DISPOSABLE & SINGLE-USE SYSTEMS

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES
Berlin
28 – 29 September, 2017

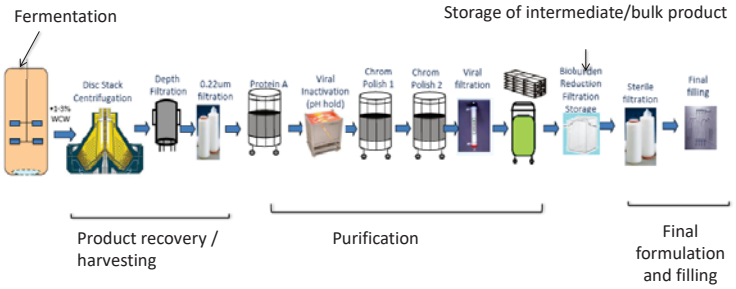
Ir. John Iannone

Table of Content

1. *The Bioproduction Process*
2. *Regulatory Requirements for SUS*
3. *Interest Groups, Trade Associations and Standardization Organizations for SUS*
4. *The BPSA Risk Assessment Aprroach*
5. *"Safety Evaluation" of a Bioprocess Based upon E/L Data. Extrapolation of PQRI (PODP) Approach*
6. *Conclusion*

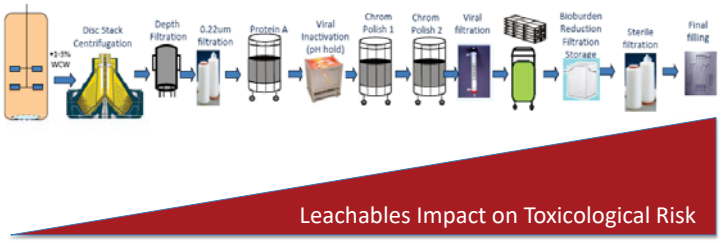
BIOPRODUCTION PROCESS

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.

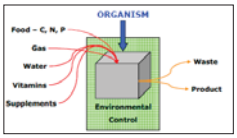
Bioproduction process



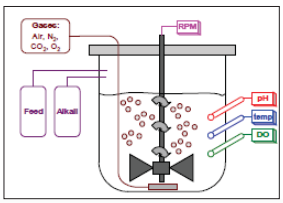
Bioproduction example from a slide from Presentation at IQPC Conference "Disposable Solutions", Munich, 18-20 FEB2014: "BPOG's Extractable Protocol Standardization Journey – Review 2013 Process ande Planning for 2014" Ken Wong (Sanofi-Pasteur), with permission of the Author.

Fermentation

Fermentation: Process where product is produced by mass culture of organisms



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



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

Fermentation

» In the past, traditional stainless steel bioreactors were used

» Over the past 10+ years, increasing implementation of single use & disposable bioreactors

- Elimination of **cleaning** & **sterilisation** proces
- Reduction of **energy cost** for steam generation
- Elimination of "**cleaning validation**" cost
- Reduced risk of **contamination**
- **Time saving** between production batches

Fermentation

Evaluation of Extractables & Leachables

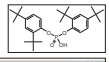
» Leachables introduced by the bioreactor might be **removed/diluted** by following process steps *(cell harvesting / purification / formulation)*

» For large batch volumes, the contact surface to volume ratio is low

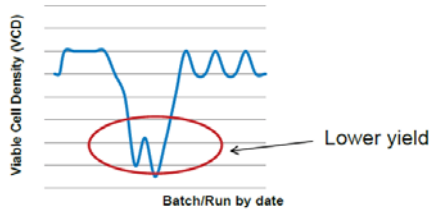
→ **Toxicological risk** to the patient of leachables introduced by the bioreactor is in most cases **quite low**

» However, the **risk to product quality** caused by leachables introduced by the bioreactor might be very relevant

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



Cell Growth Inconsistency in SUBs



- Decreased yield = less profit
- Potential root cause(s)
  - Media
  - **Leached material from Bag?**
  - Innovative idea to non-Extractable people

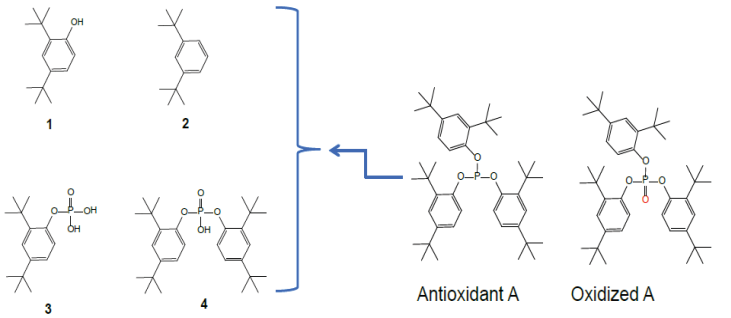
Hypothesis: SUB Leachable(s) Inhibits Cell Growth

- Get information from vendor
- Perform Extractable study and ID Extractables
- Spike in individual water soluble Extractables into Cell Culture process using bags from "good" lots.
- Measure cell growth

Extractables* → Spike in Cell Culture → Measure Cell Growth

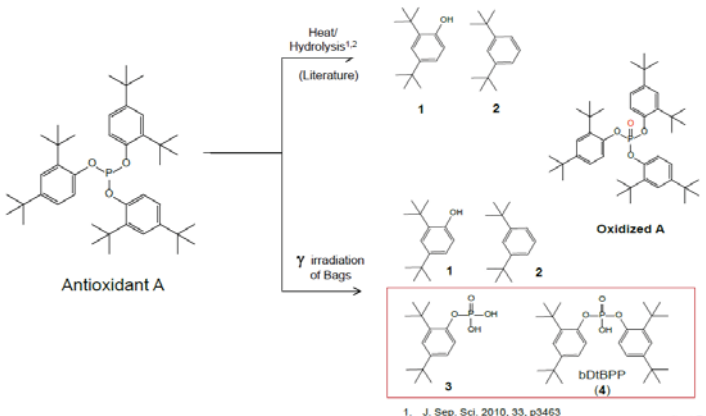
*Vendor data/information from extractables testing

Tris(2,4-di-tert-butyl-phenyl)phosphite (A): Antioxidant in Polymer Film



Extracted | Not extracted | Trace amount

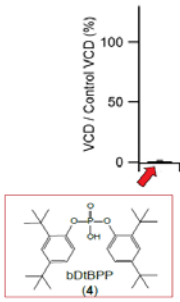
bDtBPP(4) Formation Due to Sterilization (gamma irradiation)

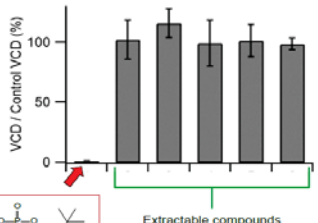


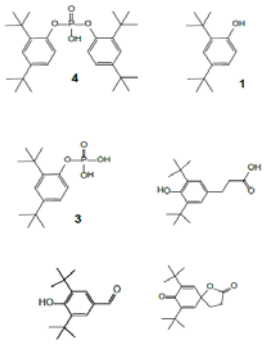
1. J. Sep. Sci. 2010, 33, p3463
2. Packag. Technol Sci. 1999, 12, p119

Extractable Detrimental Impact on Cell Culture

- Spike extractables at ~ 1ppm into cell culture medium





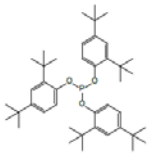


*b*DtBPP (4) is detrimental to cell growth

PDA J Pharm Sci Tech 2013, 67(2) p123 AMGEN

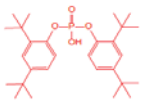
Summary/Conclusion

- Hypothesis: Extractable(s) impacts cell culture performance
- Extractables from intact bags were identified
- Poor cell culture performance correlated to an antioxidant tris(2,4-di-tert-butyl-phenyl)phosphite (A) degradant: Bis(2,4-di-t-butyl-phenyl)phosphate (bDtBPP)



Antioxidant A

Detrimental to cell growth



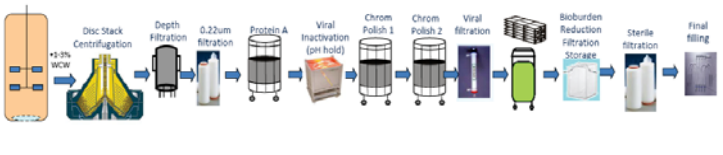
Antioxidant degradant: bDtBPP

- Currently, antioxidant A presents in many polymer films. Industry is now aware of bDtBPP.

AMGEN

PDA

Bioproduction process



Product recovery / harvesting

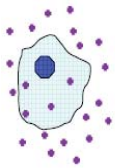
Bioproduction example from a slide from Presentation at IQPC Conference "Disposable Solutions", Munich, 18-20 FEB2014: "BPOG's Extractable Protocol Standardization Journey – Review 2013 Process ande Planning for 2014" Ken Wong (Sanofi-Pasteur), with permission of the Author.

PDA

Product Recovery

Extracellular secreted product

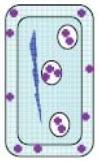
» Mammal cells



Intracellular product

» Bacteria

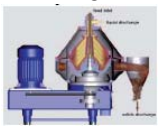
1. Cytoplasmatic expression *(e.g. E.coli)*
2. Periplasmatic expression (e.g. Gram-negative)

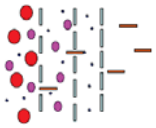


Product recovery:
Extracellular Secretion

Step 1: removal of cells

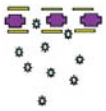
Centrifugation or Filtration

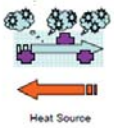


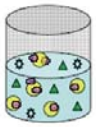


Step 2: volume reduction

Ultrafiltration or damping or batch adsorption







Product recovery:
Intracellular Secretion

Step 1: Cell recovery
centrifugation

Step 2: **Cellular disruption**

Mechanical: homogenisation, milling, sonication

Non mechanical: osmotic shock, 'freeze thaw', enzymatic

lysozyme + EDTA
of solvents: increase of celwand cell permeability
of detergents: dissolution of membrane-fosfolipids

Step 3: Clarification

Step 4: Concentration

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.

Purification

THREE STEPS

Step 1
ISOLATION: **Transfer** product to an environment which **protects** the **activity** & **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 & Purification

Evaluation of Extractables & Leachables

» Filters & chromatography resins have **high contact surface area** vs **solution volume**
- Increased exposure amount
- Higher risk for leachables

» Subsequent process steps (such as *purification & formulation*) may ***remove/dilute*** leachables introduced during the *product recovery & purification*

However, no published data is currently avaialble

Bioproduction process

Storage of intermediate/bulk product

↓

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.

Storage of Bulk Products

Storage of drug substance, buffer solutions, growth medium, etc...

Duration can be *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

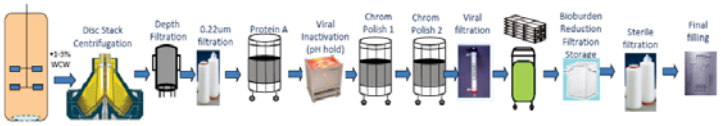
Storage of Bulk Products

Evaluation of Extractables & Leachables

» Containers with **low filling volume** have **higher contact surface area vs solution volume** ratio
→ - higher risk for leachables

» Impact of storage conditions:
↑ storage temperature: ↑ amount of leachables
↑ storage time: ↑ 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 & Filling

Adding excipients in order to obtain the **right stability & 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

Formulation & Filling

Evaluation of Extractables & Leachables

» Filters have a **high contact surface area** to **solution volume ratio**

» Filling equipment makes direct contact with the final drug product
→ all leachables will end up in the final product
(no longer any *dilution/purification steps*)

FDA 1999 "Container/Closure Guidance": also applicable for storage of Drug Substance

Processing Materials

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

2. Many of the systems are custom configs *(of components)*
   - 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 is 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

How to address: REGULATORY REQUIREMENTS

UNIQUE CHALLENGES OF BIOLOGICS

- Administration by injection is among those of highest concern
- Likelihood of interaction between packaging component and injectable dosage is high
- Biologics are complex
  - ✓ Large molecular weights
  - ✓ Abundance of binding sites on the surface (hydrophilic & hydrophobic)
  - ✓ Heterogeneous mixtures
- Biologics are sensitive to structural modifications
  - ✓ Safety considerations (immunogenicity)
  - ✓ Efficacy considerations (loss of activity, formation of neutralizing antibodies)
  - ✓ Quality considerations (protein aggregates, stability)

I. *Markovic (2014) regulatory Perspective on Extractables & Leachables in Biologics, ASTM E55 Workshop, May 21, 2014*
II. *Kim Li (2016) Predicting the risk of extractables and leachables (E&L) interacting with Therapeutic proteins, presentation at PEPTALK 2016*

How to address: REGULATORY REQUIREMENTS

E&L STRATEGY FOR BIOLOGICS MUST ADDRESS BOTH SAFETY & QUALITY CONCERNS

- The strategy can be applied to drug containers, drug delivery systems & single-use systems
- It should incorporate key ICH Q9 concepts, science- and risk based
- It should be phase appropriate, progressing from screening and selection of critical components to life cycle management of drug products

Evaluation of E/L should provide understanding of toxicity profile and likelihood of interaction with drug, excipient and/or package

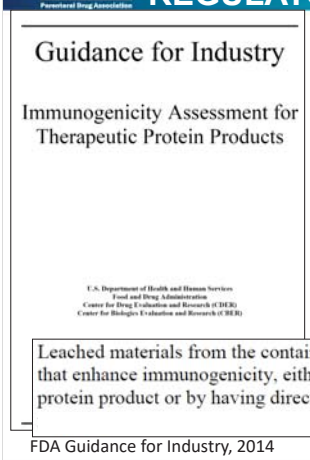
I. *Kim Li (2016) Predicting the risk of extractables and leachables (E&L) interacting with Therapeutic proteins, presentation at PEPTALK 2016*

How to address: REGULATORY REQUIREMENTS

E&L STRATEGY FOR BIOLOGICS MUST ADDRESS BOTH SAFETY & QUALITY CONCERNS

- For **Safety Evaluations**, one can **rely in well described risk based approaches**
  - ✓ E.g. Extrapolation of the PQRI Threshold approach to Single-Use Systems
  - ✓ ICH M7 for Genotoxic Impurities
  - ✓ In depth Toxicological Evaluation (see other presentation)
- However, what about **thresholds – *or acceptance criteria* – for the evaluation of leachable impact on Drug Prudct QUALITY**?
  - ✓ Not yet described
  - ✓ Not clear on "how low to go" from a quality perspective

