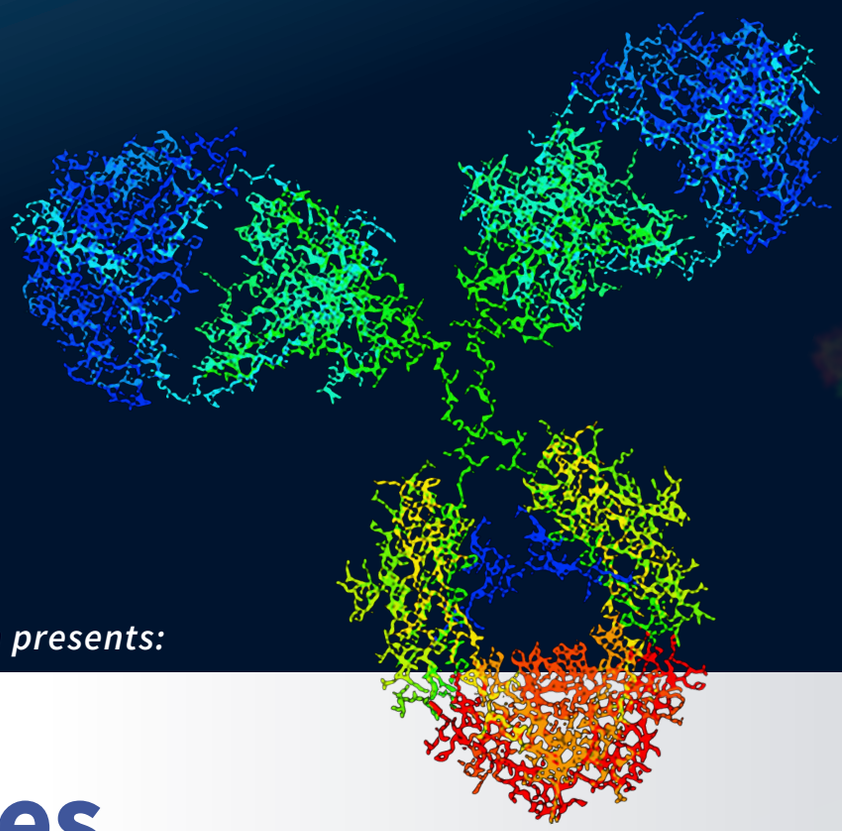
PDA Parenteral Drug Association

10 YEARS MONOCLONALS ANTIBODIES



The Parenteral Drug Association presents:

2017 PDA Europe

Extractables and Leachables

TRAINING COURSE

ATTENDEE NAME

28-29 September 2017

Berlin | Germany

Extractables & Leachables

Including: Important Regulatory Updates – Case Study Section: Selection of Toxikon's most interesting Case Studies, presented over the last 10 years!

Overview

When making Parenteral Drug Products, pharmaceutical companies are faced with the need to further investigate the materials that will be in contact with the drug product, either during manufacturing, intermediate storage, storage in its final packaging, or during the delivery of the drug to the patient. While historically, the potential safety issues were the main driver in these kinds of investigations, recently, also quality issues – i.e. for biopharmaceuticals – have become an additional concern. This workshop will look at "Extractables & Leachables" from many different angles: Definitions, Regulatory, Material & Polymer Science, Analytical E/L Methodologies, Safety Assessments, Study Design for different parenteral primary packaging systems, as well as for injection devices.

Learning Objectives

Upon completion of this workshop, you will be able to:

- Explain in detail the current regulatory requirements for container/closure qualification form an E/L perspective.
- Explain the upcoming changes in regulations, standards and recommendations from PQRI, USP and BPOG and how these changes could impact a future evaluation of a pharmaceutical C/C-system.
- Understand the materials of construction – and their composition – of container closure systems, and how they could impact the safety and quality of a parenteral drug product.
- Put together an evaluation program (review of provided documentation, analytical testing) of different types of parenteral drug product container/closure systems.
- Perform a safety/risk assessment of analytical results, obtained after completion of an E/L study.

