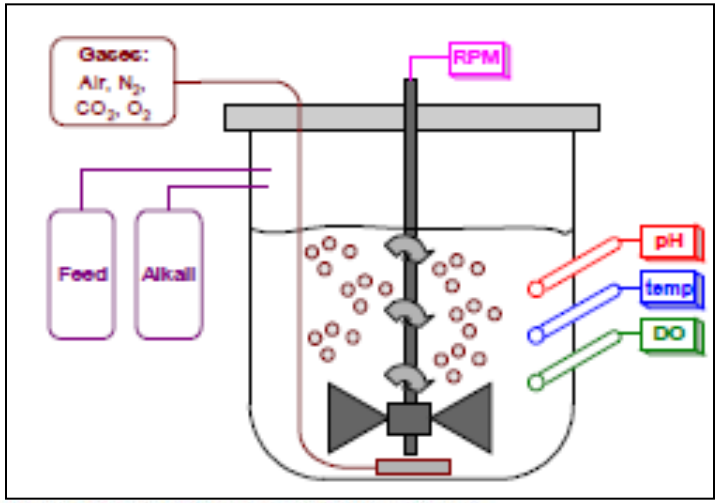
Bioproduction example from a slide from Presentation at IQPC Conference "Disposable Solutions", Munich, 18-20 FEB2014: "BPOG's Extractable Protocol Standardization Journey – Review 2013 Process ande Planning for 2014" Ken Wong (Sanofi-Pasteur), with permission of the Author.

Fermentation

Fermentation = Each Process where a product is produced by a mass culture of organisms



- Fermentation process: growth medium and cell culture in fermentation tank (bioreactor)



- Control parameters for optimalisation growth and/or production
  - Temperature
  - pH
  - Dissolved oxygen Tension
  - Mixing
  - Foam formation
  - …

Fermentation

- In the past, traditionally stainless steel bioreactors were used
- Over the past 10 years, increasing implementation of single use and disposable bioreactors:
  - Elimination of cleaning and sterilisation proces
  - Elimination energy cost for steam generation
  - Elimination of “cleaning validation” cost
  - Reduced risk of contamination
  - Time saving between production batches

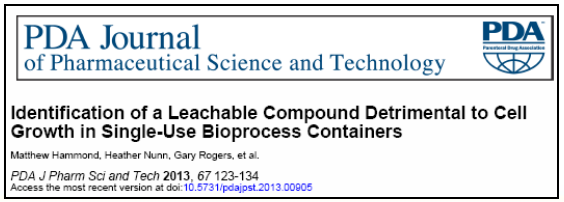
Fermentation

- Evaluation of extractables and leachables
  - Leachables introduced by the bioreactor might be removed/diluted by following process steps (cell harvesting / purification / formulation)
  - For high batch volumes, the contact surface to volume ratio is quite low

    ➡ **Toxicological risk** to the patient of leachables introduced by the bioreactor is in most cases **quite low**

  - However, the **quality risk of leachables** introduced by the bioreactor might be relevant!

    e.g. Bis(2,4-di-tert-butylphenyl)hydrogen phosphate (bDtBPP) causing cell growth inhibition

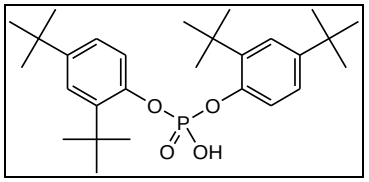

PDA Journal of Pharmaceutical Science and Technology

Identification of a Leachable Compound Detrimental to Cell Growth in Single-Use Bioprocess Containers

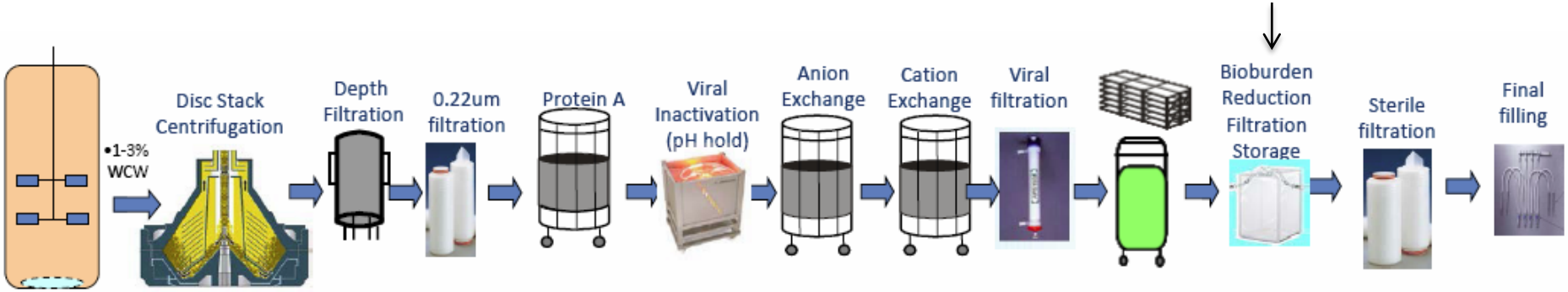
Matthew Hammond, Heather Nunn, Gary Rogers, et al.

PDA J Pharm Sci and Tech **2013**, *67* 123-134

Access the most recent version at doi:10.5731/pdajpst.2013.00905



Bioproduction process

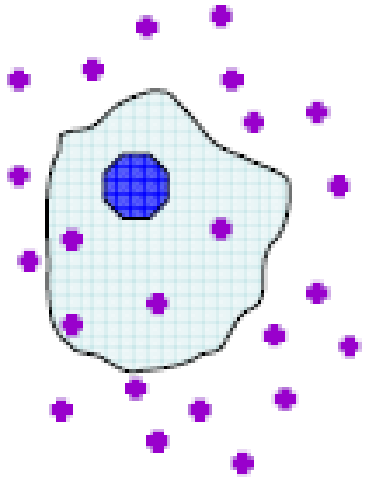


Product recovery / harvesting

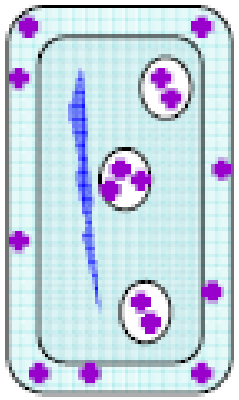
Bioproduction example from a slide from Presentation at IQPC Conference "Disposable Solutions", Munich, 18-20 FEB2014: "BPOG's Extractable Protocol Standardization Journey – Review 2013 Process ande Planning for 2014" Ken Wong (Sanofi-Pasteur), with permission of the Author.

Product recovery

- Extracellular Secreted product
  - Mammal cells

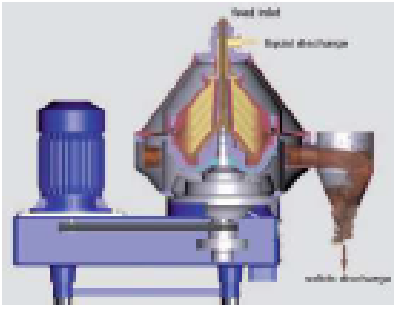


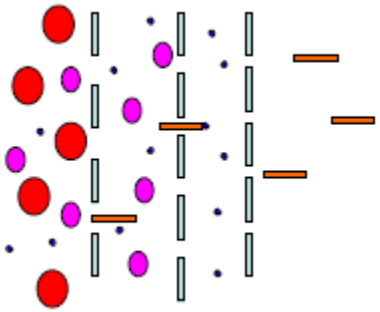
- Intracellular product
  - Bacteria
    1) Cytoplasmatic expression (e.g. E.coli)
    2) Periplasmatic expression (e.g. Gram-negative)