How to address: REGULATORY REQUIREMENTS


Guidance for Industry

Immunogenicity Assessment for Therapeutic Protein Products

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)

Consequences for EFFICACY – some of the concerns:

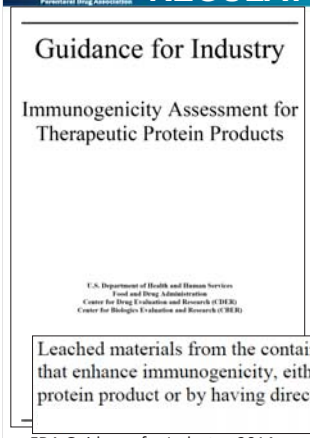
Development of "***Neutralizing Antibodies***" *(e.g. through chemically modified therapeutic protein product)* can **block the efficacy** of therapeutic protein products

May also change the Pharmacokinetics
- Enhancing Clearance
- Or Prolonging Product Activity

Leached materials from the container closure system may be a source of materials that enhance immunogenicity, either by chemically modifying the therapeutic protein product or by having direct immune adjuvant activity

FDA Guidance for Industry, 2014

How to address:
REGULATORY REQUIREMENTS


Guidance for Industry

Immunogenicity Assessment for Therapeutic Protein Products

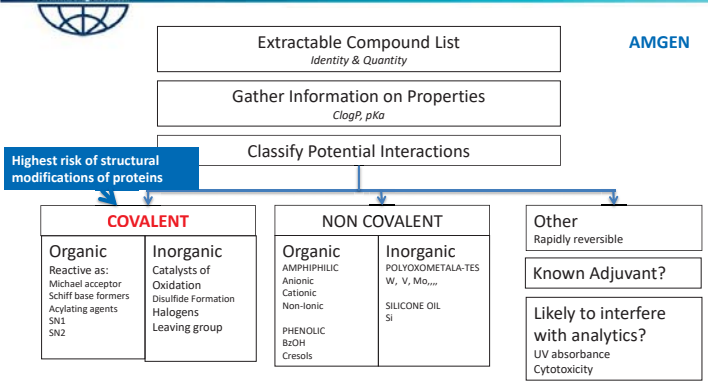
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

Leached materials from the container closure system may be a source of materials that enhance immunogenicity, either by chemically modifying the therapeutic protein product or by having direct immune adjuvant activity.

FDA Guidance for Industry, 2014

Consequences for SAFETY – some of the concerns:
(e.g. "...through chemically modified therapeutic protein product...")

- Anaphylaxis (serious, accute allergenic reaction)
- Cytokine Release Syndrome
- "Infusion Reactions"
- Non-Acute Reactions
- Cross-reactivity to Endogeneous Proteins



Li, K., Rogers, G., Nashed-Samuel, N., Lee, H., Mire-Sluis, A., Cherney, B.,... Markovic, I., (2015). Creating a Holistic Extractables and Leachables 'E&L) Program for Biotechnology Products. PDA Journal of Pharmaceutical Science and Techniology 69(5), 590-619
Kim Li (2016) Predicting the risk of extractables and leachables (E&L) interacting with Therapeutic proteins, presentation at PEPTALK 2016

Examples of Extractables that may form covalent binding with protein

- Michael acceptors
  - ✓ Acrylic acid, Methacrylic acid, 1,6-hexanediol diacrylate, dibutylmaleate
  - ✓ Schiff base formers
  - ✓ BHT-related structures (BHT-OH, BHT-aldehyde, BHT-quinone, BHT-quinone methide)
- Acylating agents
  - ✓ Phthalic anhydride
- Transition Metals
  - ✓ Cr, Cu, Fe, Mn, Ni, W, Zn

Li, K., Rogers, G., Nashed-Samuel, N., Lee, H., Mire-Sluis, A., Cherney, B.,... Markovic, I., (2015). Creating a Holistic Extractables and Leachables 'E&L) Program for Biotechnology Products. PDA Journal of Pharmaceutical Science and Techniology 69(5), 590-619
Kim Li (2016) Predicting the risk of extractables and leachables (E&L) interacting with Therapeutic proteins, presentation at PEPTALK 2016

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

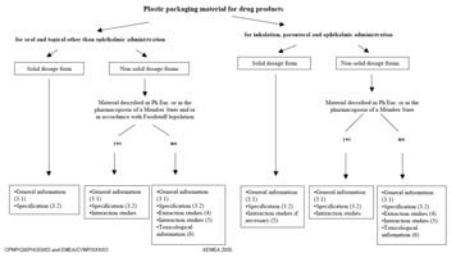
USP <1664> Table 1. Modified FDA/CDER/CBER Risk-Based Approach to Consideration of Leachables

Examples of Packaging Concerns for Common Classes of Drug Products			
Degree of Concern Associated with Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	Medium	Low
Highest	Inhalation Aerosols and Sprays	Injections and Injectable Suspensions; Inhalation Solutions	Sterile Powders and Powders for Injection; Inhalation Powders
High	Transdermal Ointments and Patches	Ophthalmic Solutions and Suspensions; Nasal Aerosols and Sprays	—
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	—	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules; Topical Powders; Oral Powders

While this table provides a convenient overview of the general level of regulatory concern with various dosage forms regarding leachables, it should not be inferred that "low-risk" dosage forms (e.g., oral tablets) by that definition carry no risk for leachables issues.

EMA Plastic Immediate Packaging materials (2005)

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



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 <665>**

BPSA
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

Bio-Process Systems Alliance (BPSA)
Selected slides with permission of the Author 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)

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

22

PALL Life Sciences

Connecting People, Science and Regulation®

Bio-Process Systems Alliance (BPSA)
Selected slides with permission of the Author 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)

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)*

26

PALL Life Sciences

Connecting People, Science and Regulation®

Bio-Process Systems Alliance (BPSA)
Selected slides with permission of the Author 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)

Analytical Methods

Analytical Techniques		Characteristics
• FTIR		• Identification
• GC/FID		• Overview
• GC/MS		• Category/Classification
• HPLC/DAD		• Sensitivity (LOD)
• HPLC/MS		• Detectable Species
• HS/GC/MS		• Sample Preparation
• IC	• Conductivity	• Strengths
• ICP	• pH	• Limitations
• NVR	• TOC	

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

27

PALL Life Sciences

Connecting People, Science and Regulation®

Bio-Process Systems Alliance (BPSA)

Selected slides with permission of the Author 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)

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?

28

PALL Life Sciences

BioPhorum Operations Group (BPOG)

Slides Selected with permission of the Author 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)

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 (BPOG)

Slides Selected with permission of the Author 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)

Standard Extractable Studies – Subset of Sample Preparation Table

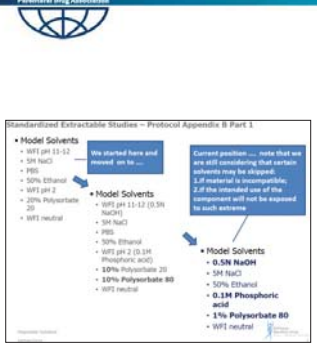
Single Use Component Type	Recommended Sample Extraction Conditions
Storage / Mixing / Bioreactor bags	Use a small bag (≤ 5L) - meet 6:1 (cm^2/mL) surface area to volume ratio. Studies performed with 2D bags with the same MOC (represent 3D bags). Shaking on an orbital shaker is recommended. Express analytical 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.

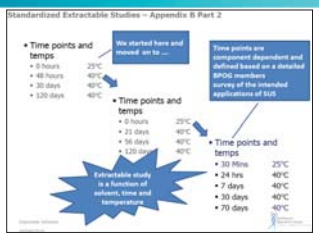
6:1 ratio can be adjusted down with justification

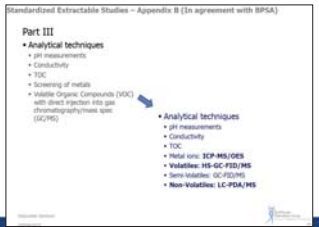
1:1 ratio is the minimum. Higher is desirable

BioPhorum Operations Group (BPOG)

Slides Selected with permission of the Author 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)







BioPhorum Operations Group (BPOG)

Slides Selected with permission of the Author 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)

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			

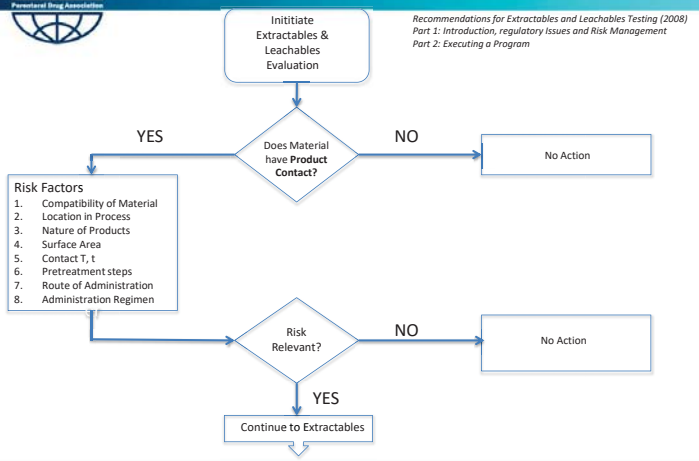
[1] *Certain solvent may be skipped:*
If material is incompatible;
If the intended use of the component will not be exposed to such extreme

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

BioProcess System Alliance (BPSA)

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,…*

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

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

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

PDA BioProcess System Alliance (BPSA)

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

Connecting People, Science and Regulation®

PDA BioProcess System Alliance (BPSA)

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

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

Connecting People, Science and Regulation®

PDA BioProcess System Alliance (BPSA)

RISK FACTOR 3: Solution Composition

- Extreme pH
- High organic or alcohol content
- Surfactants

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

Connecting People, Science and Regulation®

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

PDA BioProcess System Alliance (BPSA)

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

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

Connecting People, Science and Regulation®

PDA BioProcess System Alliance (BPSA)

RISK FACTOR 6: Pretreatment steps

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

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

Connecting People, Science and Regulation®

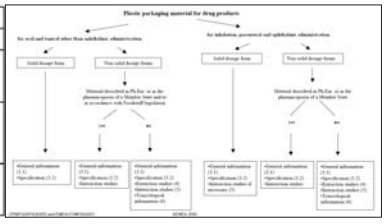
PDA BioProcess System Alliance (BPSA)

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*	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



Connecting People, Science and Regulation®

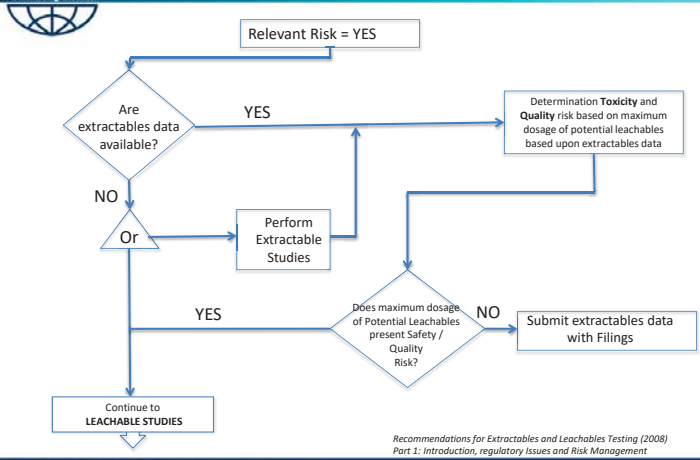
BioProcess System Alliance (BPSA)

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

What to do with RISK FACTORS?

- Create priorities for testing
  - If a change is needed, determine early
- 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 performed in this manner
  - If numerical risk values are utilized, first determine supporting data… because this potentially leads 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 Flow Chart (continued)



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

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...

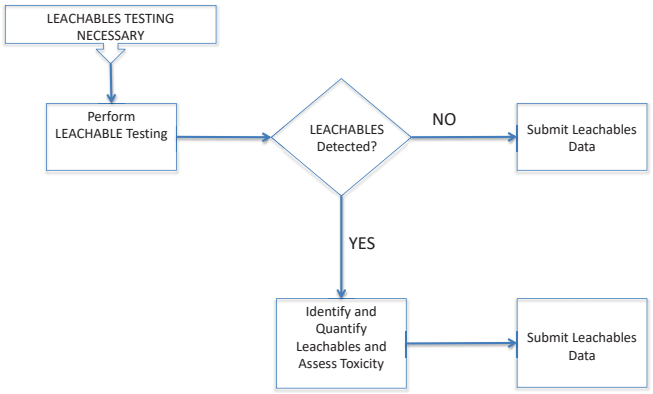
Assess toxicity based on worst-case extractables data

Many processing material applications have a high dilution factor

- **Extractable** studies are conducted with **sufficiently high surface-to-volume** ratio
- Process Materials can have **in-use surface-to-volume** ratios **1,000 times lower** than common extraction studies
- Relatively **high concentration** of extractable **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 (continued)



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: SAFETY CONCERN THRESHOLD

"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

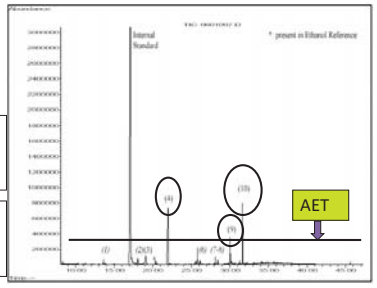
The SCT is not a Control Threshold, it is not a TTC

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)	50 ~~Under Evaluation~~ **SET**	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 expe`cted 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: ANALYTICAL EVALUATION THRESHOLD

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: 50 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):

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

$$\text{Class I: Est. AET} = \frac{50\ \mu g / day}{1\,dose\ /\ day} \cdot \frac{1000\,dose}{Filter} = 50.000\ \mu g\ /\ Filter$$

$$\text{Final AET} = 25.000\ \mu g / Filter$$ **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	50	25000	12,5
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 …/MS RESULTS FOR EXTRACTABLE ST…

	EXT result mg/L	Class	Threshold for Class (µg/day)	FINAL AET for Class (mg/L)
COMPOUND #1	0,10	Class I	50	12,5
COMPOUND #2	0,20	Class I	50	12,5
COMPOUND #3	**1,25**	**Class III**	**1,5**	**0,375**
COMPOUND #4	2,00	Class I	50	12,5
COMPOUND #5	0,40	Class II	5	1,25
COMPOUND #6	0,25	Class I	50	12,5
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**	**50**	**12,5**
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	50	12,5
COMPOUND #13	**32,50**	**Class III**	**1,5**	**0,375**
COMPOUND #14	1,20	Class I	50	12,5
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, further 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> & new(?) ASTM standard~~ USP <1665>)* 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)

United States Pharmacopeia:

INTRODUCTION TO USP <381> ELASTOMERIC COMPONENTS USED IN INJECTABLE PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS

Dennis Jenke, Ph.D.
Member, USP Packaging and Distribution Expert Committee
Member, USP <381> Expert Panel

COPYRIGHT 2013. ALL RIGHTS RESERVED.