Who Should Attend

- Pharmaceutical Packaging and Device Engineers
- Production Engineers, using SU systems
- Regulatory Affairs Officers
- Pharmaceutical R & D Managers
- Analytical Chemists, working on E/L
- Quality Assurance Officers

Dennis Jenke, *PhD, Chief Executive Scientist, Triad Scientific Solutions*

Dennis Jenke is the Chief Executive Scientist for Triad Scientific Solutions, a provider of science-based solutions to plastic/product compatibility challenges associated with packaging, manufacturing equipment and delivery devices in the pharmaceutical, cosmetic, food and related industries. He was a Distinguished Scientist at Baxter Healthcare Corporation where for more than three decades he lead a team whose primary responsibility includes the assessment of material/product compatibility, specifically with respect to establishing the suitability for use of packaging systems, manufacturing systems and administration devices for pharmaceutical products (for example, extractables/leachables and product ingredient binding). He has published extensively in the areas of analytical chemistry, environmental science and material/solution compatibility and serves as an expert reviewer for numerous pharmaceutical and analytical journals. He is the author of the book Compatibility of Pharmaceutical Solutions and Contact Materials; Safety Considerations Associated with Extractables and Leachables and a contributing author to the Leachables and Extractables Handbook. Dennis Jenke is a member of numerous industry groups whose charter is to establish best demonstrated practices in the area of material/solution compatibility.

Thursday, 28 September 2017 9:00 – 18:00

Introduction on Extractables & Leachables (E/L)

- What is the importance of a good E/L-qualification?
- Historical cases of leachables, impacting the quality or the safety of a drug product
- Regulatory requirements (FDA, EMA…) for primary packaging

Understanding the Materials, Used in the Manufacture of Pharmaceutical Containers & Closures

- Types of polymers – examples in medical/pharmaceutical use
- Understanding the composition of polymers
- The issues with glass in parenteral applications

Analytical Techniques to Perform Extractables & Leachables Research

- The importance of sample preparation: the corner stone in E/L research
- What are the target compounds for material research
- How does a classification of these compounds assist in finding the right analytical technique
- From basic "screening" methodologies to state-of-the-art equipment

How to Set-up Extractables & Leachables Studies

- Selecting the right conditions for extraction
- How to select the right compounds to monitor in a leachable study
- Designing a leachable study

FULL Session on Updates of E/L- Regulations, Standards and Recommendations

- Pharma Packaging:
  - Preview of the final PQRI Parenteral Drug Product (DPD) & ODP Chemistry group
  - Update on the most recent developments on the USP <661> chapters
- Devices
  - Chemical characterization of devices according to ISO 10993-18: What changes are coming up?
  - Upcoming Revisions of the USP <87> and USP <88>: Where could it go to?
- (Bio)Pharmaceutical Manufacturing
  - The BPOG protocol
  - Where is USP with the update on the USP <661.3> Plastic Manufacturing Components standard

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

- Toxicology 101
- EMA Guideline on Genotoxic Impurities
- ICH M7 (DNA reactive Impurities) and its suggested staged approach
- The Threshold Concept of PQRI (OINDP and PDP/ODP)
- Examples

Piet Christiaens, *PhD, Scientific Director, Toxikon Europe*

Piet Christiaens received his Ph.D. from the Analytical Chemistry Department of the University of Leuven (Belgium) in 1991. From 1992 to 1997, he was Lab Manager in two Analytical Contract Laboratories. From 1997 to 2000, he worked as an independent consultant with Shell Chemical Company in Houston, Texas where he conducted research on a new hydrogenation catalyst system for Hydrogenated Triblock Co-Polymers (Kraton Polymers). Since 2001, Mr. Christiaens has been Scientific Director at Toxikon Europe where he develops analytical methods and protocols for both extractables and leachables studies for the Medical and Pharmaceutical Industries. Mr. Christiaens oversees all laboratory operations at Toxikon Europe and is also supports the European business development team.