Product recovery: extracellular secretion

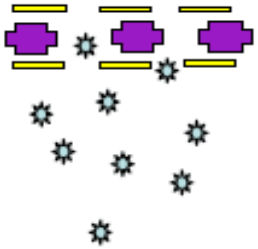
- Step 1: removal of cells
- Centrifugation or Filtration

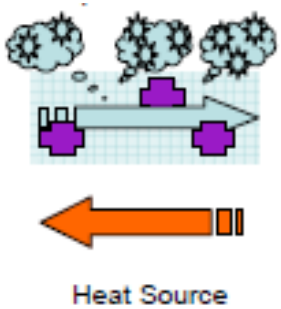


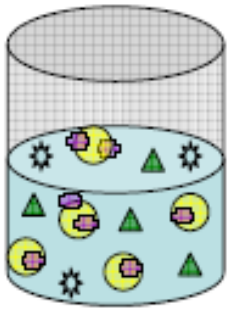


- Step 2: volume reduction

Ultrafiltration or damping or batch adsorption







Product recovery: intracellular secretion

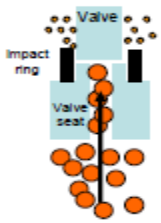
- Step 1: cell recovery

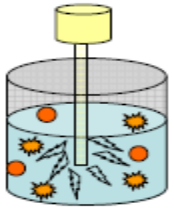
  centrifugation

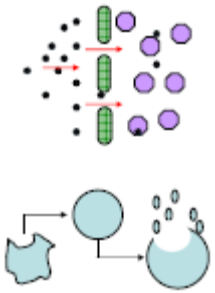
- Stap 2: **Cellular disruption**

Mechanical / Non mechanical

homogenisation milling sonication / osmotic 'freeze thaw' enzymatic







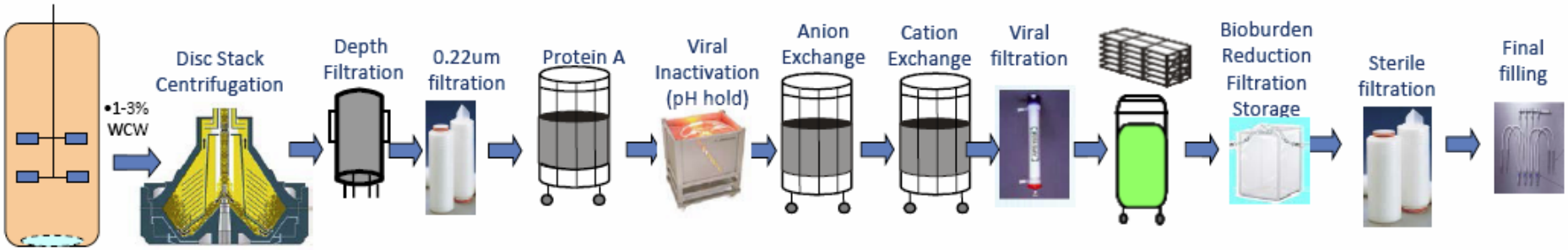
lysozyme + EDTA

of solvents:
increase of
cell permeability

of detergents:
dissolution of
membrane-
fosfolipids

- Stap 3: Clarification
- Stap 4: Concentration

Bioproduction process



Purification

Bioproduction example from a slide from Presentation at IQPC Conference "Disposable Solutions", Munich, 18-20 FEB2014: "BPOG's Extractable Protocol Standardization Journey – Review 2013 Process ande Planning for 2014" Ken Wong (Sanofi-Pasteur), with permission of the Author.

Purification

- Three Steps:
  - Step 1: isolation:
    - Transfer of product to an environment which protects the activity and functionality
  - Step 2: intermediate purification
    - Removal of bulk impurities: e.g. DNA, guest cell proteïns, virusses, endotoxines
  - Step 3: polishing
    - final purification to remove impurities similar to the product

Purification

- **Techniques used in Purification**:
  - Chromatografic techniques:
    - Affinity chromatografy
    - Hydrofobic interaction chromatography
    - Reverse phase chromatography
    - Ion exchange chromatography

  - Filtration
    - Gel filtration
    - Ultrafiltration
    - Virus filtration (20 nm filters)

  - Low pH treatment (viral inactivation)

Product recovery and purification

- **Evaluation of extractables and leachables**

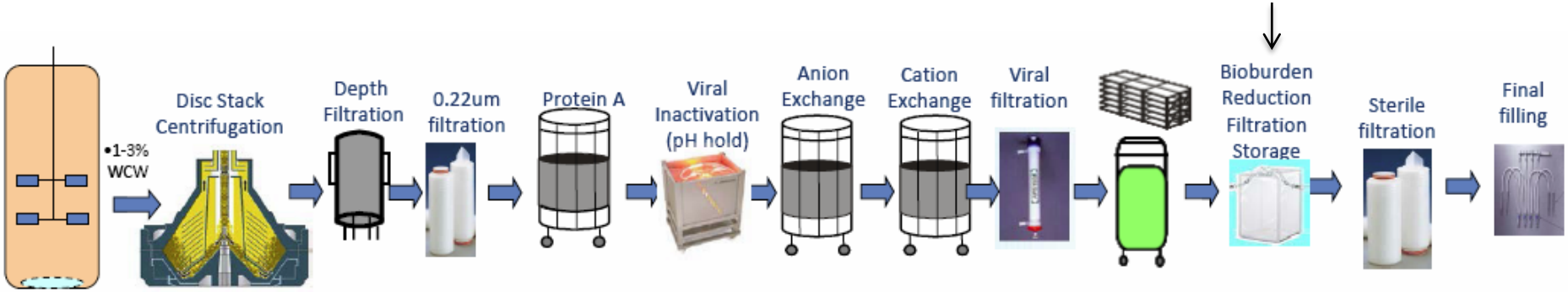
  - Filters and chromatography resins have a high contact surface versus volume

    ➡ higher risk for leachables

  - Subsequent process steps (purification/formulation) might remove/dilute leachables introduced during the product recovery and purification

Bioproduction process

Storage of intermediate/bulk product



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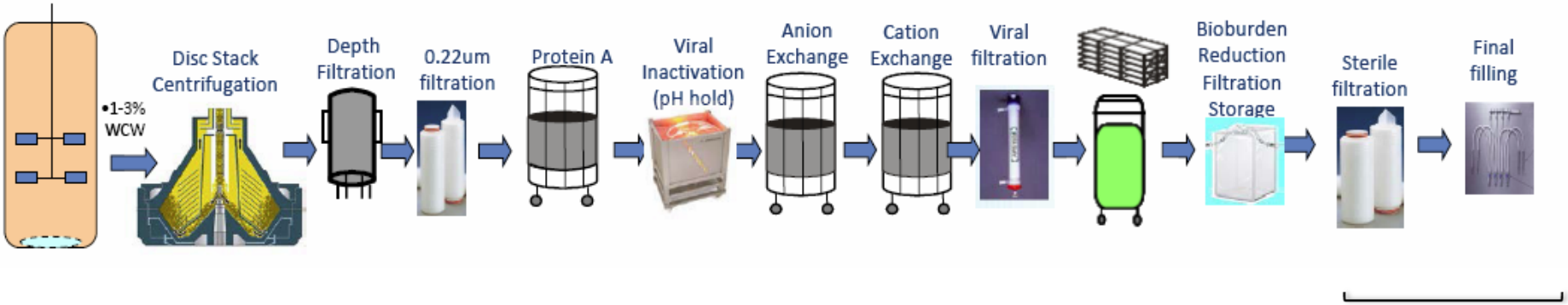
Storage of bulk products

- Storage of drug substance, buffer solutions, growth medium, etc... During several weeks, months, years...
- Bulk Containers of different material types might be used
  - PET(G)
  - Polycarbonate
  - Polypropylene
  - High Density Polyethylene (HDPE)
  - Flexible bags with multilayer films

Storage of bulk products

- Evaluation of extractables and leachables
  - Containers with low filling volume have higher contact surface versus volume ratio
    → higher risk for leachables
  - Impact of storage conditions:
    - Higher storage temperature: higher amount of leachables
    - Longer storage time: higher amount of leachables

Bioproduction process



Final formulation and filling

Bioproduction example from a slide from Presentation at IQPC Conference "Disposable Solutions", Munich, 18-20 FEB2014: "BPOG's Extractable Protocol Standardization Journey – Review 2013 Process ande Planning for 2014" Ken Wong (Sanofi-Pasteur), with permission of the Author.