USP <381>, A Whole New Ball-game?

⟨381⟩ Elastomeric Closures for Injections, USP 40 page 326:

The Packaging and Distribution Expert Committee is proposing the following revisions which will update and expand the scope of the current chapter.

If you liked one monograph, just think how happy you will be with four!

- **In-Process Revision: <381> ELASTOMERIC COMPONENTS USED IN INJECTABLE PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS.**
- **In-Process Revision: <1381> ELASTOMERIC EVALUATION OF ELASTOMERIC COMPONENTS USED IN PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS.**
- **In-Process Revision: ⟨382⟩ ELASTOMERIC CLOSURE FUNCTIONALITY IN INJECTABLE PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS.**
- **In-Process Revision: ⟨1382⟩ ASSESSMENT OF ELASTOMERIC CLOSURE FUNCTIONALITY IN INJECTABLE PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS.**

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Modifications to USP <381> (1)

Listed below are the key changes being proposed:

1.Change the title to “Elastomeric Components Used in Injectable Pharmaceutical Packaging/Delivery Systems”.

2.Emphasize the baseline requirements for the selection of thermoset and thermoplastic elastomeric components.

3.Expand the scope to include all elastomeric components used in an injection packaging system. Elastomeric components include, but are not limited to, those used for vials, bottles, prefilled syringes (plungers, needle shields, and tip caps), cartridges (plungers and seal liners), injection ports for flexible bags and infusion sets, and plungers for single-use syringes.

4.Delete the *Heavy Metals ⟨231⟩* testing and add a modern method for extractable element determination.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Modifications to USP <381> (2)

5.Omit functionality tests and assessment from the chapter and move them to new chapters appearing in this issue of PF.

a.Functionality tests appear in Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems ⟨382⟩.
b.Baseline information for the assessment is provided in Assessment of Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems ⟨1382⟩.

6.Develop a new informational chapter, Elastomeric Evaluation of Elastomeric Components Used in Pharmaceutical Packaging/Delivery Systems ⟨1381⟩, that is meant to support the current chapter revision by:

a.Describing elastomeric components and their materials of construction for use in pharmaceutical packaging systems
b.Providing a high-level introduction to elastomer chemistry, manufacturing technology, and the post processing of components
c.Explaining basic functional characteristics of components
d.Discussing identification testing

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Contents of the Proposed <381> Chapter

1. **INTRODUCTION**
2. **SCOPE**
3. SPECIFICATIONS
3.1 **Biological Reactivity***
3.2 Physicochemical
3.3 **Extractable Elements**

4. TEST METHODS
4.1 **Biological Reactivity***
4.2 Physicochemical
4.3 Appearance (Turbidity/Opalescence)
4.4 Color
4.5 Acidity or Alkalinity
4.6 Absorbance
4.7 Reducing Substances
4.8 Volatile Sulfides
4.9 Ammonium
4.10 **Extractable Elements**

Bolded titles indicate sections which were significantly changed or are new.

* Changes to the Biological Reactivity sections are largely cosmetic and not substantial.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

A Brief Introduction to <381> (1)

1. Every elastomeric component used in a pharmaceutical packaging/delivery system should be proven safe and compatible for its intended use.
2. The purpose of this chapter is to provide baseline requirements for the selection of elastomeric components to be further qualified for use in a given system.
3. The chemical testing prescribed is orthogonal:
   - the physicochemical tests provide a general overview of extracted chemical entities,
   - the extractable elements test provides a quantitative assessment of extractable elements of concern,
   - Because chemical testing alone may not be adequate, it is augmented with establishing biological reactivity

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

A Brief Introduction to <381> (2)

4. If components comply with requirements outlined in the chapter, studies should then be designed to determine safety and compatibility as recommended in *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* ⟨1663⟩ and *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* ⟨1664⟩.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

The Scope of <381> (1)

1. Elastomeric components include, but are not limited to, those used for vials, bottles, prefilled syringes (plungers, needle shields, and tip caps), cartridges (plungers and seal liners), injection ports for flexible bags and infusion sets, and plungers for single-use syringes.
2. Elastomeric components are formulated with elastomeric substances and can be either thermoset or thermoplastic in nature.
3. Tests are always conducted on the components after surface modifications.
   - chlorinated surface treatments,
   - fluoropolymer coatings and films,
   - cross-linked polydimethylsiloxane,
   - polydimethylsiloxane that has been applied to the component surface as a lubricant

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

The Scope of <381> (2)

4. Baseline testing (biological reactivity, physicochemical, and extractable elements) is to be performed on the finished components after completion of all manufacturing and processing (e.g., molding conditions, sterilization, etc.).

5. The tested components need to be representative of the final components as intended for use in a packaging or delivery system.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

What is outside the Scope of <381>

The following elastomer evaluation requirements are beyond the scope of this chapter:

- Verification of elastomer interactions with the packaged drug product
- Identification and safety qualification of component leachables found in a packaged product
- Verification of packaged product component functionality under actual storage and use conditions
- Specific test conditions for performing all relevant functionality studies

Identification tests are also beyond the scope of this chapter. The applicant is responsible for verifying that the component's elastomeric formulation and any coating or laminate materials used are consistent with the qualified component.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

An Important Distinction; Type I vs Type II

Current Text: Type I closures are those used for aqueous preparations. Type II closures are typically intended for non-aqueous preparations and are those which, having properties optimized for special uses, may not meet all requirements listed for Type I closures because of physical configuration, material of construction, or both.

All elastomeric closures suitable for use with injectable preparations must comply with either Type I or Type II test limits. However, this specification is not intended to serve as the sole evaluation criteria for the selection of such closures.

Proposed Text: Type I components have stricter physicochemical test limits than Type II components. If a component fails to meet one or more of the Type I requirements, but still meets the Type II requirements, the component is assigned a final classification of Type II. Meeting the specifications, or the designations of Type I and Type II, is not intended to serve as the sole criterion for the selection of the elastomeric component.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

The Major Chemical Modification to <381>; Extractable Elements

Because the <231> Heavy Metals is being discontinued, a new approach, based on recent (more rigorous) expectations around material characterization and modern analytical capabilities, for dealing with extracted metals and other relevant elements was required.

Major Changes:

1. A new extraction and analysis methodology was established based on extensive laboratory investigations,
2. Specifications were replaced with "report as found" requirements.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Extractable Elements - Extraction

Extraction solution: Prepare a solution of a mixture of acids with gold (Au) to stabilize mercury (Hg) in the following ratio: 0.2 N nitric acid (HNO_3), 0.05 N hydrochloric acid (HCl), and 200 ppb gold (Au). Prepare the solution in a volume sufficient to prepare all standards, blanks, spikes, and extractions. Care should be taken to use high-purity reagents.

Extraction: Place whole, uncut components equivalent to 1 g/2.5 mL of the Extraction solution into a suitable plastic container and record the weight. Prepare two extraction blank solutions (one for spiking) using a container of the same type as that used for the samples, omitting the closures. Seal the containers and place in an oven at 70° . Remove containers after 24 h and allow to cool. Analyze within 48 h.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Extractable Elements - Analysis

Analysis: Extracts, spikes, and blanks are to be analyzed by inductively coupled plasma–mass spectrometry (ICP–MS) and/or inductively coupled plasma–optical emission spectroscopy (ICP–OES). Refer to *Elemental Impurities—Procedures ⟨233⟩* for analytical procedures and system suitability.

Method Suitability (Extraction recovery): Prepare a 10 µg/mL solution of antimony (Sb), arsenic (As), cadmium (Cd), cobalt (Co), copper (Cu), lead (Pb), lithium (Li), mercury (Hg), nickel (Ni), vanadium (V), and zinc (Zn) in Extraction solution [0.2 N nitric acid (HNO_3), 0.05 N hydrochloric acid (HCl), and 200 ppb gold (Au)]. Using a suitable pipet, spike one of the blank extraction solutions with the appropriate volume of the 10-µg/mL solution, resulting in a concentration of 0.05 µg/g.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Extractable Elements - Reporting

Test Results: Antimony, arsenic, cadmium, cobalt, copper, lead, lithium, mercury, nickel, vanadium, and zinc are reported in amounts greater than 0.05 µg/g converted to µg/component with two significant figures. If the measured values are below these values, report the result as less than 0.05 µg/g.

Method Suitability (Extraction recovery): Refer to *Elemental Impurities—Procedures ⟨233⟩* for system suitability requirements.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Key User Questions Concerning <381>

1. **What were they thinking?**
2. **How do I use these chapters?**

Answers provided in:

<1381> ELASTOMERIC EVALUATION OF ELASTOMERIC COMPONENTS USED IN PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

The Purpose of <1381>

The new chapter:

1. Describes elastomeric components and their materials of construction for use in pharmaceutical packaging systems
2. Provides a high-level introduction to elastomer chemistry, manufacturing technology, and the post processing of components
3. Explains basic functional characteristics of components
4. Designates baseline requirements
5. Discusses identification testing

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Elastomeric Components: Compounds of Concern (Table 4)

Compound of Concern	Source	Concern	Comment
Latex	Associated with compounds containing dry natural rubber or derivatives	Allergic reaction	—
Materials of animal origin	Stearic acid salts and esters used as slip agents	Transmissible spongiform encephalopathies (TSEs) including bovine spongiform encephalopathy (BSE)	Equivalent materials from vegetable origin are not associated with BSE/TSE risks.
MBT (2-mercapto-benzothiazole) and derivatives	Associated with cure system	Carcinogenic	—
Phthalates: [bis(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DINP), diisodecyl phthalate (DIDP)]	Used as a plasticizer in polymers used in TPEs	Toxicity	—
PNAs (polynuclear aromatic compounds)	Associated with carbon black (colorant)	Carcinogenic	The PNA content of carbon black depends on its production process.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Key Points in <1381>, Section 6.1, Test Requirements and Responsibilities (1)

- Elastomeric closures should conform both when they are shipped by the closure supplier to the injectable product manufacturer (the end user) and in their final state, ready for use by the end user.
- For elastomeric closures processed by the supplier before distribution to the end user, the supplier should demonstrate compendial conformance of closures exposed to such processing and/or sterilization steps.
- If elastomeric closures are subsequently processed or sterilized by the end user, the end user is responsible for demonstrating the continued conformance of the closures to compendial requirements after such processing and/or sterilization conditions (i.e., in their ready-to-use state).

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Key Points in <1381>, Section 6.1, Test Requirements and Responsibilities (2)

- For closures that are normally lubricated with silicone prior to use, it is permissible to perform physicochemical testing on non-lubricated closures to avoid potential method interference and/or difficulties in interpreting test results.
- For closures supplied with other lubricious non-barrier coatings, all tests are to be performed using the coated closure.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Key Points in <1381>, Section 6.1, Test Requirements and Responsibilities (3)

- For closures coated or laminated with coatings intended to provide a barrier function, physicochemical compendial tests apply to the uncoated base elastomer, as well as to the coated closure.
  - Suppliers are responsible for demonstrating physicochemical compendial compliance of the coated closure, as well as of the uncoated closure, processed or treated in a manner simulating conditions typically followed by the supplier for such coated closures before shipment to the end user.
  - End users of coated closures are also responsible for demonstrating the continued physicochemical compendial conformance of the coated closure, processed or treated in a manner simulating conditions typically employed by the end user prior to use.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Key Points in <1381>, Section 6.1, Test Requirements and Responsibilities (4)

Identification Tests:

it is the responsibility of the closure supplier and the injectable product manufacturer (the end user) to verify the closure's elastomeric formulation and any coating or laminate material used according to suitable identification tests.

Tests to Use:

- specific gravity,
- percentage of ash analysis,
- sulfur content determination,
- Fourier transform infrared spectroscopy-attenuated total reflectance (FTIR-ATR) test,
- thin-layer chromatography of an extract,
- UV absorption spectrophotometry of an extract,
- infrared absorption spectrophotometry of a pyrolysate.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Key Points in <1381>, Function of the Various Physicochemical Tests (1)

Determination of turbidity (opalescence): a nonspecific test for all the extractable species in a rubber formulation that are not soluble in an aqueous solution. A high turbidity is the indication of a high extractable potential. Species promoting turbidity have numerous origins in a rubber formulation, including fatty acid derivatives, residues of curing systems, and oligomers from the elastomer.

Acidity/alkalinity: a nonspecific test indicative of the acidic, basic, or buffering power of the aqueous extractables from the rubber formulation. High values in the acidity/alkalinity test may need to be evaluated in conjunction with the specifics of a drug solvent vehicle and anticipated specification of the drug product for pH.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Key Points in <1381>, Function of the Various Physicochemical Tests (2)

Color: a nonspecific test indicative of the presence of extractable species in a rubber formulation that have the capacity of attributing color to an aqueous solution. Species that cause color may have several origins in a rubber formulation. Aqueous solutions are common in pharmaceutical packaging/delivery systems.

Absorbance: The UV spectrum of an aqueous extract from a rubber formulation is indicative of the unsaturated or aromatic character of the chemical species extracted. Unsaturated compounds in the extracts may originate from many raw materials and additives of a rubber formulation such as antioxidants, preservatives, and curing or dying agents.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Key Points in <1381>, Function of the Various Physicochemical Tests (3)

Reducing substances: a nonspecific test. Extracted species from a rubber formulation with potential reducing power may originate from most raw materials of a rubber formulation (polymer, curing system, preservatives, antioxidants, etc.).

Ammonium: a specific test for rubber formulations with nitrogen-containing raw materials. Ammonium ions can be generated during the curing process. Thiurams and thiazoles are examples of nitrogen-containing curing systems used.