Friday, 29 September 2017 9:00 – 16:30

E/L Testing for a Pre-filled Syringe (Glass & Polymer)

- Glass Syringes: the issues with tungsten, glue residues and silicone oil and glass metals leaching
- The Issue with rubbers: the plunger, the needle shield or the tip cap: different approaches needed?
- The impact of secondary packaging – option or necessity?
- Setting up extractable & leachable studies for a pre-filled Syringe

E/L Testing for Lyophilized Drug Products

- Primary packaging for the lyophilized drug product – modus of interaction with the DP
- Impact of the "21CFR Part 4" on combination products, used in the administration of a lyo DP
- Critical aspects when designing leachable studies for lyophilized DP
- Integration of the administration procedure (e.g. IV-set, pump system) in leachables evaluation

How to Look at Injection Devices from an E/L Perspective

- Medical device regulations versus pharma packaging
- Test selection process for devices: What to do?
- USP and ISO 10993 series for biocompatibility testing
- Case: Injection device

Large Volume Parenterals

- The challenge in E/L testing for LVP's
- Primary packaging for LVP's – critical materials and components
- Secondary packaging for LVP: critical points to consider

E/L Testing for Disposable and Single-Use Systems in Bioproduction

- How to classify the risk of different single-use systems in the bioproduction process?
- Understanding BPSA & BPOG recommendations, and how they can be implemented in the study design
- Performing E/L studies on filters: potential approaches

John Iannone, *Director of Extractables/Leachables and Impurities, Albany Molecular Research, Inc. (AMRI)*

John Iannone has a background in Biomedical Engineering from Boston University, where he later became a research engineer. Since going from Academia to Industry 13 years ago, John has assisted multiple pharmaceutical & medical device companies with the development of their product safety evaluation strategies. Previously a Technical Specialist at Toxikon, he now is the Director of Extractables/Leachables and Impurities at Albany Molecular Research, Inc (AMRI). His areas of expertise include Material Qualification & Biocompatibility, Extractables & Leachables, Chemical Characterization, and attainment of Biological or Toxicological risk assessments for medical devices, pharmaceutical container systems, bioprocessing systems, and combination products. John has given numerous technical presentations and has led several workshops on Extractable & Leachable Considerations, Biocompatibility, Microbiology, and Regulatory Testing Requirements. He also participates in the development of both industry groups' recommendations and regulatory guidelines through Expert Panel membership, global Technical Committees, and industry collaborations. Additional responsibilities have included providing technical consultation to clients regarding unique testing requirements in an effort for them to meet global regulatory expectations.

Agenda

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES

Berlin
28-29 September, 2017

Dr. Piet Christiaens
Dr. Dennis Jenke
Ir. John Iannone

DAY 1: Morning Session

- **Introduction & Regulatory Aspects of E/L**
- **Polymers 101 – Glass 101**
- **The Mechanism of Polymer Leaching**

DAY 1: Afternoon Session

- **Final Recommendations of the PQRI PDP/ODP Chemistry Workgroup**
- **ISO 10993-18 UPDATE: Material Characterization for Medical Devices**
- **USP <381> UPDATE: Elastomeric Closures - UPDATE**
- **Biodisposable & Single Use Systems**
- **USP <665> UPDATE: Plastic Components Pharmaceutical Manufacturing**
- **Toxicology 101**

DAY 2: Morning Session

- **Setting-up Extractable & Leachable Studies**
- **Understanding different Physico-Chemical Parameters in optimizing a Simulation Study Set-up**
- **Analytical Approach in E/L studies**

DAY 2: Afternoon Session

- **Small Volume Parenterals: E&L Considerations**
- **Large Volume Parenterals: E&L Considerations**
- **Closing Gap between Extractables & Leachables**
  - **Reactive Leachables**
  - **(if timing does not allow, it will be presented as a free webinar)**

REGULATORY REQUIREMENTS

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

Dr. Piet Christiaens

Table Of Content

What is expected from the Container/Closure Systems, used for Pharmaceutical Packaging?