Formulation and Filling

- Adding excipients in order to obtain the right stability and administration composition
- Sterile filtration
- Filling in final packaging container via tubing
  - Pharmaceutical grade tubings:
    - Silicone: Pt-cured or peroxide cured
    - TPE (thermoplastic elastomer)
    - PTFE coated
    - ...
- not only used in bioproduction, but also relevant for conventional small molecule drug products.

Final formulation and filling

- **Evaluation of extractables and leachables**
  - Filters have a high surface to volume ratio
  - Filling equipment makes direct contact with the final drug product
    → all leachables will end up in the final product
    (no dilution/purification steps anymore)

PROCESS MATERIALS

1. Bioproduction process typically contains a lot of individual process components

2. Many of the components are custom packaged
   - Bag from Vendor A
   - Tubing from Vendor B
   - Filter from Vendor C
   - Connectors from Vendor D

3. Complete E/L assessment for each component can be a challenging task

   → A good risk assessment to define critical process steps/components will be important

REGULATORY REQUIREMENTS FOR SINGLE USE SYSTEMS

REGULATORY ASPECTS – PRODUCTION COMPONENTS - MATERIALS

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..."

REGULATORY ASPECTS – PRODUCTION COMPONENTS - MATERIALS

OBSERVATIONS

The CFR 211.65 and GMP's do ***not only*** refer to the ***impact on Safety***, but also on:

- Quality
- Purity
- Strength (e.g. Adsorptive behavior)
- Reactive behavior
- Additive behavior

Reasoning of Regulators

- Know your Process
- Know the impact of SUS on the quality of the Product
- Prove that you have made an assessment

Disposable Production is fairly new, may trigger additional questions

For Safety Considerations, the main concern for SUS systems is their contribution to potential Immuno-responses (**IMMUNOGENICITY**) to the Drug Product

PDA Technical Report 26: “Sterilizing Filtration of Liquids”

“...It is the user’s responsibility to demonstrate that the product does not contain objectable levels of extractables from the filter...”

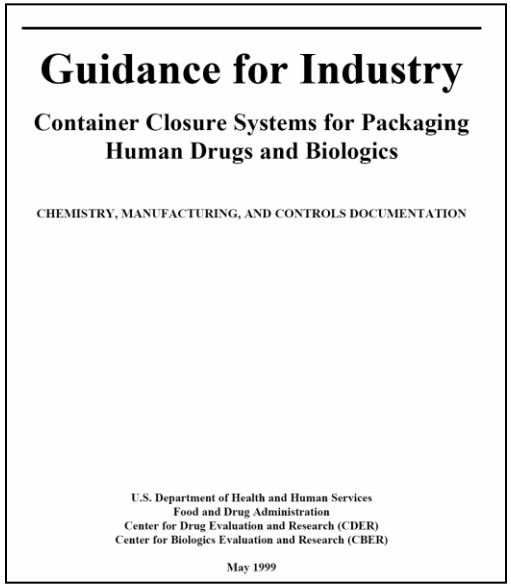
“...The Filter user is responsible for obtaining the extractable data for the drug product formulation...”

TR26 is in Revision

FDA Container/Closure systems for packaging Human Drugs and Biologics (1999)

- Also for Containers for bulk substances and products

- A specific Paragraph is dedicated to the bulk containers for substances and final DP



Guidance for Industry

Container Closure Systems for Packaging Human Drugs and Biologics

CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 1999

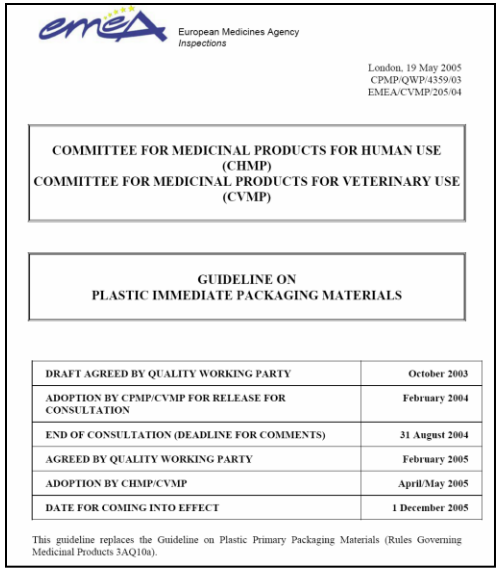
Table 1
Examples of Packaging Concerns for Common Classes of Drug Products

Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	**Medium**	**Low**
Highest	Inhalation Aerosols and Solutions; Injections and Injectable Suspensions[a]	Sterile Powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules

EMA Plastic Immediate Pachkaging materials (2005)

- Applicable to Active Substances or Drugs

- "Packaging materials intended to be in contact with the active substances or medicinal products"



European Medicines Agency
Inspections

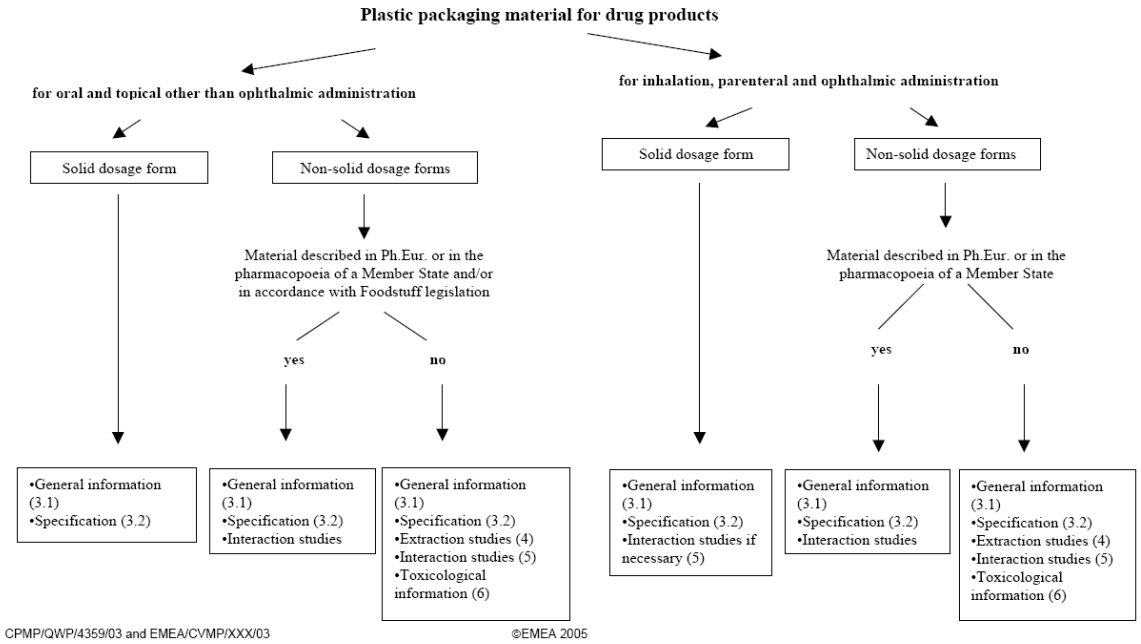
London, 19 May 2005
CPMP/QWP/4359/03
EMEA/CVMP/205/04

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)
COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

GUIDELINE ON
PLASTIC IMMEDIATE PACKAGING MATERIALS

DRAFT AGREED BY QUALITY WORKING PARTY	October 2003
ADOPTION BY CPMP/CVMP FOR RELEASE FOR CONSULTATION	February 2004
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 August 2004
AGREED BY QUALITY WORKING PARTY	February 2005
ADOPTION BY CHMP/CVMP	April/May 2005
DATE FOR COMING INTO EFFECT	1 December 2005

This guideline replaces the Guideline on Plastic Primary Packaging Materials (Rules Governing Medicinal Products 3AQ10a).