Volatile sulfides: a specific test for rubber formulations containing sulfur. Sulfur and sulfur precursors are often used as components of curing systems for rubber.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2015. ALL RIGHTS RESERVED.

Current Status, <381> and <1381>

- **In-Process Revision: <381> ELASTOMERIC COMPONENTS USED IN INJECTABLE PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS.**
- **In-Process Revision: <1381> ELASTOMERIC EVALUATION OF ELASTOMERIC COMPONENTS USED IN PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS.**

Both these documents are in the Pharmacopeial Forum; 43(3), 2017.

Both these documents are currently in their public review stage (first cycle). The public review stage ends September 30, 2017.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2015. ALL RIGHTS RESERVED.

Thank You!

Contact the presenter at: dennisjenke@triadscientificsolutions.com
www.triadscientificsolutions.com

COPYRIGHT 2015. ALL RIGHTS RESERVED.

United States Pharmacopeia:

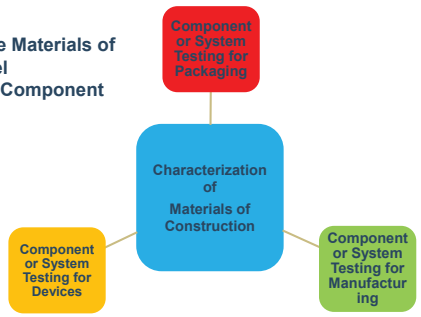
Introduction to USP <665> POLYMERIC COMPONENTS AND SYSTEMS USED IN THE MANUFACTURING OF PHARMACEUTICAL AND BIOPHARMACEUTICAL DRUG PRODUCTS

Dennis Jenke, Ph.D.
Member, USP Packaging and Distribution Expert Committee
Chair, USP <665> Expert Panel

COPYRIGHT 2013. ALL RIGHTS RESERVED.

The Essence of the USP Strategy for Plastics

- Standardize at the Materials of Construction level
- Customize at the Component or System level



COPYRIGHT 2013. ALL RIGHTS RESERVED.

Packaging Materials/Components

<665> POLYMERIC COMPONENTS AND SYSTEMS USED IN THE MANUFACTURING OF PHARMACEUTICAL AND BIOPHARMACEUTICAL DRUG PRODUCTS

Scope: Items covered

- Active pharmaceutical ingredients and drug products
- Pharmaceuticals, Small Molecules, Biopharmaceuticals products and Vaccines
- Single-Use Systems and Multi-Use Systems

COPYRIGHT 2013. ALL RIGHTS RESERVED.

A Brief Introduction to <665> (1)

1. <665> speaks to the characterization of materials of construction, enabling the selection of proper materials used in manufacturing components, and to the characterization of components, enabling the proper selection of components used in manufacturing operations.
2. <665> does not speak to the qualification of materials, components or systems, although testing performed for the purpose of selection may be relevant to qualification.
3. Materials of construction must be tested consistent with, and meet the requirements of, <661.1>.

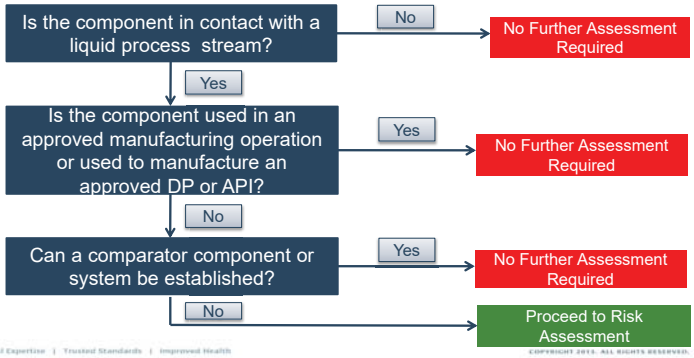
COPYRIGHT 2013. ALL RIGHTS RESERVED.

A Brief Introduction to <665> (2)

4. Components are further characterized depending on the level of risk associated with their application in a particular manufacturing operation. USP <1665>, which is essentially a "user's manual for <665>, contains a Risk Evaluation Matrix whose purpose is to classify components and their associated conditions of use into three risk categories.
5. High risk components must be profiled for extractables using a Standard Extraction Protocol (SEP) as provided in <665>.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Navigating through <665> for Component Characterization



Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

What the Risk Evaluation Matrix Accomplishes

1. Establishes the appropriate contributors to, or dimensions of, risk,
2. Provides a means of quantifying the risk, in each of its dimensions, and
3. Links the quantified risk to appropriate characterization strategies.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Use of the Risk Evaluation Matrix (1)

The *Risk evaluation matrix* considers four dimensions that address the risk that a plastic component will be leached by a process stream to such an extent that process streams could contain potentially impactful extractables.

1. The duration of contact,
2. The temperature of contact,
3. The chemical composition of the process stream,
4. The nature of the component's materials of construction.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Use of the Risk Evaluation Matrix (2)

The matrix considers each dimension separately and assigns a level of risk associated with certain measures relevant to each dimension.

Table 2. Dimensions Relevant to Risk Level

Risk Dimension	Duration	Temperature[a]	Solvent	Material Reactivity
Level 1	<24 h	Frozen (< −10°)	Aqueous pH >3 and pH <9	Inert
Level 2	1–7 days	Refrigerated (2°–8°) Ambient (15°–25°)	Somewhat organic	Intermediate
Level 3	>7 days	Elevated (>30°)	Highly organic or extreme pH (pH <3 or pH >9)	Reactive

[a] The gaps in the temperature ranges reflect temperature ranges that are rarely experienced in manufacturing processes.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Applying of the Risk Evaluation Matrix (1)

The *Risk Evaluation Matrix* uses a three-step process.

Step 1: Establish values for each risk dimension:

A component being assessed for risk is "rated" with respect to these four dimensions shown in *Table 3*, and the resulting rating results in a level assignment of either *1*, *2*, or *3* in each of the four dimensions. A numerical risk sequence can be generated based on these assignments. For example, a component or system that is rated as highest risk in all four dimensions has a generated numerical risk sequence of *3333*.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Applying of the Risk Evaluation Matrix (2)

Step 2: Linking the numerical risk sequence with a level of characterization.

Table 3. Linking the Numerical Risk Sequence with a Level of Characterization

If ...	And ...	Characterization Level
Four dimension scores are Level 3	No additional qualifier (3333)	Level C
Three dimension scores are Level 3	Other dimension score is Level 2 (3332)	Level C
	Other dimension score is Level 1 (3331)	Level C
	Other two dimension scores are both Level 2 (3322)	Level C
Two dimension scores are Level 3	One dimension score of Level 2 (3321)	Level B or C[c]
	Other two dimension scores are Level 1 (3311)	Level A or B[a]
One dimension score is Level 3	All of the three other dimension scores are Level 2 (3222)	Level B
	One of the other dimension scores is Level 1 (3221)	Level B
	Two of the other dimension scores are Level 1 (3211)	Level A or B[a]
	All of the three other dimension scores are Level 1 (3111)	Level A
No dimension score is Level 3	All of the dimension scores are Level 2 (2222)	Level B
	Not all of the four dimension scores are Level 2	Level A

[a] If the Level 2 score is in temperature, solvent, or duration dimensions, then Level C; otherwise, Level B.
[b] If one of the Level 1 scores is in the material reactivity dimension, then Level B; otherwise, Level A.
[c] If one of the Level 1 scores is in the material reactivity dimension, then Level B; otherwise, Level A. In these cases the temperature, solvent, or duration dimensions have a greater influence on risk than does material reactivity.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Applying of the Risk Evaluation Matrix (3)

Step 3: Using mitigating factors to adjust the characterization level:

Mitigating factors take into account circumstances that mitigate patient exposure to PerIs, including clearance of the PerI via one or more manufacturing steps and the clinical use of the manufactured drug product.

Clearance: Is there a post-contact processing step that is capable of clearing extracted substances?

- Yes, use the mitigating factor (clearance mitigating factor value = 1).
- No, do not use the mitigating factor.

Clinical use: What is the safety risk of leachables given the clinical use of the process output consider dosage form, duration of clinical use, daily dose volume?

- If the dosage form is solid or liquid oral, mitigating factor value = 1.
- If the duration of clinical use is <7 days, mitigating factor = 1.
- If the daily dose volume is <10 mL, mitigating factor = 1.
- If the daily dose volume is <10 mL, mitigating factor = 1.
- Otherwise, mitigating factor = 0.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Applying of the Risk Evaluation Matrix (4)

Using mitigating factors to adjust the characterization level:

Add up the mitigating factors from clearance and clinical use.

- If the sum = 0, then there is no adjustment of the characterization level.
- If the sum is = 1, then the characterization level established by the Matrix is reduced by one level of testing (e.g., *Level B* testing is reduced to *Level A* testing).
- If the sum is = 2, then characterization *level A* is applicable in all circumstances.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Linking the Characterization Level to the Required Level of Assessment (1)

- *Level A* = Baseline Assessment
- *Level B* = Expanded Baseline Assessment
- *Level C* = Full Testing

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

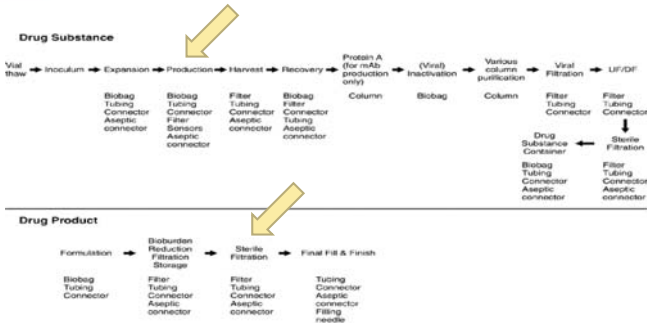
Linking the Characterization Level to the Required Level of Assessment (2)

Table 1. Testing Requirements for Three Risk Levels

Risk Level	Assessment Level	Testing Requirements	
		Materials of Construction	**Component or System**
A	Baseline	All individual materials of construction comply with <661.1> as follows: • Identity • *Biological Reactivity Tests, In Vitro* <87> • Physicochemical characteristics • Extractable metals • Additives are addressed by proper reference to 21 CFR 174-179 Indirect Food Additive regulations	• Biological Reactivity per <87>. If a test failure is obtained during <87> testing, then test to Class VI designation per <88>.
B	Expanded Baseline	All individual materials of construction comply with <661.1> as follows: • Identity • *Biological Reactivity Tests, In Vitro* <87> and ***Biological Reactivity Tests, In Vivo* <88>, Class VI designation** • Physicochemical characteristics • Extractable metals • **Additives determined by testing as specified in <661.1>**	• Biological Reactivity <87> and **Class VI per <88>.** • **Extractable Metals (in extract *Solution C1*)**
C	Full	All individual materials of construction comply with <661.1> as follows: • Identity • *Biological Reactivity Tests, In Vitro* <87> and *Biological Reactivity Tests, In Vivo* <88>, Class VI designation • Physicochemical characteristics • Extractable metals • Additives determined by testing as specified in <661.1>.	• Biological Reactivity <87> and Class VI per <88>. • **Full Extractables Profiling via *Standard Extraction Protocol***

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Examples of Using the Risk Assessment Matrix



Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Example 1: Biobag used in Production

1. **Dimension 1:** Duration = 72 hours
2. **Dimension 2:** Temperature = Ambient
3. **Dimension 3:** Solvent = pH 6 buffer
4. **Dimension 4:** Materials of Construction = multiple materials, total additives between 0.1% and 1%

Table 2. Dimensions Relevant to Risk Level

Risk Dimension	Duration	Temperature[a]	Solvent	Material Reactivity
Level 1	<24 h	Frozen (< −10°)	Aqueous pH >3 and pH <9	Inert
Level 2	1–7 days	Refrigerated (2°–8°) Ambient (15°–25°)	Somewhat organic	Intermediate
Level 3	>7 days	Elevated (>30°)	Highly organic or extreme pH (pH <3 or pH >9)	Reactive

[a] The gaps in the temperature ranges reflect temperature ranges that are rarely experienced in manufacturing processes.

Score = 2212

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Example 1: Biobag used in Production

Table 3. Linking the Numerical Risk Sequence with a Level of Characterization

If ...	And ...	Characterization Level
Four dimension scores are Level 3	No additional qualifier (3333)	Level C
	Other dimension score is Level 2 (3332)	Level C
Three dimension scores are Level 3	Other dimension score is Level 1 (3331)	Level C
	Other two dimension scores are both Level 2 (3322)	Level C
	One dimension score of Level 2 (3321)	Level B or C[a]
Two dimension scores are Level 3	Other two dimension scores are Level 1 (3311)	Level A or B[b]
	All of the three other dimension scores are Level 2 (3222)	Level B
	One of the other dimension scores is Level 1 (3221)	Level B
	Two of the other dimension scores are Level 1 (3211)	Level A or B[b]
One dimension score is Level 3	All of the three other dimension scores are Level 1 (3111)	Level A
	All of the dimension scores are Level 2 (2222)	Level B
No dimension score is Level 3	Not all of the four dimension scores are Level 2	Level A

[a] If the Level 2 score is in temperature, solvent, or duration dimensions, then Level C; otherwise, Level B.
[b] If one of the Level 1 scores is in the material reactivity dimension, then Level B; otherwise, Level A.
[c] If one of the Level 1 scores is in the material reactivity dimension, then Level B; otherwise, Level A. In these cases the temperature, solvent, or duration dimensions have a greater influence on risk than does material reactivity.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Example 1: Biobag used in Production

- *Level A* = Baseline Assessment
- *Level B* = Expanded Baseline Assessment
- *Level C* = Full Testing

Additionally, there is a potential mitigating factor involved with clearance.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Example 2: Sterilizing Filter prior to Final Fill

1. **Dimension 1:** Duration = 40 hours
2. **Dimension 2:** Temperature = Ambient
3. **Dimension 3:** Solvent = formulation contains 1% solubilizing agent
4. **Dimension 4:** Materials of Construction = multiple materials, total additives > 1%

Table 2. Dimensions Relevant to Risk Level

Risk Dimension	Duration	Temperature[a]	Solvent	Material Reactivity
Level 1	<24 h	Frozen (< −10°)	Aqueous pH >3 and pH <9	Inert
Level 2	1–7 days	Refrigerated (2°–8°) Ambient (15°–25°)	Somewhat organic	Intermediate
Level 3	>7 days	Elevated (>30°)	Highly organic or extreme pH (pH <3 or pH >9)	Reactive

[a] The gaps in the temperature ranges reflect temperature ranges that are rarely experienced in manufacturing processes.