What is expected from Container/Closure Systems

The selected
Container / Closure system
must be

“suitable for its intended use”

A C/C-system that is suitable for 1 Drug Products, may not be suitable for another DP!

Suitability of Containers:

The Container / Closure system:

1. Should **Protect** the Drug Product
2. Should **not introduce toxic compounds** (safety)
3. Should be **Compatible** with the Drug Product
   - No Change in Drug Product
   - No Change in Packaging
4. Should **guarantee the Performance & Functionality** and guarantee the delivery of the drug/dose

Protection of the Drug Product from:

- Degradation
- Product loss
- Reactive gasses
- Water vapor
- Microbial contamination

C/C should **not introduce Toxic** Compounds:

- Leachables from the container closure
- Leachables that undergo a physical/chemical change in the drug product
- Leachables that react with the API
- Toxicological Assessment should address potential Safety Issues

C/C should be **Compatible** with the Drug Product:

- Loss of potency
- Adsorption
- Precipitation
- Discoloration
- pH shift
- Interaction products
- Failure of container/closure integrity because of DP contact
- ...

2. Are Material-DP interaction concerns for real?

Focus on Safety/Quality issues

The New England Journal of Medicine

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VOLUME 346 FEBRUARY 14, 2002 NUMBER 7

PURE RED-CELL APLASIA AND ANTIERYTHROPOIETIN ANTIBODIES IN PATIENTS TREATED WITH RECOMBINANT ERYTHROPOIETIN

NICOLE CASADEVALL, M.D., JOELLE NATAF, M.D., BEATRICE VIRON, M.D., AMIR KOLTA, M.D., JEAN-JACQUES KILADJIAN, M.D., PHILIPPE MARTIN-DUPONT, M.D., PATRICK MICHAUD, M.D., THOMAS PAPO, M.D., VALÉRIE UGO, M.D., IRÈNE TEYSSANDIER, B.S., BRUNO VARET, M.D., AND PATRICK MAYEUX, PH.D.

Conclusions Neutralizing antierythropoietin antibodies and pure red-cell aplasia can develop in patients with the anemia of chronic renal failure during treatment with epoetin. (N Engl J Med 2002;346: 469-75.)

Historical Cases caused by Impurities from Packaging (E/L)

EPREX

EPO-product, distributed by Janssen-Cilag, to **increase the hematocrit** values.

- At first, HSA (Human Serum Albumin) was added as a protein stabilizer
- In 1998, **HSA was replaced by 0.03% Tween 80** (Polysorbate) with Glycine as protein stabilizer
- **Increased incidence of PRCA (*Pure Red Cell Aplasia*)** in patients with **Chronic renal desease**, using EPREX formulation. The timing of occurrence indicated a link to the switch from HSA to Tween/Glycine as protein stabilizer.
- In an Analytical study, it was confirmed that **leachables started to occur after** the **change** from HAS to 0.03% Tween/Glycine.
- Identified leachables:
  - Bisphenol A
  - 4-t-Amylphenol
  - 2-Chloro-t—Amylphenol
  - 2,2'-methylenebis-(4-t-amyl) phenol
  - List of sulfur-bridged rubber additives (see articles) originating from the VULTAC, a rubber additive.

Historical Cases caused by Impurities from Packaging (E/L)

EPREX

EPO-product, distributed by Janssen-Cilag, to increase the hematocrit values.

- **It was hypothesized** that the leachables (one or more) could cause adjuvant-like properties, which caused a decrease of Hematocrit as a result of the generation of Anti-EPO-antibodies!!
- Changing to a coated rubber stopper reduced the occurrence of PCRA

HOWEVER

Pharm Res (2012) 29:1454–1467
DOI 10.1007/s11095-011-0621-4

RESEARCH PAPER

Tungsten-Induced Denaturation and Aggregation of Epoetin Alfa During Primary Packaging as a Cause of Immunogenicity

Andreas Seidl • Otmar Hainzl • Marleen Richter • Robert Fischer • Stephan Böhm • Britta Deutel • Martin Hartinger • Jörg Windisch • Nicole Casadevall • Gerard Michel London • Iain Macdougall

Conclusions We propose tungsten-mediated unfolding and aggregation of epoetin alfa in pre-filled syringes as a potential root cause for increased immunogenicity. This finding may be more broadly applicable to this and other classes of therapeutic proteins.