INTEREST GROUPS, TRADE ASSOCIATIONS AND STANDARDIZATION ORGANIZATIONS FOR SINGLE USE SYSTEMS

ON THE WAY TO HARMONISATION

INTEREST GROUPS, TRADE ASSOCIATIONS *STANDARIZATION ORGINIZATIONS*

1. **Bio-Process Systems Alliance (BPSA)**

2. **Biophorum Operations Group (BPOG)**

3. **ASME-BPE** ***(only mentioned) – In Preparation***

   ASME: American Association for Mechanical Engineers
   BPE: BioProcessing Equipment

4. **ISPE – BPOG – ASTM** ***– In Preparation***

   ISPE: International Society for Pharmaceutical Engineering

5. **USP <661.3> Manufacturing Systems** ***– In Preparation***

   Test Methods and Standards for single-use materials, components and systems

1. Bio-Process Systems Alliance (BPSA)

6 Selected slides from Presentation at IQPC Conference "Disposable Solutions", Munich, 18-20 FEB2014: "Collaborative Efforts to Standardise Supplier's Extractable Data for Single-Use Components", Jerold Martin (BPSA, Chairman, Pall Life Sciences), with permission of the Author.

Bio-Process Systems Alliance

Bio-Process Systems Alliance

- Trade association of suppliers and users
- Facilitates implementation of single-use
  - Networking opportunities
  - Safe harbor for dialogue among suppliers
  - End-user / supplier forums
  - Best practice guides

www.bpsalliance.org

BPSA Extractables Guides (2008, 2010)

- Consensus of suppliers and independent labs
- Reviewed with FDA and users
- Many successful approved applications
- Risk-based approach
  - Water and ethanol extractions
  - Broad analyses (e.g. FTIR, LC-MS, GC-MS, ICP-MS)
- Available at www.bpsalliance.org

BPSA Extractables Guides (2008, 2010)

- Recommendations for Extractables and Leachables Testing (2008)
  - Part 1: Introduction, Regulatory Issues, and Risk Assessment
  - Part 2: Executing a Program

- Recommendations for Testing and Evaluation of Extractables from Single-use Process Equipment (2010)

- Available at www.bpsalliance.org

Extraction Conditions

- Test Articles
- Pre-conditioning
  - Autoclave, irradiate, flush
- Solvents
  - Water, ethanol, high/low pH, low polarity, surfactants
- Temperature
- Time
- Dynamics (e.g. Agitation)
- Surface area : volume ratio
- Component types
  - Biocontainer/Bioreactor, Filter, Connector, Tubing, Mixing Bag, Integrated System

** BPSA Recommendations for Extractables and Leachables from Single-Use Process Equipment (2010)*

Analytical Methods

Analytical Techniques

- FTIR
- GC/FID
- GC/MS
- HPLC/DAD
- HPLC/MS
- HS/GC/MS
- IC
- ICP
- NVR
- Conductivity
- pH
- TOC

Characteristics

- Identification
- Overview
- Category/Classification
- Sensitivity (LOD)
- Detectable Species
- Sample Preparation
- Strengths
- Limitations

** BPSA Recommendations for Extractables and Leachables from Single-Use Process Equipment (2010)*

PALL Life Sciences

Summary Recommendations

- Extractables data = potential leachables
- Perform extractions with at least two solvents
  - Water and low MW alcohol
  - Low MW organic or pH extremes where applicable
- Use exaggerated time, temperature, surface area/volume ratio and pretreatment steps
- Apply analytical methods to characterize, identify and quantify
- Supplier data is acceptable where applicable
- Perform risk assessment – impact on final drug?

2. BioPhorum Operations Group (BPOG)

12 Selected Slides from Presentation at IQPC Conference "Disposable Solutions", Munich, 18-20 FEB2014: "BPOG's Extractable Protocol Standardization Journey – Review 2013 Process ande Planning for 2014" Ken Wong (Sanofi-Pasteur), with permission of the Author.

Who are We - BioPhorum Operations Group (BPOG) ?

- BPOG is a global collaboration of biopharmaceutical manufacturers. Since 2008 it has grown to…
  - 23 member companies
  - 750 active representatives working in 12 workstreams including Disposables
  - Extractables is the largest sub group in the Disposables workstream – it started up in late 2012, involves 19 member companies and a mix of analytical chemists and process engineers/scientists who are subject matter experts.
- BPOG mission
  - To accelerate the rate of the journey to industrial maturity.
- BPOG is not a standards body or representative of suppliers
  - BPOG enables companies to collaborate, build and share solutions to the most significant common challenges they face.
  - BPOG works with and through other bodies to realise change.

Disposable Solutions

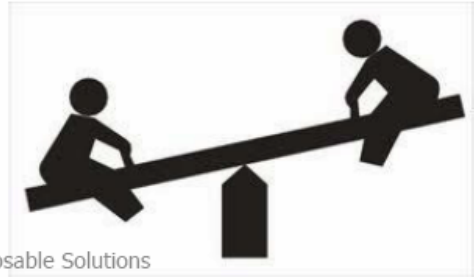
18/Feb/2014

BioPhorum Operations Group
Connect · Collaborate · Accelerate

3

Business Case – Why There is a Need for Standardized Extractable Protocol

- Extractables data is key to effective SUS implementation
  - Screening and selecting a product – confirming fitness for use in the BioPharma manufacturing process
  - Identifying potential process leachables and what further testing may be required
- No specific Regulatory guidance on how to handle process related extractables, only container closure extractables
  - A Standardized Extractable Protocol can help bridge this gap with regulators
- Suppliers extractables data lacks consistency and in some cases is not technically adequate
  - Suppliers are using different solvents, time periods and testing methods
  - Model solvents and test conditions are often not representative enough for expected process conditions
  - Extractable data is not comparable between suppliers and is not presented in a standard format
  - Net result is that each company is doing lots more testing than it should at great expense.
- Adoption of SUS is being slowed by
  - The inconsistency of extractable data available for a product
  - Companies having to complete testing to plug gaps
  - Regulator's questions reflect the current state of uncertainty around use of SUS



We believe the balance needs to change, that too much is falling to users at present and control of the supply chain end to end is way behind that of other industries and where it could and should be

Value Add: Win-Win proposition for Suppliers, End Users and Regulators

- **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

Standard Extractable Studies – Subset of Sample Preparation Table

Single Use Component Type	Recommended Sample Extraction Conditions
Storage / Mixing / Bioreactor bags	Use a small bag (≤ 5L) - meet 6:1 (cm^2/mL) surface area to volume ratio. Studies performed with 2D bags with the same MOC (represent 3D bags). Shaking on an orbital shaker is recommended. Express analytical results in µg/cm^2.
Tubing	Use tubing with ½'' ID - meet 6:1 (cm^2/mL) surface area to volume ratio. Record and report the length and ID of the tubing. Shaking on an orbital shaker is recommended. Express analytical values in µg/cm and µg/cm^2.
Sterilizing-grade/ Process Filters	Use filter with effective filtration area (EFA) equal to or greater than 0.1 m^2 (if possible) for study and maintain at least 1:1 (cm^2/mL) EFA to volume ratio. Either recirculating solvent through the filter or filling the filter and shaking on an orbital shaker is recommended. Express the analytical values in µg/cm^2.