Score = 3322

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Example 2: Sterilizing Filter prior to Final Fill

Table 3. Linking the Numerical Risk Sequence with a Level of Characterization

If ...	And ...	Characterization Level
Four dimension scores are Level 3	No additional qualifier (3333)	Level C
	Other dimension score is Level 2 (3332)	Level C
Three dimension scores are Level 3	Other dimension score is Level 1 (3331)	Level C
	Other two dimension scores are both Level 2 (3322)	Level C
	One dimension score of Level 2 (3321)	Level B or C[a]
Two dimension scores are Level 3	Other two dimension scores are Level 1 (3311)	Level A or B[b]
	All of the three other dimension scores are Level 2 (3222)	Level B
	One of the other dimension scores is Level 1 (3221)	Level B
	Two of the other dimension scores are Level 1 (3211)	Level A or B[c]
One dimension score is Level 3	All of the three other dimension scores are Level 1 (3111)	Level A
	All of the dimension scores are Level 2 (2222)	Level B
No dimension score is Level 3	Not all of the four dimension scores are Level 2	Level A

[a] If the Level 2 score is in temperature, solvent, or duration dimensions, then Level C; otherwise, Level B.
[b] If one of the Level 1 scores is in the material reactivity dimension, then Level B; otherwise, Level A.
[c] If one of the Level 1 scores is in the material reactivity dimension, then Level B; otherwise, Level A. In these cases the temperature, solvent, or duration dimensions have a greater influence on risk than does material reactivity.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Example 2: Sterilizing Filter prior to Final Fill

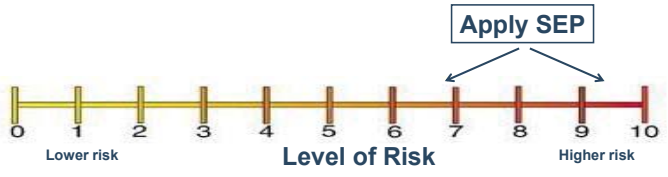
- *Level A* = Baseline Assessment
- *Level B* = Expanded Baseline Assessment
- *Level C* = Full Testing

Additionally, there are no mitigating factors associated with this case.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Key Points, Application of the SEP

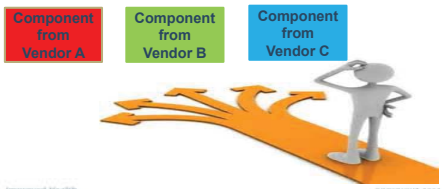
The Standard Extraction Protocol (SEP) is used to characterize high risk manufacturing components or systems for extractables.



Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Key Points, Purpose of the SEP

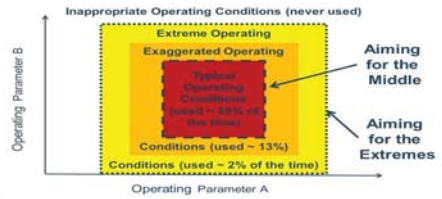
The Standard Extraction Protocol (SEP) is used to generate extractables data to aid in the selection of components to be used in a particular manufacturing operation.



Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Key Points, Focus of the SEP

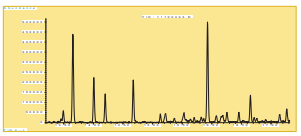
The Standard Extraction Protocol (SEP) "aims for the middle", seeking to represent those conditions most commonly encountered in pharmaceutical manufacturing.



Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Key Points, Objective of the SEP

The Standard Extraction Protocol (SEP) seeks to generate extractables information which informs effective and science-based component selection via hazard identification.



Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Is/Is Not Diagram for SEP

Aspect	Is	Is Not
Application	Components (systems)	Materials of Construction
	High Risk	Low or Moderate Risk
Purpose	Component Selection[1]	Component Qualification[1]
Scope	Hazard Identification	Risk Assessment
Focus	"Aim for the Middle" (most commonly encountered)	"Aim for the Extreme" (most extreme conditions possible)
Objective	Generate Useful Information	Generate Worst Case Information

Note: (1) Under certain circumstances, information for selection may be appropriate as information for qualification.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

The <665> SEP Solvents (1)

Standard Extraction Protocol for Components or Systems Designated as Risk Level C

- **Extraction Solvents**
  - **Solution C1, Acidic Extraction, pH 3**
  - **Solution C2, Basic Extraction, pH 10**
  - **Solution C3, Organic Extraction, 1/1 (v/v) Ethanol/water**

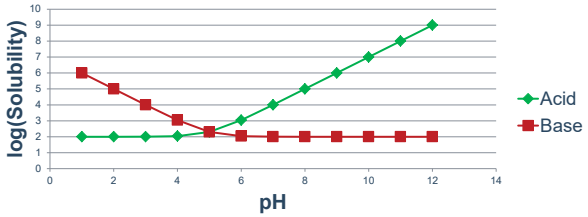
Concept: Extractables profiles obtained with these three solvents will capture those extractables that are present in the most commonly encountered process streams and will provide an estimate of the extractable's typical accumulation levels in those process streams.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

The <665> SEP Solvents (2)

Justification of Extraction Solvents, pH (1)

The Effect of pH on the Solubility of an Acidic or Basic Extractable. The Figure considers an acidic or basic extractable with a pK_a of 5.0 and a solubility of 100 (arbitrary units). As the pH of the extracting medium increases, the solubility (and thus the concentration) of the acidic extractable increases. Similarly, as the pH of the extracting medium decreases, the solubility 9and thus the concentration of a basic extractable increases.

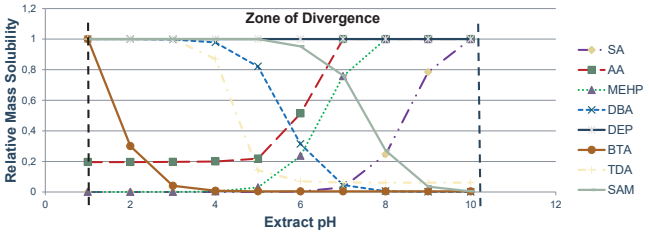


Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013, ALL RIGHTS RESERVED.

The <665> SEP Solvents (3)

Justification of Extraction Solvents, pH (2)

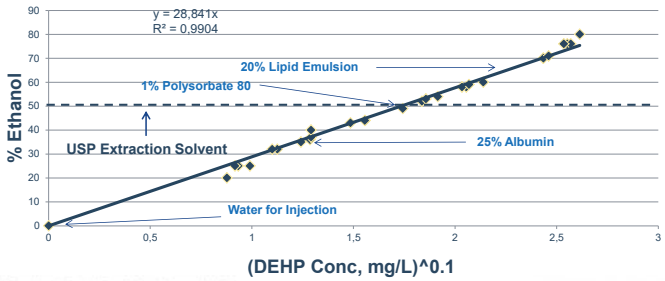
As DEP is non-ionic, its solubility is unaffected by pH. The solubility of the acidic extractables (AA, SA and MEHP) increases with increasing pH, depending on their pK_a. The solubility of the basic extractables (SAM, DBA, TDA, BTA) increases with decreasing pH, consistent with their pK_a. The Zone of Divergence spans those pH values where the weakest acid (SA) and the weakest base (BTA) achieve their maximum solubilities. A set of extraction solvents that captures essentially all possible acidic or basic extractables at their likely highest concentration must have pH values that span the Zone of Divergence.



Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013, ALL RIGHTS RESERVED.

The <665> SEP Solvents (4)

Justification of Extraction Solvents, Ethanol/Water The Relative "Leaching Power" of Drug Products



Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013, ALL RIGHTS RESERVED.

The <665> SEP Solvents (5)

Considering Additional Extraction Solvents

1. Any additional extraction solvent should provide information in addition to information provided by the adopted solvents.

2. Any additional extraction solvent should be analytically expedient.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013, ALL RIGHTS RESERVED.

The <665> SEP Solvents (6)

What about Water?

- Water provides no additional information that is not already provided by the pH extreme solvents.

What about 5 M NaCl?

- 5 M NaCl is the weakest extraction solvent (for organics) and provides no additional information that is not already provided by the pH extreme solvents.
- 5 M NaCl is an analytically challenging solution.

What about 1% Polysorbate 80?

- 50% Ethanol may be an appropriate simulant for 1% PS80.
- 1% PS80 is an **extremely** challenging solution to analyze.

Thus, the USP sees no compelling reason to include these solvents in its SEP.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

The <665> SEP Solvents (7)

What about low pH?

- Data suggests that pH 3 salt solution and 0.1% phosphoric acid produce similar extractables profiles.
- Phosphate matrix produces minor analytical challenges.
- **USP has adopted a statement that makes 0.1% phosphoric acid and pH 3 salt solutions (including its own Solution C1) "interchangeable".**

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

The <665> SEP Solvents (8)

What about high pH?

- In certain situations, 0.5 N NaOH may be a more aggressive extraction solvent than pH 10 buffer.
- 0.5N NaOH can be an analytically challenging matrix, especially related to instrument "wear and tear".
- 0.5N NaOH may not fit the intent of the SEP to "aim for the middle".
- Applications of caustic solutions in manufacturing operations are generally limited to two circumstances:
  - Use of caustics in cleaning, which is not of concern with respect to process-related leachables as any extractables entrained in the caustic solutions are directed to waste and thus out of the process stream.
  - Use of high pH concentrates for pH adjustment, which is not of concern due to large dilution factors.
- **USP considers the pH 10 extraction solvent to be consistent with the intent of the SEP and thus it is the required high pH solvent. However, if the pH of a contact solution exceeds 11, then the pH 10 solvent may be replaced with the contact solution or an appropriate higher pH simulant (with justification).**

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

The <665> SEP Solvents (9); Score Card

- 50% Ethanol; **Alignment**
- Water, 5 M NaCl, 1% Polysorbate 80; **Alignment** (USP allows for the use of additional solvents at the discretion of the sponsor)
- Low pH; **Alignment** (interchangeable solvents)
- High pH; Alignment (pH 10 is the standard, other alternate or additional solutions may be used, at the sponsor's discretion, with justification).

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

<665> Temperature/Duration of Extractions (1)

Standard Extraction Protocol for Components or Systems Designated as Risk Level C

Component	Extraction Solutions C1 through C3	Extraction Temperature 40°	Extraction Duration		
			1 day	7 days	21 days
Storage Container	X	X			X
Mixing Bag	X	X	X		
Bioreactor Bag	X	X			X
Tubing Connector/disconnector	X	X			X
Aseptic/Sterile Connector/disconnector	X	X		X	
Sensor/Valve	X	X	X		
Molded Parts of Mixers	X	X	X		
Polymer pump surfaces	X	X	X		
Tubing	X	X			X
Gasket, O-ring	X	X		X	
Sterilizing Filter	X	X	X		
Process Filter	X	X	X		
Tangential flow Filtration	X	X	X		
Chromatography Column	X	X	X		
Filling Needle	X	X	X		

COPYRIGHT 2013. ALL RIGHTS RESERVED.

<665> Temperature/Duration of Extractions (2)

Rationale for Accelerated Extraction Conditions

$$AAF = Q_{10}^{[(TAA - TREF)/10]} \quad \text{(Equation 1)}$$

where
AAF = Accelerated aging factor
Q10 = aging factor, which has an conventionally accepted value of 2.0 for a 1st order chemical reaction,
TAA = accelerated temperature of contact, and
TREF = reference temperature of typical use.

$$AAT = tref/AAF \quad \text{(Equation 2)}$$

where
AAT = accelerated aging time
tref is the reference time of typical use.

Reference: ASTM F1980-07 (Reapproved 2011). Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices. ASTM International, West Conshohocken, PA; approved Aug. 1, 2011. DOI: 10.1520/F1980-07R11.

COPYRIGHT 2013. ALL RIGHTS RESERVED.

The <665> Temperature and Duration of Extractions (3)

Extrapolating USP SEP Extraction Conditions to Manufacturing Use Conditions			
Extraction Time (days) at 40° C per USP SEP	Corresponding Extraction Time (days) at Clinical Contact Temperatures		
	25° C (ambient)	5° C (refrigerated)	-10° C (frozen)
1	3	11	32
7	20	80	220
21	60	240	670
70 (longest BPOG)	200	790	2240

The USP believes that its values for the temperature and duration of extraction reflect appropriate accelerations of more or less common manufacturing conditions and provide useful extractables profiles.

COPYRIGHT 2013. ALL RIGHTS RESERVED.

The <665> Temperature and Duration of Extractions (4); Score card

- The USP has adopted an extraction process (solvents and conditions) which are a subset of the BPOG protocol. Thus the USP is fully aligned with the BPOG protocol because USP allows for the use of additional conditions at the discretion of the sponsor.

COPYRIGHT 2013. ALL RIGHTS RESERVED.

How to Perform the <665> SEP
General Guidance

- Extractions performed in the SEP are dynamic in nature, accomplished by either agitation of the test system or circulation of the extraction solvent.
- Extractions are based on a defined contact surface area to extraction solution volume ratio.
- If addition of the extracting solvent to a test unit creates an open extraction system, the open access points must be closed by an appropriate means with inert materials.
- Extraction at higher temperature/longer durations may lead to loss of extraction solvent due to transpiration through the test article/unit. To mitigate this, the filled test article can be encased in inert secondary containment materials (for example, properly chosen aluminum foil).
- Extraction blanks, which are portion of the extracting solutions that are not contacted by the test article, must be generated and tested in order to differentiate extracted substances from analytical artifacts.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Profiling the <665> SEP Extracts

- The extracts and extraction blanks shall be analytically tested to establish the identities of the extractables and to estimate their concentration in the extracts using appropriate and orthogonal analytical methods, consistent with *Good Manufacturing and Stability Practices—Determination of Extractables Associated with Pharmaceutical Packaging Systems, <1663>* .
- The reporting of extractables shall be consistent with the application of relevant and appropriate reporting thresholds, such as the analytical evaluation threshold (AET) as defined in *<1663>*.
- Considering the extraction of elemental impurities, the extracts shall be tested for such elemental impurities via methodologies consistent with *Elemental Impurities – Procedures* <233>.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Current Status, <665> and <1665>

- **In-Process Revision: <665> POLYMERIC COMPONENTS AND SYSTEMS USED IN THE MANUFACTURING OF PHARMACEUTICAL AND BIOPHARMACEUTICAL DRUG PRODUCTS. Pharmacopeial Forum; 43(3), 2017.**
- **In-Process Revision: <1665> PLASTIC COMPONENTS AND SYSTEMS USED TO MANUFACTURE PHARMACEUTICAL DRUG PRODUCTS Pharmacopeial Forum; 43(3), 2017.**

Both these documents are currently in their public review stage (second cycle). The public review stage ends September 30, 2017.