2. Are interaction concerns for real?

- **34,000 Tylenol bottles recalled for musty smell**
- *NEW YORK (CNNMoney) -- Johnson & Johnson is recalling yet another batch of Tylenol medicines due to consumer complaints about a musty, moldy smell.... The company said at the time that the smell was caused by trace amounts of a chemical called 2,4,6-tribromoanisole, which is applied to wooden pallets that are used to transport and store packaging materials….*

- **38,000 more bottles of Lipitor recalled over odor complaints**
- **(CNN)** *-- Pfizer is recalling an additional 38,000 bottles of the cholesterol-fighting drug Lipitor after reports of an odor linked to the packaging bottles, the drug company said in a statement…. "Research indicates that a major source of TBA appears to be 2, 4, 6-tribromoanisole(TBP), a chemical used as a wood preservative," the company said. "Although TBP often is applied to pallets used to transport and store a variety of products, Pfizer prohibits the utilization of TBP-treated wood in the shipment of its medicines."*

- **Glumetza Recall: 52 Lots of Diabetes Drug May Have Chemical Contamination**
- *More than 200,000 bottles of the diabetes drug Glumetza have been recalled due to the same chemical contamination from wood pallets that led to a Tylenol recall late last year.*

TBA: a "Migrant " from Wooden Pallets (wood preservative)
Due to Lack of Barrier Properties of the Primary Packaging System

2. Are interaction concerns for real?

- **BPA, chemical used to make plastics, found to leach from polycarbonate drinking bottles Into humans - *Exposure to BPA May Have Harmful Health Effects***
- *For immediate release: Thursday, May 21, 2009*
- *Boston, MA — A new study from Harvard School of Public Health (HSPH) researchers found that participants who drank for a week from polycarbonate bottles, the popular, hard-plastic drinking bottles and baby bottles, showed a two-thirds increase in their urine of the chemical bisphenol A (BPA). Exposure to BPA, used in the manufacture of polycarbonate and other plastics, has been shown to interfere with reproductive development in animals and has been linked with cardiovascular disease and diabetes in humans. The study is the first to show that drinking from polycarbonate bottles increased the level of urinary BPA, and thus suggests that drinking containers made with BPA release the chemical into the liquid that people drink in sufficient amounts to increase the level of BPA excreted in human urine.*

- **Leaching of the plasticizer di(2-ethylhexyl)phthalate (DEHP) from plastic containers and the question of human exposure.**
- **Abstract**
- *Di(2-ethylhexyl)phthalate (DEHP) is a widely used plasticizer to render poly(vinyl chloride) (PVC) soft and malleable. Plasticized PVC is used in hospital equipment, food wrapping, and numerous other commercial and industrial products. Unfortunately, plasticizers can migrate within the material and leach out of it over time, ending up in the environment and, frequently, the human body.*

2. Are interaction concerns for real?

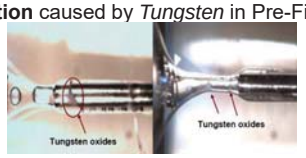
- **Release of (Halogenated) Rubber Oligomers,** causing interaction with the API *(see later)*

- **PolyNuclear Aromatics (PNA's, carcinogenic)** released from rubbers *(when Carbon Black is used as a colorant (Black)*

- **N-Nitrosamines** leaching from rubbers
  (when using certain accelerators for cross linking the rubber)

2. Are interaction concerns for real?

- **Release of Iron** (from Rubber Closure) causing oxidative degradation of protein*
- **Silicone oil,** causing protein aggregation*
- **(Reactive) Acrylates** - from incompete glue curing of staked needle in PFS - causing degradation*
- **Barium and Aluminum,** released from glass, to form particles*
- **Protein degradation** caused by *Tungsten* in Pre-Filled Syringes*.