6:1 ratio can be adjusted down with justification

1:1 ratio is the minimum. Higher is desirable

Standardized Extractable Studies – Protocol Appendix B Part 1

- 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

Standardized Extractable Studies – Appendix B Part 2

- Time points and temps
  - 0 hours 25°C
  - 48 hours 40°C
  - 30 days 40°C
  - 120 days 40°C

We started here and moved on to ....

- Time points and temps
  - 0 hours 25°C
  - 21 days 40°C
  - 56 days 40°C
  - 120 days 40°C

Time points are component dependent and defined based on a detailed BPOG members survey of the intended applications of SUS

- Time points and temps
  - 30 Mins 25°C
  - 24 hrs 40°C
  - 7 days 40°C
  - 30 days 40°C
  - 70 days 40°C

Extractable study is a function of solvent, time and temperature

SUS Category	SOLVENTS[1]						TIME				
	50% Ethanol	1% PS-80	5M NaCl	0.5N NaOH	0.1M Phosphoric acid	WFI neutral	Time 0 (≤ 30mins)	24 hrs	7 days	30 days	70 days
							25° C	40° C			
Storage bags	X	X	X	X	X	X	X	X		X	X
Mixing bags / mixing device	X	X	X	X	X	X	X	X		X	
Bioreactor bags	X	X	X	X	X	X	X	X		X	X
Tubing, Liquid injection materials	X	X	X	X	X	X	X			X	
Process (UF/DF) filters	X	X	X	X	X	X	X		X		
Bioreactor Sensors	X	X	X	X	X	X	X			X	
Other Sensors	X	X	X	X	X	X	X		X		
Sterile (~0.2µm) and viral filters	X	X	X	X	X	X	X	X			
Aseptic/non-aseptic tubing dis/connectors	X	X	X	X	X	X	X			X	
Prepacked column body	X	X	X	X	X	X	X				X
Filling manifold	X	X	X	X	X	X	X	X			

[1] *Certain solvent may be skipped:*

If material is incompatible;

If the intended use of the component will not be exposed to such extreme

Standardized Extractable Studies – Appendix B (In agreement with BPSA)

Part III

- Analytical techniques
  - pH measurements
  - Conductivity
  - TOC
  - Screening of metals
  - Volatile Organic Compounds (VOC) with direct injection into gas chromatography/mass spec (GC/MS)

- Analytical techniques
  - pH measurements
  - Conductivity
  - TOC
  - Metal ions: **ICP-MS/OES**
  - **Volatiles: HS-GC-FID/MS**
  - Semi-Volatiles: GC-FID/MS
  - **Non-Volatiles: LC-PDA/MS**

Our 2014 Goals and Plans

- Establish jointly published standardized extractable protocol with BPSA
  - Joint task group meetings are planned and ongoing
  - Target completion date – End of Feb 2014 (Will probably go on until March)
- Provide joint standardized extractable protocol to USP, ASTM and ASME-BPE for reference
- Collaborate with BPSA on implementation plan for new and existing SUS

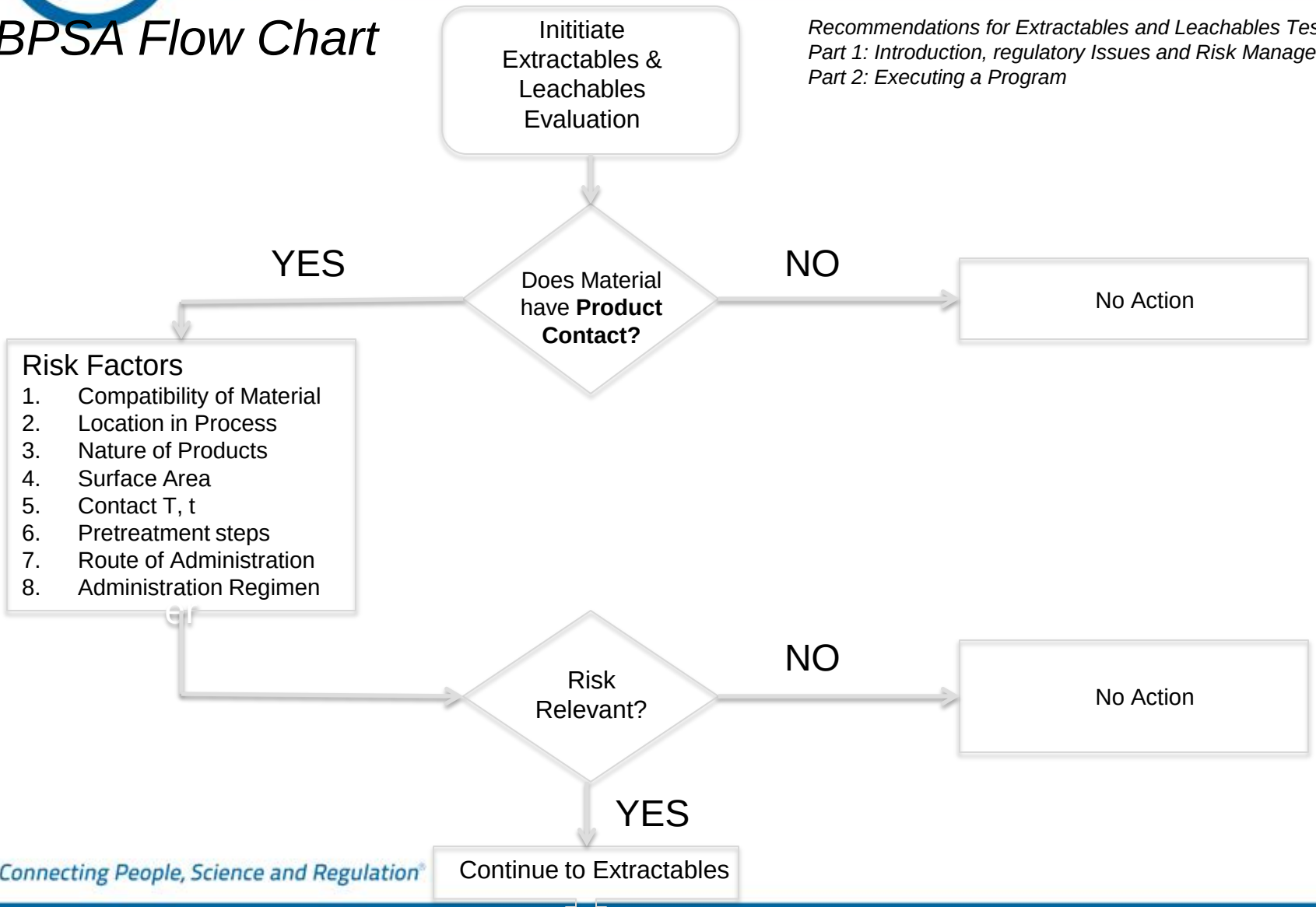
BIOPRODUCTION PROCESS

THE ***BPSA***
RISK ASSESSMENT
APPROACH

Recommendations for Extractables and Leachables Testing (2008)
Part 1: Introduction, regulatory Issues and Risk Management
Part 2: Executing a Program

BPSA Flow Chart

Recommendations for Extractables and Leachables Testing (2008)
Part 1: Introduction, regulatory Issues and Risk Management
Part 2: Executing a Program



Create a list of Product Contact Materials

- Any Material that has the potential to migrate into the final product
- List begins UPSTREAM with starting Buffers
- List Finishes with Materials used directly before the final fill & finish of containers
- Can include: *Tubing, Bags, Filters, Connectors, O-rings, Tangential Flow Cassettes, Syringes, Chromatographic resins, Final Bulk Storage vessels,…*