Global Expertise | Trusted Standards | Improved Health
COPYRIGHT 2013. ALL RIGHTS RESERVED.

Thank You!

Contact the presenter at: dennisjenke@triadscientificsolutions.com
www.triadscientificsolutions.com

COPYRIGHT 2013. ALL RIGHTS RESERVED.

A Preliminary Discussion of the Essential Aspects of a Revised ISO Standard; 10993-18: **Biological evaluation of medical devices — Part 18: Chemical characterization of materials**

John Iannone, Director, Extractables/Leachables & Impurities, Albany Molecular Research Inc. (AMRI)
Dennis Jenke, Chief Executive Scientist, Triad Scientific Solutions, LLC

What is a Medical Device?

A **medical device** is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

What is a "Safe" Medical Device?

"Essential principles of safety and performance of medical devices"

Medical devices should be designed and manufactured in such a way that, when used under the conditions and for the purposes intended and, where applicable, by virtue of the technical knowledge, experience, education or training of intended users, they **will not compromise** the clinical condition or **the safety of patients, or the safety and health of users or, where applicable, other persons**, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.

GHTF.SG1.N0020R5. Essential Principles of Safety & Performance of Medical Devices. The Global Harmonization Task Force. 30-June-1999.

Chemical Characterization and its Role in the Biological Evaluation of Medical Devices

From the Introduction: The role of this part of ISO 10993 is to serve as a framework in which to plan a biological evaluation which … minimizes the number and exposure of test animals by giving preference to chemical constituent testing…

From Section 4.2: Identification of material chemical constituents and consideration of chemical characterization (see ISO 10993-18) shall precede any biological testing (See Figure 1).

Source: ISO 10993-1:2009. Biological evaluation of medical devices. Part 1: Evaluation and testing within a risk management process.

chemical characterization
process of obtaining chemical information, accomplished by either information gathering or by information generation, for example, by chemical testing

chemical information
qualitative and quantitative information gathered related to the configuration and composition of the device and/or its materials of construction, thereby establishing the identities and levels of chemical present in the materials and device (including any additives and processing aids)

Objectives of 10993-18

The requirements specified in this document are intended to yield the following information, which will be of value in assessing the biological response of the materials as represented in the final product:

- The identities and quantities, as appropriate, of the materials of construction of the medical device (device configuration).
- The identities and quantities, as appropriate, of the chemical substances intentionally and unintentionally present in each material of construction (material composition).
- The identities and quantities, as appropriate, of chemical substances used in the device's manufacturing process including processing aids and residues.
- The potential of the medical device and/or its materials of construction to release chemical substances to which the patient could be exposed to during clinical conditions of use.

Scope of 10993-18

This document specifies a framework for the characterization of a device through:

- the identification of its materials of construction (device configuration),
- the characterization of the materials of construction via the identification and quantification of their chemical constituents, both intentionally and unintentionally present (material composition),
- the characterization of the device for chemical substances that were introduced during manufacturing (e.g., mold release agents, DEHP contaminants), and
- the assessment of the potential of the device, or its materials of construction, to release chemical substances under clinical use conditions.

Applicability of 10993-18 (1)

The ISO 10993 series of standards is applicable when the material or device has direct or indirect tissue contact with a patient (see ISO 10993-1 for categorization by nature of body contact). Part 1 also describes instances in which direct or indirect contact with a clinician's body should be considered; that is, if the device is intended to protect the clinician (e.g., surgical gloves, masks and others). Throughout this part, references to patient contact shall be understood to include contact with the clinician for devices intended to protect the clinician.

Applicability of 10993-18 (2)

This document is intended for suppliers of materials and manufacturers of medical devices, to support a biological evaluation.

Applications of 10993-18 (1)

- Supporting the overall biological safety of a medical device (ISO 10993-1 and ISO 14971).
- Supporting the overall biological safety of a reprocessed medical device.
- Determining the level of chemical substances that might be leached from a medical device under the conditions of its clinical use, to assess conformance to the allowable limit of those substances as derived from health based risk assessment (ISO 10993-17).
- Screening of potential new materials for chemical suitability in a medical device for a proposed clinical application.

Applications of 10993-18 (2)

- Establishing equivalence of a proposed device to a legally marketed device with regard to either the device's configuration or its extractables/leachables profiles and any subsequent relevant evaluations.
- Establishing equivalence of a legally marketed device after changes in the manufacturing process, (including, but not limited, to changes in the sterilization process), manufacturing sites, suppliers of materials or components, etc.
- Establishing equivalence of a proposed material of construction to a clinically established material of construction with regard to either the material's composition or its extractables profiles and any subsequent relevant evaluations.
- Establishing equivalence of a final device to a prototype device in regards to the use of data secured on the prototype to support the assessment of the final device, specifically considering relevant information such as composition, device configuration and extractable profile obtained for either the device or its materials of construction.

An Important Caveat

… chemical characterization alone may be insufficient to establish the equivalence or biocompatibility of materials and devices, and cannot unilaterally substitute for biological testing. However, chemical characterization in combination with risk assessment may be a necessary part of judging chemical equivalence and assessing biocompatibility, and if appropriately conducted can be used in lieu of certain biocompatibility tests.

More on this later …

Key Definitions (1)

chemical safety risk assessment
process of establishing that a medical device, when used in its clinically prescribed manner, is safe, meaning that there is a negligible risk to the health of potentially affected individuals, based on the individual's exposure to the device's chemical constituents

Key Definitions (2)

extractables
substances that are released from a medical device or material of construction when the device or material is extracted using laboratory extraction conditions and vehicles

leachables
substances that are released from a medical device and to a patient during its clinical use

Key Definitions (3)

device configuration
listing of a device's components (qualitative), augmented by a listing of the component's materials of construction (qualitative) and the proportion of each material in each component (quantitative)

material composition
listing of the substances that are contained in a material (qualitative) and the amount of each substance in the material (quantitative)

Key Definitions – Types of Extractions (4)

Extraction: chemical process performed to separate a chemical substance from a test article by exposing the test article to an extraction vehicle under defined and controlled conditions

Exhaustive: extraction, accomplished using multiple extraction steps, that solubilizes the total amount of extractable substances present in a test article, as evidenced when the amount of extractables released in a subsequent extraction step is less than 10% of the amount of extractables released in the first extraction step

Exaggerated: extraction that is intended to result in a greater number or amount of chemical constituents being released as compared to the amount generated under the clinical conditions of use but is not expected to result in a chemical change of the substances being extracted

Accelerated: extraction whose duration is shorter than the duration of clinical use but whose conditions do not result in a chemical change of the substances being extracted

Simulated-use: extraction, performed using an extraction method that simulates clinical use, which is conducted to evaluate those extractable substances which could be available as leachables from a device during the routine clinical use of the device

Key Definitions – Types of Extractions (5)

Why are there so many different types of extractions?

Because the extraction should match the objective of the chemical characterization!

In general, there can be four objectives of a chemical characterization:

1) To correlate chemical data to the results of biological testing performed as described elsewhere in ISO 10993 (**"standard" extraction as described in 10993-12**),
2) To establish the compositional aspects of the configuration of a medical device or the composition of a material of construction (**digestion, dissolution or exhaustive extraction**),
3) To establish the worst case extractables profile of a medical device or material as either the total pool of extractables in the device (exhaustive extraction) or the maximum amount that can be extracted under defined experimental conditions that exaggerate a device's typical conditions of use (**exaggerated or accelerated extraction**), and
4) To establish the extractables profile of a medical device or material under its typical conditions of use (**simulated extraction**).

General Principles (1)

Chemical characterization can facilitate the biological safety assessment process in three ways:

1. By providing the chemical information that is a necessary input into comparing the medical device in question with potential predicate devices (establish equivalence),
2. By providing the chemical basis for comparing the medical device in question to a relevant standard (establish conformance),
3. By providing the chemical information that serves as the basis for a toxicological risk assessment (enable assessment).

General Principles – Characterization Procedures (2)

The chemical characterization procedure is based on the following considerations:

1. The issue of biocompatibility is only relevant for devices that have direct or indirect patient contact.
2. The extent of chemical characterization should reflect the nature and duration of the clinical exposure and the physical form of the materials used and shall be determined **with the toxicological risk assessor** based on the data necessary to evaluate the biological safety of the device.
3. Establishing the configuration of a device is the necessary first step in establishing the device's biocompatibility as (a) use of appropriate materials of construction predisposes a device to be biocompatible and (b) knowledge of the materials of construction could provide the starting point for establishing chemical equivalence.
4. Establishing the chemical composition of the materials of construction is a necessary step in establishing a device's biocompatibility, as (a) the composition of the individual materials can serve as the basis for establishing chemical equivalence to a clinically established device, and (b) the chemical entities contained in a material are logical sources of extractables and leachables.

General Principles – Characterization Procedures (3)

The chemical characterization procedure is based on the following considerations:

5. Determining the device's potential to release chemical substances under clinical use conditions can provide the basis for understanding and assessing the device's potential patient safety impact. Although any of the substances in a material or additives used in the process of manufacturing a medical device could be leached from the device and thereby become bio-available, it could potentially be necessary to obtain information demonstrating the extent to which the substances will be leached under the clinical use conditions of the finished product to estimate the risk arising from them. This can be estimated by conducting extraction studies of the device.

General Principles – Close Collaboration (4)

The successful completion of the chemical characterization outlined in this document requires expertise in material science and analytical chemistry to provide the necessary qualitative and quantitative data that a risk assessor can use to assess device safety. Toxicology expertise is required in understanding the types of compounds that might be of toxicological concern so that the materials and chemistry experts can design appropriate experiments.

General Principles – Change Control (5)

… the biological safety of the medical device is inferred over the device's time in market only so long as the device's materials of construction and manufacturing process remain unchanged. It is important that controls be introduced to prevent a material supplier from changing the composition of a material supplied without prior notification to the medical device manufacturer. **The manufacturer** shall assess the consequences of any notified changes on the biological safety of the product.

Characterization Procedure (1)

Chemical Characterization Parameters and Methods (1)

Although chemical characterization data can be produced by testing a test article (device or material) directly in its natural state (for example, IR analysis of a film), it is more typically the case that the generation of such chemical characterization data requires two processes,

1. the solubilisation of all or part of the test article (where solubilisation refers to processes such as extraction and dissolution) and
2. the analytical testing of the resulting solution.

Chemical Characterization Parameters and Methods – Solubilization (2)

Important Considerations:

1. The nature of the solubilisation step shall match the intent and purpose of the testing.
2. The vehicles/media used for solubilisation should be considered in the context of the methods chosen for testing those extracts, as the vehicles should be compatible with the test methods employed to analyse the extracts.
3. If visible particles or precipitates occur during extraction, and are not solubilized, these should be analysed as well, using applicable methods.

Chemical Characterization Parameters and Methods – Analytical Testing (3)

Items Relevant to Analytical Testing:

1. Analytical test methods are provided (in name but not in detail) and discussed for establishing chemical composition.
2. Analytical test methods are provided (in name but not in detail) and discussed for extractables and leachables profiling (organic and elemental).
3. Analytical test methods are provided (in name but not in detail) and discussed for assessing the structural composition of device materials.
4. Considerations around the qualification of analytical methods are discussed.

Reporting of Data (1)

Reports for the Communication of Chemical Data Should Include:

1. Test article (material or device) description and details;
2. Analytical methods and extraction conditions;
3. Surrogate standard information and detection method for the estimation of unknowns observed in the analysis of the test solutions;
4. Qualitative data generated;
5. Quantitative data generated;
6. Estimated clinical exposure to chemicals.

See also Annex E.

Reporting of Data (2)

Requirements for Reporting Data:

1. As necessary and appropriate, identified substances in the test solutions could be grouped into compound classes, based on structural or functional similarities, to assist in any toxicological risk assessment.
2. Any quantitative data shall be presented in a way that permits estimation of human exposure.
3. Data establishing the identity of relevant substances (e.g., extractables and leachables) shall be presented in a way that permits the toxicological safety assessment of the substance.
4. Reports containing vendor data would include a discussion of the relevance of the vendor data to the toxicological safety assessment.
5. The Report should contain detailed information that establishes the appropriateness of the analytical process employed.

Informative Annexes

- **Annex A**: Information sources for chemical characterization
- **Annex B**: Principles for judging chemical equivalence in support of a toxicological risk assessment
- **Annex C:** Principles of sample extraction
  - Extraction performed for correlating chemical characterization with biological testing (containing a Table of proposed extraction solvents)
  - Approaches to establishing the compositional aspects of the configuration of a medical device or the composition of a material of construction
  - Exaggerated extraction to establish the worst-case extractables profile of a medical device or material
  - Simulated or accelerated extractions to establish clinical use extractables profiles
- **Annex D:** Calculation and application of the analytical evaluation threshold (AET)
  - Calculation of the AET
  - Determination of the uncertainty factor, UF
  - Use of the AET
  - Exclusions to the AET; cohorts of concern
- **Annex E:** Reporting details for analytical methods and chemical data

Contact the presenters at:
John.Iannone@amrisglobal.com
dennisjenke@triadscientificsolutions.com (www.triadscientificsolutions.com)

Thank you!