Perform Risk Assessment

- **GOAL**: to determine the product contact materials that have the greatest potential for an objectable level of leachables

- Must be performed using criteria that are specific to the end user – cannot be generalized between applications

- Best Performed early in the process development when changes are more easily addressed

RISK FACTOR 1: Material Compatibility

- Most biopharmaceutical products are aqueous and therefore are compatible with many materials
- Most biopharmaceutical materials PASS USP<87> or USP<88> testing
- First, obtain manufacturers recommended operating parameters, such as pH, temperature, pressure…
- Check to be sure the material is being used within the recommended normal operating procedures

Recommendations for Extractables and Leachables Testing (2008)
Part 1: Introduction, regulatory Issues and Risk Management
Part 2: Executing a Program

RISK FACTOR 2: Proximity to Final Product

- Location directly upstream of final fill has direct risk to final product
- Location upstream in process MAY have reduced risk
- This is true if there are steps where contaminants can leave the process
  - Diafiltration – diafiltrate volume can be 100x the process volume
  - Lyophilization – volatiles may be removed
- Ideally, supporting data should be obtained

RISK FACTOR 3: Solution Composition

- Extreme pH
- High organic or alcohol content
- Surfactants

RISK FACTOR 4: Surface-to-Volume ratio

- The higher the ratio, the higher the risk!!
- Filters – porous structure leads to area much larger than filtration area
- Smaller process volume usually has higher surface-to-volume ratio's

RISK FACTOR 5: Contact time and temperature

EVIDENTLY:

- The longer the contact time, the higher the risk
- The higher the temperature, the higher the risk

RISK FACTOR 6: Pretreatment steps

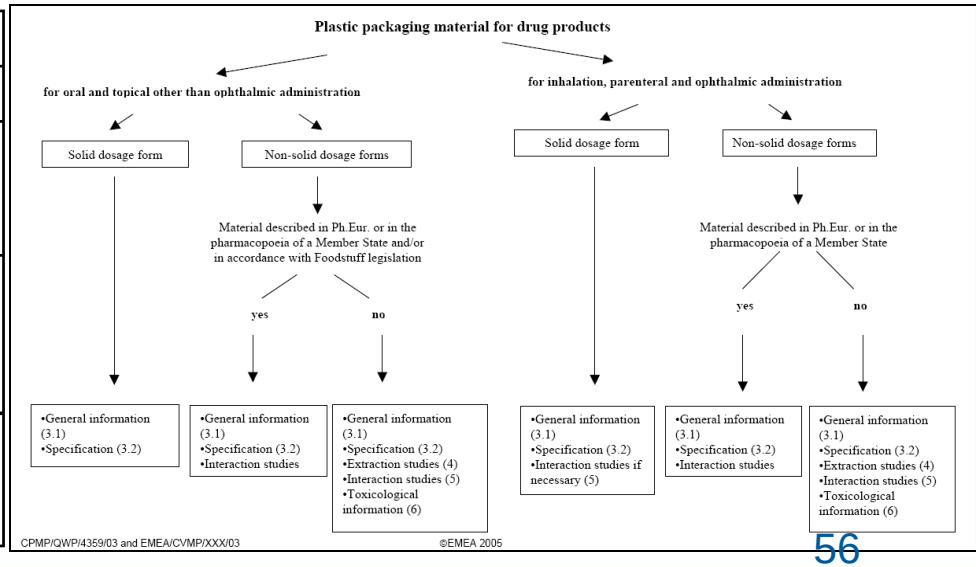
- STERILIZATION (e.g. gamma, EtO, autoclave) tends to increase leachables
- RINSING prior to product contact tends to lower leachables
  - E.g. Preflush for filters

RISK FACTOR 7: Route of Administration

- The Classification, presented in the FDA-Guidance (Table 1) and the EMEA-Guideline (Decision Tree), is also valid for the concern on impurities (leachables) introduced in the (bio)pharmaceutical production!!

Table 1
Examples of Packaging Concerns for Common Classes of Drug Products

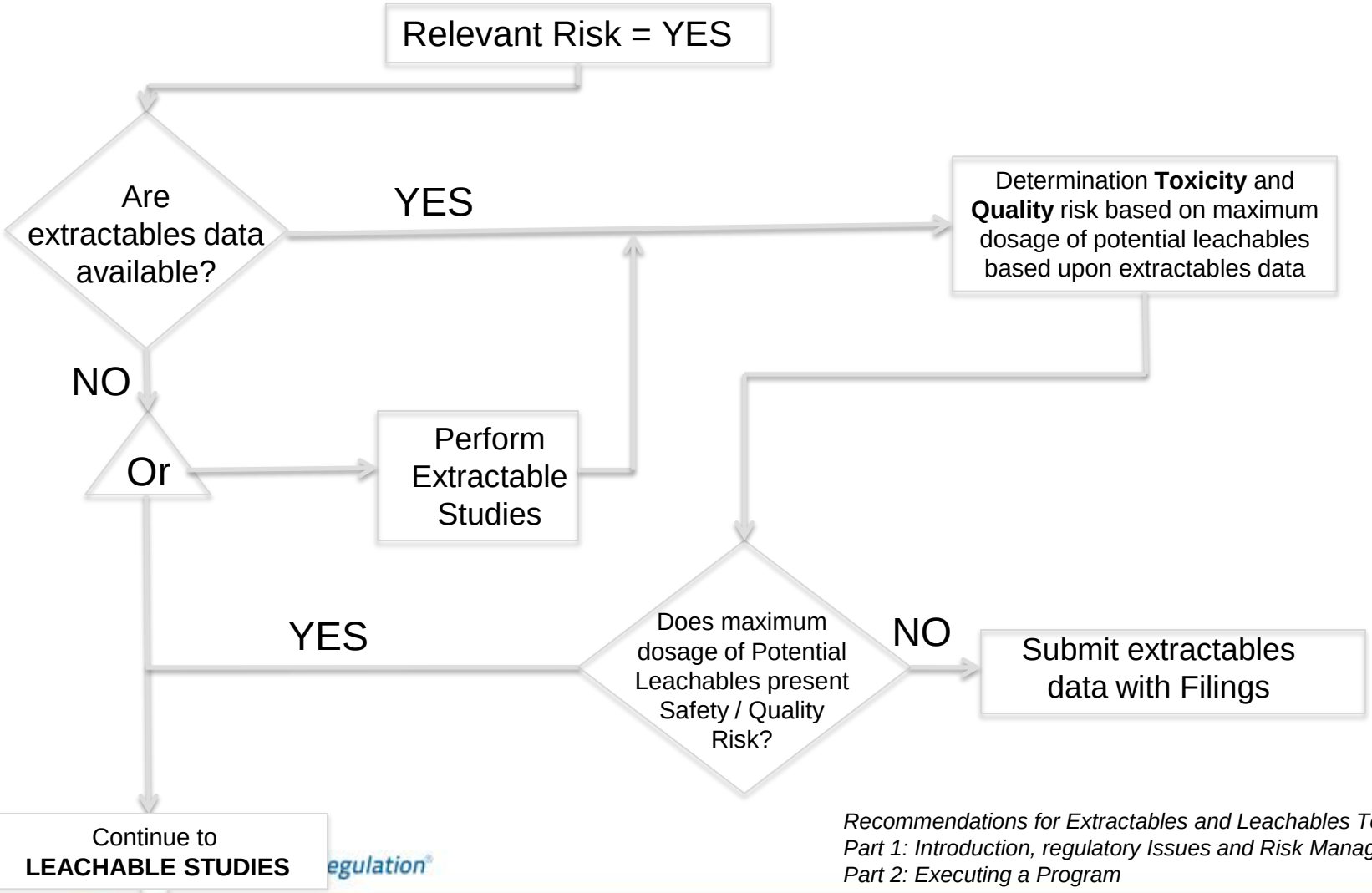
Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	Medium	Low
Highest	Inhalation Aerosols and Solutions; Injections and Injectable Suspensions[a]	Sterile Powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules



What to do with RISK FACTORS?

- Create priorities for testing
  - If a change is needed, better find out soon
- Weight according to end-user specific criteria
  - EXAMPLE: the presence of surfactants may be considered a high risk automatically requiring more testing for a particular end-user
- Although the Use of Numbers to assess risk (e.g. 1 to 10) is discouraged, it is often used in this way
  - Unless associated with supporting data because numerical risk values have the potential to lead to a pseudo-scientific conclusion based on arbitrarily assigned numbers
- If it is determined there is no relevant regulatory or safety risk for a specific product contact/material interaction, then submit vendor information for regulatory filings
- If there is relevant risk, then proceed to extractables evaluation

BPSA FLOWCHART, Continued



Recommendations for Extractables and Leachables Testing (2008)
Part 1: Introduction, regulatory Issues and Risk Management
Part 2: Executing a Program

Extractable Studies

- To Determine the conditions of Sample Prep:
  Look at the evaluation of the SUS and the product(s) that will be in contact to determine the right conditions

- BPSA-testing Protocol
- BPOG-testing Protocol

- Analytical Techniques
  Compound Specific:
  Headspace GC/MS, GC/MS, UPLC/HRAM, ICP-MS, IC
  Not Compound Specific:
  pH, Conductivity, TOC, NVR, FTIR on NVR...

Assess toxicity based on worst-case extractables data

Many processing material applications have a high dilution factor

- *Extractables studies are conducted with a high surface-to-volume ratio*
- *Process Materials can have surface-to-volume ratios 1000 times lower*
- *Relatively high concentration of extractables may be acceptable when converted to dosage*
- *Must be evaluated case by case*

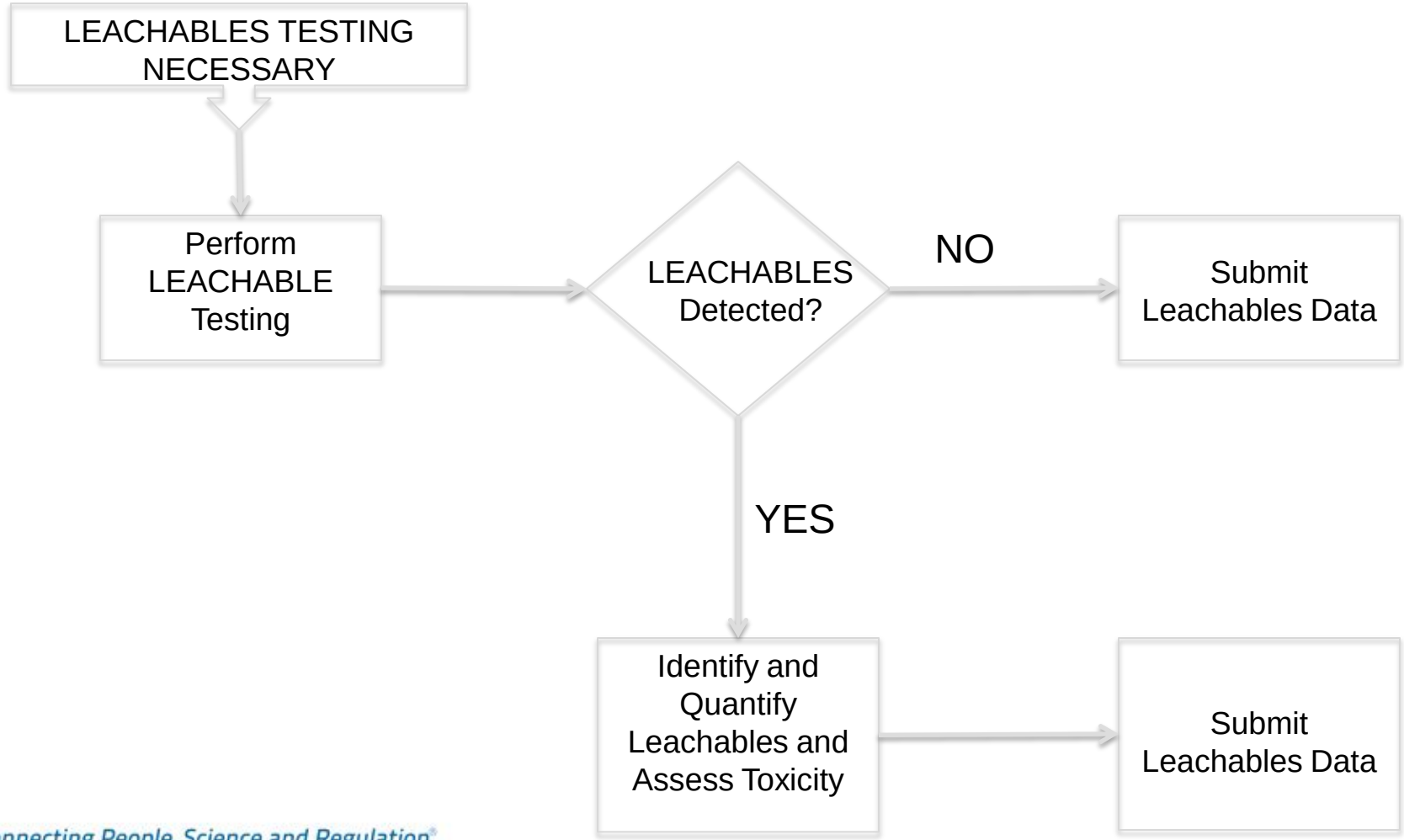
- *Determine if extractables **data** is available **from vendor** or other reference source*

- *The most useful extractables data leads to a comprehensive list of potential leachables.*

- ***GOAL**: to identify as many potential leachable compounds as possible*

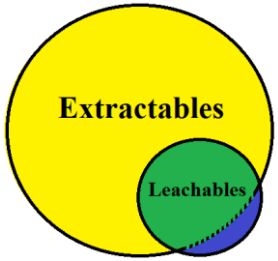
- *A vendor who performs high quality extractables testing and identifies many extractables should be admired and not punished!*

BPSA FLOW CHART: FINAL (LEACHABLE STUDIES)



REMARKS

1. The BPSA Flow Chart holds the **assumption that Leachables are a Subset of Extractables, which is not always the case**!



2. **Immediate step towards Leachables Tersting** (with skipping Extractables Evaluation), as proposed in the BPSA Flow Chart, can be cumbersome, as it is not always clear what to look for. **Need for Excellent Screening Methodologies in LEACHABLE STUDIES!!**

3. There is **more and more a trend towards Leachables testing, backed by Suppliers Extractable Data**, where the actual interaction between the product stream and the SUS is studied.