How to perform a Safety Evaluation – Risk Assessment on Extractables & Leachables

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES
Berlin
28 – 29 September, 2017

Ir. John Iannone

Topics Covered

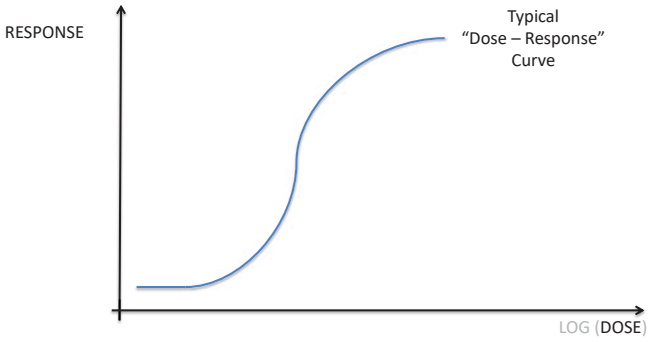
- Basic Toxicological Principles dose response relationship
- Key Toxicological end-points
- General Impurity Qualification
- Solvents – Permissible Limits
- Mutagenic Impurities
- E&Ls
- Conclusions

THE DOSE-RESPONSE RELATIONSHIP

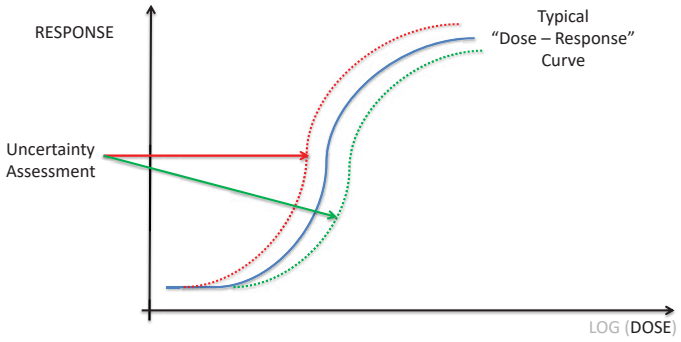
"The Dose Makes the Poison"
Paracelsius

THE DOSE-RESPONSE RELATIONSHIP

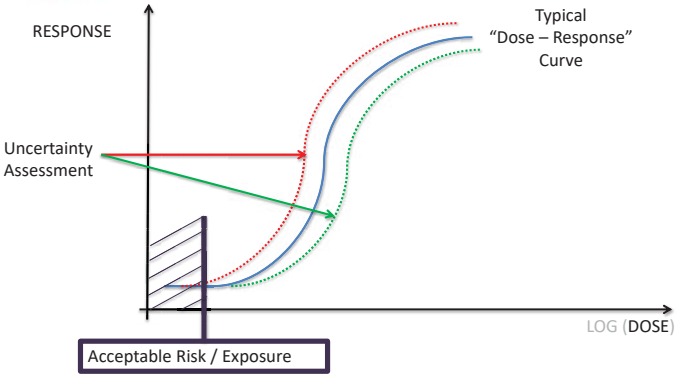
THE DOSE-RESPONSE RELATIONSHIP



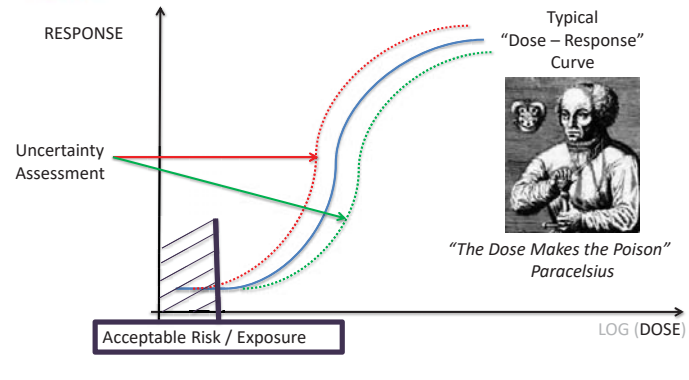
THE DOSE-RESPONSE RELATIONSHIP



THE DOSE-RESPONSE RELATIONSHIP

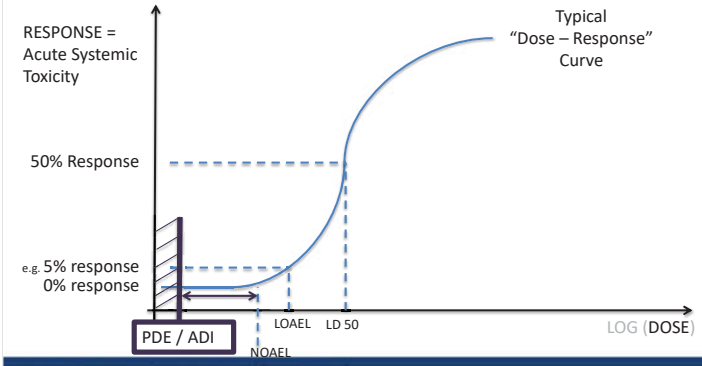


THE DOSE-RESPONSE RELATIONSHIP



THE DOSE-RESPONSE RELATIONSHIP

EXAMPLE: **ACCUTE SYSTEMIC TOXICITY**



KEY ENDPOINTS

Toxicological endpoints to be considered (non – limitative):

- Acute Systemic Toxicity → Often most readily available information
- Genotoxicity
- Irritation
- Sensitization
- Reproduction Toxicity
- Carcinogenicity

} The "BIG FIVE"

KEY END-POINTS

Acute Systemic Toxicity

Definition:

Acute systemic toxicity testing is the **estimation** of the **human hazard potential** of a substance by determining its **systemic toxicity** in a test system (currently animals) following an **acute exposure**.

Source: alttox.org

KEY ENDPOINTS

Genotoxicity

Definition:

Genotoxicity is a broad term referring to **genetic damage**. This may be at a ***DNA level*** i.e. mutagenicity, or at a ***chromosomal level*** e.g. Clastogenicity / Aneugenicity.

This term has in the context of **ICH M7** been **replaced** by the more specific term mutagenicity that relates specifically to **DNA mutation**.

Carcinogenicity

Definition:

The term *carcinogen* denotes a chemical substance or a mixture of chemical substances which **induce cancer** or **increase its incidence**".

An alternate definition is that carcinogenic substances are ones that "**induce tumors** (benign or malignant), **increase** their **incidence or malignancy**, or **shorten** the **time** to **tumor occurrence** when they are inhaled, injected, dermally applied, or ingested

Carcinogens are classified according to their mode of action as *genotoxic* or *non-genotoxic* carcinogens.

General Impurity Qualification

ICH Q3A / Q3B

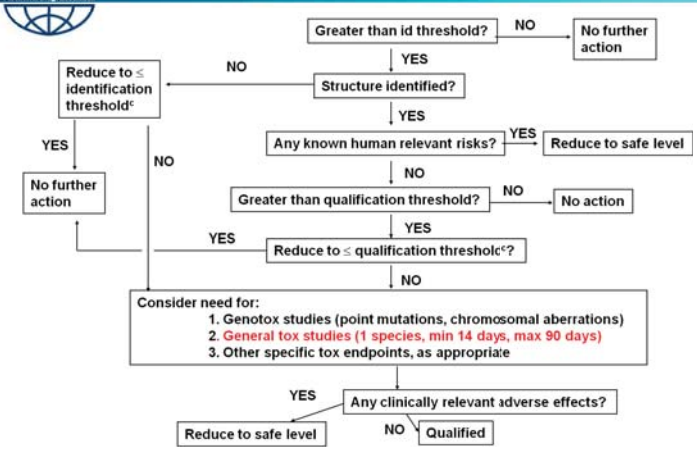
Qualification

'The process of **acquiring** & **evaluating** data that establishes the **biological safety** of an **individual impurity** *or* a **given impurity profile** at the level(s) specified.'

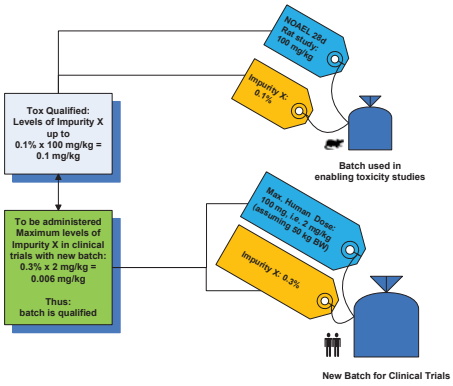
Qualification of Impurities – Basic points

- **Before** actives go into clinical trials the **impurities** present **must be qualified** in **preclinical** studies.
  - Typically includes a 14 -28 day study in rodents *(amongst others)*
- Qualification of Impurities is described in ICH Q3A (API) & ICH Q3B (drug product)
  - **Process** described & illustrated through **Decision tree**
  - Defines thresholds for reporting, identification & qualification of impurities for Marketing Authorisation Applications
    - *E.g. For a drug dosed at up to 2g/day, the threshold for qualification for impurities is 0.15% or 1.0mg/day, whichever is lower*
- Important to note that ICH limits are not appropriate during drug development; guidance is likely to be company-specific

ICH decision tree for qualification studies



Basic qualification assessment



DERIVING LIMITS FROM TOX DATA MOVE!

Where can we find the Toxicological Data to be used in the assessment?

http://toxnet.nlm.nih.gov
http://echa.europa.eu/
http://www.epa.gov/hpvis/
http://webnet.oecd.org/hpv/
http://www.inchem.org/
http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm

Role of Toxicologist:

- Find as much information as possible
- On all possible Toxicological End-Points
- Evaluate the weight of Evidence
- Judge the Quality of Data!!

DERIVING PDE'S FROM TOX DATA

How to evaluate the Quality and Relevancy of Tox Data?

- Duration of Studies
- Nature of Studies
- Quality of the dose-response established
- Route of Administration
- Mechanisms
- Relevance to Humans
- ...

THIS NEEDS TO BE DONE BY A TOXICOLOGIST

Permissible Daily Exposure (PDEs)

ICH Q3C(R4): Residual Solvents

DERIVING PDE'S FROM TOX DATA

ICH Q3C Appendix 3
WHO EHC 170

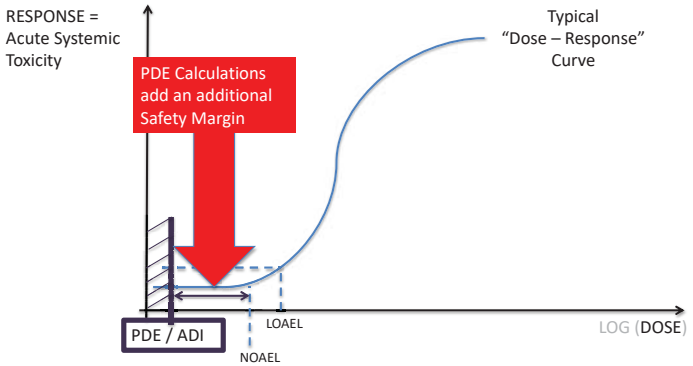
$$PDE = \frac{\text{NO(A)EL x Weight Adjustment}}{\text{F1 x F2 x F3 x F4 x F5}}$$

F1 = Variation between Species
F2 = for Variation between individual Humans
F3 = Short Duration in Animals to Chronical Human Exposure
F4 = Teratogenicity, Neurotoxicity and non-genotoxic carcinogens
F5 = 10 for using LOAEL

Sometimes **F6:** route of administration: factor 10 from oral to I.V.

DERIVING PDE'S FROM TOX DATA

EXAMPLE: **ACCUTE SYSTEMIC TOXICITY**



ICH Q3C(R4): RESIDUAL SOLVENTS

ORGANIC IMPURITIES:

TABLE 1. Class 1 solvents in pharmaceutical products (solvents that should be avoided).

Solvent	Concentration limit (ppm)
Benzene	2
Carbon tetrachloride	4
1,2-Dichloroethane	5
1,1-Dichloroethene	8
1,1,1-Trichloroethane	1500

NB – Limits for Class 1 Solvents are expressed in terms of concentration limits

ICH Q3C(R4): RESIDUAL SOLVENTS

ORGANIC IMPURITIES:

TABLE 2. Class 2 solvents in pharmaceutical products.

Solvent	PDE (mg/day)
Acetonitrile	4.1
Chlorobenzene	3.6
Chloroform	0.6
Cyclohexane	38.8
1,2-Dichloroethene	18.7
Dichloromethane	6.0
1,2-Dimethoxyethane	1.0
N,N-Dimethylacetamide	10.9
N,N-Dimethylformamide	8.8
1,4-Dioxane	3.8
2-Ethoxyethanol	1.6
Ethyleneglycol	6.2
Formamide	2.2
Hexane	2.9
Methanol	30.0
2-Methoxyethanol	0.5
Methylbutyl ketone	0.5
Methylcyclohexane	11.8
N-Methylpyrrolidone[1]	5.3
Nitromethane	0.5
Pyridine	2.0
Sulfolane	1.6
Tetrahydrofuran[2]	7.2
Tetralin	1.0
Toluene	8.9
1,1,2-Trichloroethene	0.8
Xylene*	21.7

ICH Q3C(R4): RESIDUAL SOLVENTS

ORGANIC IMPURITIES:

Table 3. Class 3 solvents which should be limited by GMP or other quality-based requirements.

PDE > 50 mg/day

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethyl ketone
tert-Butylmethyl ether	Methylisobutyl ketone
Cumene	2-Methyl-1-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	

Mutagenic Impurities

ICH M7: Assessment & Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

ICH M7: DNA REACTIVE IMPURITIES

PURPOSE:

Provide a framework for

- Identification
- Categorization
- Quantification
- Control

... of mutagenic impurities to limit potential carcinogenic risk

To establish levels of Mutagenic Impurities that are expected to pose negligible Carcinogenic Risk.

ICH Q3A&B: Provide Guidance for Qualification & Control of Majority of Compounds

Limited Guidance for Impurities that are DNA Reactive

ICH M7 Complements ICH Q3A, ICHQ3B and ICH M3(R2)

ICH M7: DNA REACTIVE IMPURITIES

SCOPE:

Provide Guidance for

- New Drug Substances
- New Drug Products

During Clinical Development & subsequent Marketing Applications.

Also Applies for **New Marketing Applications** & **Post Approval Submissions, for Changes in:**

- Drug Substance SYNTHESIS
- Formulation, Composition or Manufacturing Process
- Dosing Regimen

ICH M7: DNA REACTIVE IMPURITIES

SCOPE:

LEACHABLES

» Although not intended, the safety assessment principles, outlined in ICH M7, can be used for the assessment of Leachables

EXCIPIENTS

» If used for the first time in a DP and are chemically synthesized.

EXCLUDED from SCOPE:

» Excipients, used in Existing Marketed Products

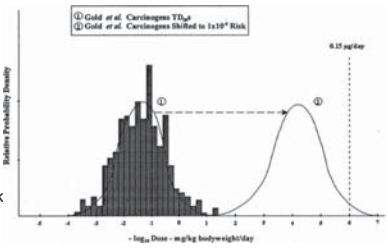
» Flavoring Agents

ICH M7: DNA REACTIVE IMPURITIES

KEY PRINCIPLES:

Limits are predicated on the basis of the **Threshold of Toxicological Concern (TTC)**

TTC based on analysis of **730 carcinogens** (genotoxic and non-genotoxic), using **linear extrapolation** from animal onco data; estimates daily exposure to 1.5µg/day for most (genotoxic) carcinogens **not likely to exceed lifetime cancer risk** of 1 in 105 – risk considered acceptable for pharmaceuticals as drugs have a benefit, not normally used for lifetime and precedent of benzene in Q3C.



Exceptions include aflatoxin-like, azoxy and N-nitroso compounds – need case-by-case assessment.

ICH M7: DNA REACTIVE IMPURITIES

HAZARD ASSESSMENT:

Table 1: Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions (according to Ref. 17 with modifications)

Class	Definition	Proposed action for control (details in Section 7)
1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)	Control at or below acceptable limits (generic or adjusted TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data.	Control at or below acceptable limits (generic or adjusted TTC) or do bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance which has been tested and is non-mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity	Treat as non-mutagenic impurity

THE DOSE-RESPONSE RELATIONSHIP –

Haber's Rule

$$C \times t = k$$

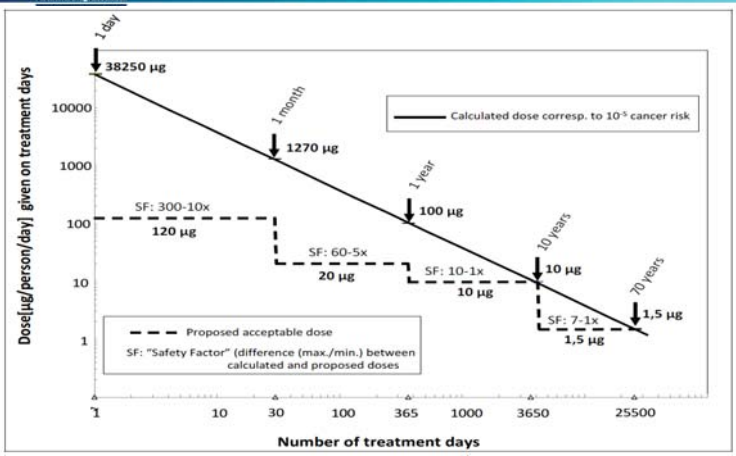
With *C = Concentration*
t = time
k = constant

This means that the toxic effect e.g. stays the same when concentration is doubled in half of the time of exposure

*IMPORTANT, because this is the basis for the **Staged Approach**, suggested in **ICH M7***

Remark: Not applicable to all toxicological end points – Can it be applied to general toxicity ?

ICH M7: DNA REACTIVE IMPURITIES

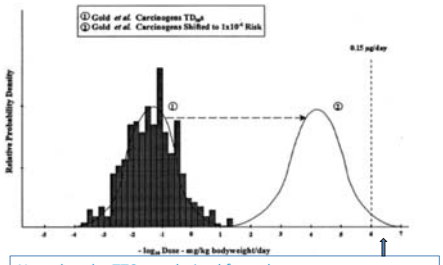


ICH M7 - Compound Specific Limits

Introduction

TTC based on data from **approximately 800 carcinogens**

Put another way we have carcinogenicity data on 800 compounds which can be used where relevant to calculate individual specific limits.



Note that the TTC was derived from the more potent carcinogens after exclusion of cohort of concern

•In reality only a proportion of these are relevant to the synthesis of APIs but considerable data exists in respect to a number of common reagents

Compound Specific Limits

Historical Perspective

The rationale for conducting a compound-specific assessment rather than relying on a generic application of the TTC is highlighted in the EMEA guideline on the Limits of Genotoxic Impurities (EMEA, 2006) :

'The TTC concept should not be applied to carcinogens where adequate toxicity data (long-term studies) are available and allow for a compound-specific risk assessment.'

The FDA draft guideline (FDA, 2008) also indicates support for such an approach and indeed goes further by indicating that the use of risk assessments based on structural similarity to known carcinogens, may also be appropriate to establish appropriate limits:

'When a significant structural similarity to a known carcinogen is identified, the drug substance and drug product acceptance criteria can be set at a level that is commensurate with the risk assessment specific to that of the known compound.'

Compound Specific Limits

ICH M7

Compound-specific risk assessments to derive **acceptable intakes** should be applied instead of the **TTC-based acceptable intakes** where **sufficient carcinogenicity data** exist.

For a known mutagenic carcinogen, a compound-specific acceptable intake can be calculated based on carcinogenic potency & linear extrapolation as a default approach.

PQRI –OINDP (2006):
The Threshold Approach for OINDP
(Orally Inhaled and Nasal Drug Products)

THE PQRI-OINDP THRESHOLD APPROACH

INITIAL PQRI EFFORTS: ESTABLISH SAFETY THRESHOLDS FOR OINDPs – 2006

- Toxicologists: acquired data through extensive literature and database searches and analyses
- Chemists: acquired data by conducting extractions studies and placebo LEA studies
- Assess data and reach consensus
- Develop L & E Recommendations Document
  Submitted to FDA in 2006 for consideration in support of Regulatory Submission
- Recommendations widely used in Industry
  Not a policy/regulatory document

In 2008, PQRI started a similar approach for Parenteral & Ophthalmic DP. Expected to be finalized in ~~2015~~ → 2016? 😉

Information, from presentation D. Paskiet, CPhI Pharma Extractables & Leachables, November 29,2012, Hyderabad.

THE PQRI-OINDP THRESHOLD APPROACH

SCT: SAFETY CONCERN THRESHOLD

*"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

Exceptions: MBT, Nitrosamines, PNA's: as low as possible!

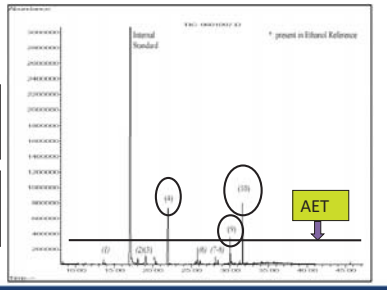
THE PQRI-OINDP THRESHOLD APPROACH

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

Translate SCT

into Analytical Thresholds
for Extractable Studies

Taking into account:
- *Total N° of doses / packaging*
- *Max. N° of doses administered / day*



THE PQRI-OINDP THRESHOLD APPROACH

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

Formula used (see PQRI recommendations):

$$\text{Est. AET} = \frac{\text{SCT}}{\text{dose/day}} \cdot \frac{\text{total dose}}{\text{cartridge}}$$

$$\text{Est. AET} = \frac{0.15\ \mu g/\text{day}}{2\ \text{Units/day}} \cdot \frac{12\ \text{Units}}{\text{cartridge}} = 0.90\ \mu g / \text{cartridge}$$

FINAL AQT (incl 50% uncertainty factor) : 15 µg/cartridge

THE PQRI-OINDP THRESHOLD APPROACH

QT: **Q**UALIFICATION **T**HRESHOLD

*"**Threshold** below which a given **non-carcinogenic leachable** is not considered for **safety qualification** (i.e. Tox Assessments) **unless** the leachable presents **"Structure-Activity Relationship" (SAR) concerns**."*

PQRI for OINDP's: QT = 5 µg/day

THE PQRI-OINDP THRESHOLD APPROACH

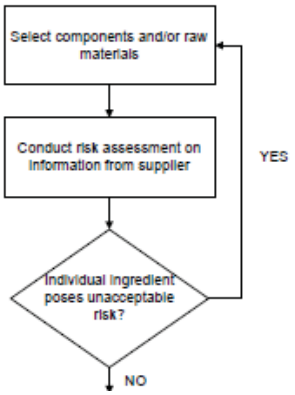
Formula used (see PQRI recommendations, *applied for QT*):
Analytical **Q**ualification **T**hreshold

$$\text{AQT} = \frac{\text{QT}}{\text{dose/day}} \cdot \frac{\text{total dose}}{\text{cartridge}}$$

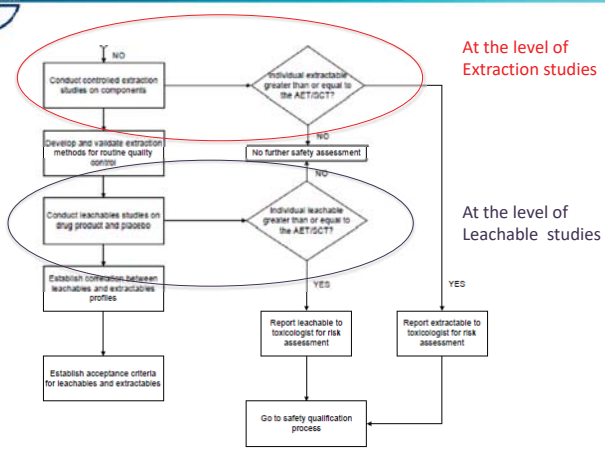
$$\text{AQT} = \frac{5\ \mu g/\text{day}}{2\ \text{Units/day}} \cdot \frac{12\ \text{Units}}{\text{cartridge}} = 30\ \mu g / \text{cartridge}$$

FINAL AQT (incl 50% uncertainty factor) : 15 µg/cartridge

THE PQRI-OINDP THRESHOLD APPROACH



THE PQRI-OINDP THRESHOLD APPROACH



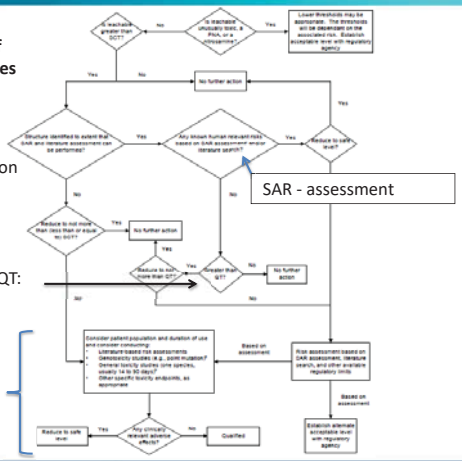
THE PQRI-OINDP THRESHOLD APPROACH

At the level of Leachable studies

if [ ] > SCT:
Structure Elucidation

What to do if [ ] > QT:

Qualification as per Q3A



PQRI –PODP (2008 - current status):
The Threshold Approach for PODP
*(**P**arenteral and **O**phthalmic **D**rug **P**roducts)*

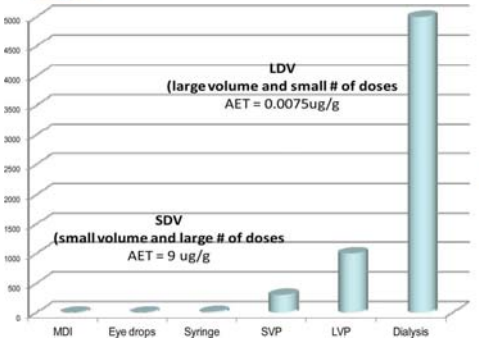
THE PQRI-PODP THRESHOLD APPROACH

Extrapolates the OINDP threshold concepts and best practices recommendations to PODP based on following principles:

- **Threshold concepts** developed for safety qual of leachables in **OINDP can be extrapolated** for the evaluation & safety qualification of packaging systems (such as container closure systems) of **PODP**
- **Threshold & best practice concepts** can be **integrated** into a comprehensive **process for characterizing** packaging systems with respect to leachable substances and their associated **impact on PODP safety**.

PASKET et al, PDA Journal of Pharmaceutical Science and Technology September/October 2013 vol. 67 no. 5 430-447

The effect of daily dose volume on the analytical evaluation threshold (AET).



The AET is related to the safety concern threshold (SCT), which is a fixed quantity the value of the AET is inversely proportional to the daily dose volume. Thus an AET which is analytically achievable in a small daily dose volume (SDV) dosage form (e.g., metered dose inhaler, MDI) may not be achievable in a large daily dose volume (LDV) dosage form (e.g., large volume parenteral, LVP).

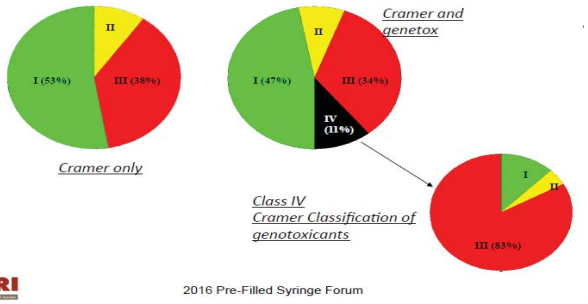
Paskiet D et al. PDA J Pharm Sci and Tech 2013;67:430-447

PDA Journal of Pharmaceutical Science and Technology

PQRI-PODP THRESHOLD APPROACH

Classification Outcome

- 606 Compounds:



PQRI

2016 Pre-Filled Syringe Forum

THE PQRI-PODP THRESHOLD APPROACH

Table III
Proposed Safety Classification of Extractables/ Leachables

Statistical Evaluation of Class 1

Dose (µg/day)	Pass (%) (Dose Margin ≥1)	90 % Confidence Interval		95% Confidence Interval		99% Confidence Interval	
		Lower Bound	Upper Bound	Lower Bound	Upper Bound	Lower Bound	Upper Bound
90	55/60 (91.7)	82.8	96.4	80.9	96.9	76.8	97.6
150	48/60 (80.0)	69.4	87.8	67.3	88.8	63.1	90.6

Paskiet D et al. PDA J Pharm Sci and Tech 2013;67:430-447

CONCLUSIONS

CONCLUSIONS

- Safety principles underpinned by Paracelsian principle – poison is in the dose.
- Such concepts partially recognised in approaches to general qualification / solvents
  - ICH Q3A – 1mg limit
  - PDE approach to solvents – use of NOEL

CONCLUSIONS

- Conservative approach taken for Mutagenic Impurities
  - Use of Linear extrapolation to 1 in 100,000 risk, used to establish TTC – lifetime limit of 1.5 ug/day.
  - Highly theoretical – Ignores protective mechanisms

CONCLUSIONS

- Approach for E&Ls even more conservative
  - Based on principle of SCT, 0.15 ug/day
    (this being based on same principle as TTC, except 1 in 1,000,000 risk)
  - Also fundamental differences in terms of approaches
  - SCT used to define an AET
    - Evaluate ALL components > AET
  - ICH M7 more of a risk based approach.

Vs.

CONCLUSIONS

- ICH M7 – takes into consideration duration of exposure
- Addendum table offers a means by which PDEs can be calculated using a systematic approach
  - To date little traction within E&L area for similar approach.

CONCLUSIONS

- Ultimately there would appear to be a significant need for closer / better alignment of best practice / best science across different impurity classes.