“SAFETY EVALUATION” OF A BIOPROCESS, BASED UPON E/L DATA

EXTRAPOLATION OF PQRI APPROACH

SCT: **S**AFETY **C**ONCERN **T**HRESHOLD

"Threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects"

PQRI for **OINDP's**: SCT = 0,15 µg/day

The SCT is not a Control Threshold, it is not a TTC

AET: ANALYTICAL EVALUATION THRESHOLD

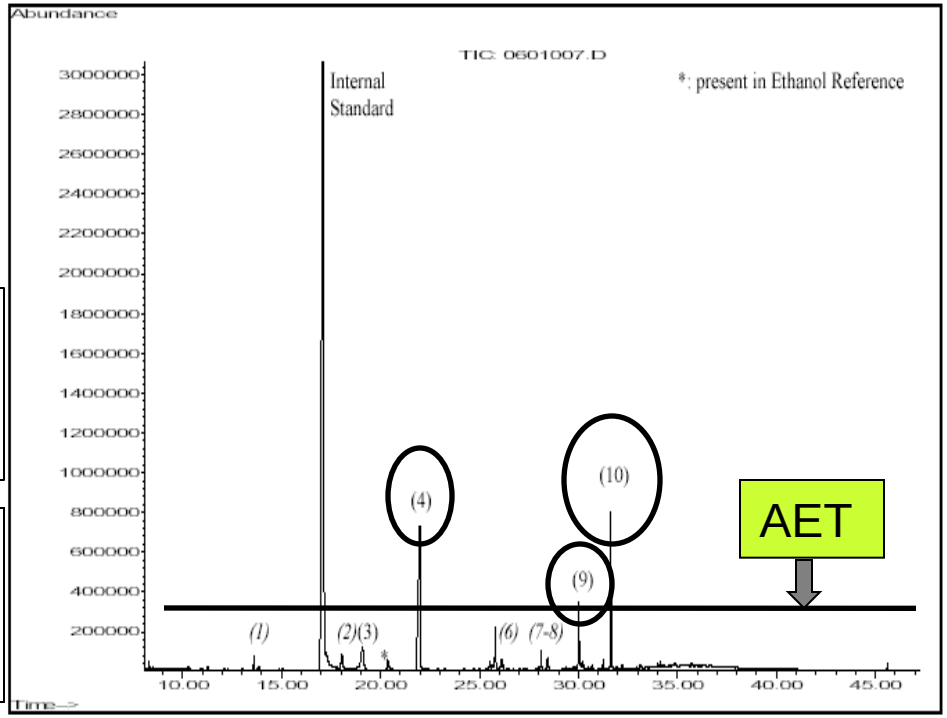
Translate SCT

into Analytical Thresholds

for Extractable Studies

Taking into account:

- *Total N° of doses / packaging*
- *Max. N° of doses administered / day*



PQRI: SUGGESTED THRESHOLDS FOR **PARENTERAL** & OPHTHALMIC APPLICATIONS (PQRI-PODP) – current status

	Class I	Class II	Class III
Threshold Level (µg/day)	150 Under Evaluation	5	1.5

Class I: class of compounds which are **no** sensitizers, irritants, genotoxicants or carcinogens.
Class II: class of compounds which are known or expected to have sensitizing or irritating properties, but do not have any indications of genotoxicity or carcinogenicity.
Class III: class of compounds which are known or expected to be genotoxic or carcinogenic.

AET: **A**NALYTICAL **E**VALUATION **T**HRESHOLD

Example:

Filter is used to produce 1000 vials

Maximum Daily Intake: 1 vial

Evaluation of Filter

Extraction ratio: 1 Filter is filled with 2 L an Extraction Solution that Substantially Exaggerates the worst case use

EXTRACTABLES:

Threshold Class I: 150 µg/day: final AET level: 75.000 µg/Filter

Threshold Class II: 5 µg/day: final AET level: 2.500 µg/Filter

Threshold Class III: 1,5 µg/day: final AET level: 750 µg/Filter

AET: **A**NALYTICAL **E**VALUATION **T**HRESHOLD

Formula used (see PQRI recommendations):

$$\text{Est. AET} = \frac{\text{Threshold}}{\text{dose/day}} \cdot \frac{\text{total dose}}{\text{PFS}}$$

$$\text{Class I: Est. AET} = \frac{150\ \mu\text{g / day}}{1\text{dose / day}} \cdot \frac{1000\ \text{dose}}{\text{Filter}} = 150.000\ \mu\text{g / Filter}$$

$$\text{Final AET} = 75.000\ \mu\text{g / Filter}$$

50% uncertainty for screening methods

Further Calculations will give the following AET levels for the respective Classes:

	Threshold (µg/day)	Final AET (µg/Filter)	Final AET (mg/L)
Class I	150	75000	37,5
ClassII	5	2500	1,25
Class III	1,5	750	0,375

Extr. Ratio:
1Filter / 2 L

Typical Results for an Exhaustive Extraction on a Filter Unit

	EXT result mg/L extract	EXT result µg / Filter
COMPOUND #1	0,1	200
COMPOUND #2	0,2	400
COMPOUND #3	1,25	2500
COMPOUND #4	2	4000
COMPOUND #5	0,4	800
COMPOUND #6	0,25	500
COMPOUND #7	13	26000
COMPOUND #8	0,1	200
COMPOUND #9	47	94000
COMPOUND #10	0,4	800
COMPOUND #11	0,1	200
COMPOUND #12	5,5	11000
COMPOUND #13	32,5	65000
COMPOUND #14	1,2	2400
COMPOUND #15	0,35	700

> ?

EXAMPLE OF GC S RESULTS FOR EXTRACTAB TUDY

	EXT result mg/L	Class	Threshold for Class (µg/day)	FINAL AET for Class (mg/L)
COMPOUND #1	0,10	Class I	150	37,5
COMPOUND #2	0,20	Class I	150	37,5
COMPOUND #3	**1,25**	**Class III**	**1,5**	**0,375**
COMPOUND #4	2,00	Class I	150	37,5
COMPOUND #5	0,40	Class II	5	1,25
COMPOUND #6	0,25	Class I	150	37,5
COMPOUND #7	**13,00**	**Class II**	**5**	**1,25**
COMPOUND #8	0,10	Class III	1,5	0,375
COMPOUND #9	**47,00**	**Class I**	**150**	**37,5**
COMPOUND #10	0,40	Class II	5	1,25
COMPOUND #11	0,10	Class III	1,5	0,375
COMPOUND #12	5,50	Class I	150	37,5
COMPOUND #13	**32,50**	**Class III**	**1,5**	**0,375**
COMPOUND #14	1,20	Class I	150	37,5
COMPOUND #15	0,35	Class II	5	1,25

Conclusion of the Threshold Evaluation (Safety):

- Exaggerated/Exhaustive Extraction Results indicate that – if all would come out – these compounds would be detected as leachable above their respective threshold level

- Were Compounds 3, 7, 9 and 13 identified?
  In some cases, furthe attention to additional identification needs to be given

- Analytical methods for compounds 3, 7, 9 and 13 will need to be validated for the subsequent leachable study

- The validation range will be different for the 4 compounds as a result of:
  - The concentration level of the compound, found in the Filter
  - The different classess for the respective compounds:
  - The validation range should always include the AET level for the respective compound, as a minimum

- Presence of other compounds may be monitored (semi-quantitatively) in Leachable Study, using screening methodology

Footmark:

- The **Threshold Approach only evaluates "Safety Aspects**" of the leachables

  Other Concerns, like QUALITY PURITY, STRENGTH, REACTIVE or ADDITIVE BEHAVIOR are not assessed via the Threshold Approach

  Nor are IMMUNOGENICITY concerns addressed

- Even if an evaluation of a Single Use System (SUS)
  - Based open the initail (paper) risk assessment
  - Based upon the analytical data

  Shows no concern

Even then it may (need to) be considered to document impact of the SUS contact on the impurities profile of the product stream

CONCLUSION

1. When looking at a Bioproduction Process, **- potentially – a lot of materials, components and/or systems may need to be evaluated**

2. The **"BPSA Risk Evaluation"** of a Bioproduction Process may be a good guidance to determine what to focus on in a subsequent E/L efforts

3. Both the **BPSA & BPOG Protocol** *(later on, USP<661.3> and new ASTM standard)* give very good guidance and indications on how to put together a E/L-testing programme

4. **Optimize the BPSA & BPOG protocol** to the actual gaps in the documentation

5. Perform E/L testing

6. Perform a Risk Assessment
   - Quality
   - Safety (extrapolated PQRI PODP Approach)

Questions?