** Presented By I. Markovic, "Regulatory Perspective on Extractables & Leachables for Biologics, Quality Perspective" PDA E/L-Workshop, Brussels , 2014*

2. Are interaction concerns for real?

In General: Be cautious when working with Proteins

- Proteins = Very Large Molecules!
- Some of them: dosed at low concentrations!
- **High Surface area:** a lot of potential interactions at surface
- A lot of **Reactive Sites at surface** of the protein molecule!
- **If tertiary/quaternary structure of protein is affected**: the drug efficacy may be affected
  (loss in potency, immunomodulatory responses)

** Presented By I. Markovic, "Regulatory Perspective on Extractables & Leachables for Biologics, Quality Perspective" PDA E/L-Workshop, Brussels , 2014*

Connecting People, Science and Regulation®

With increasing knowledge and understanding
of how the impurities from a Container /Closure
may impact the safety and quality
of a drug product

Need for Regulations/Guidance!

Connecting People, Science and Regulation®

3. Regulatory Requirements

REGULATORY REQUIREMENTS

WHAT?	HOW?
What kind of information should be provided?	How can the testing be performed?
• US Guidances • EU Guidelines	• Pharmacopoeias • Standards Organizations • Recommendations of Workgroups • Consortia
• Code of Federal Regulations (CFR) • ICH Q7 – GMP Practice Guide • EU – Good Manufacturing Practices	

Connecting People, Science and Regulation®

REGULATORY REQUIREMENTS:

WHAT?

WHAT kind of information needs to be provided wrt the Qualification of the selected Container / Closure system to the authorities?

PRIMARY PACKAGING

PRIMARY PACKAGING

REGULATORY ASPECTS – PARENTERALS – NON-LIMITATIVE LIST

<1999: 21CFR 211.94(a) "DRUG PRODUCT CONTAINERS AND CLOSURES"
...not reactive, additive, absorptive to alter
safety, identity, strength, quality or purity of drug...

1999: "CONTAINER/CLOSURE SYSTEMS FOR PACKAGING HUMAN DRUGS AND BIOLOGICS" (FDA-Guidance for Industry)

2003: EU COMMISSION DIRECTIVE 2003/63/EC, (§ 3.2.2.2 g)
- *CCS-information is part of the Market Authorization dossier.*

2005: "GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS" (EMEA Guideline)
- *Contains "Decision Tree" for different dosage forms*

2006: ICH Q8 "PHARMACEUTICAL DEVELOPMENT", § 2.4 CCS

2014: USP <1663> (Extractables) & USP <1664> (Leachables)

2015: ICH M7: DNA reactive impurities in Pharmaceuticals

REGULATORY ASPECTS – PARENTERALS – NON-LIMITATIVE LIST

<1999: 21CFR 211.94(a) "DRUG PRODUCT CONTAINERS AND CLOSURES"
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1999: "CONTAINER/CLOSURE SYSTEMS FOR PACKAGING HUMAN DRUGS AND BIOLOGICS" (FDA-Guidance for Industry)
- *Classification, based on likelihood of interaction and route of administration*

2003: EU COMMISSION DIRECTIVE 2003/63/EC, § 3.2.2.2 g)
- *CCS-information is part of the Market Authorization dossier.*

2005: "GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS" (EMEA Guideline)
- *"Decision Tree" what information to provide for different dosage forms*

2006: ICH Q8 "PHARMACEUTICAL DEVELOPMENT", § 2.4 CCS

2014: USP <1663> (Extractables) & USP <1664> (Leachables)

2015: ICH M7: DNA reactive impurities in Pharmaceuticals

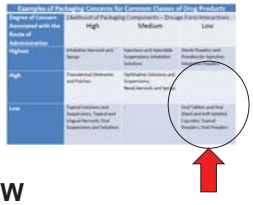
3. REGULATORY REQUIREMENTS: **WHAT?**

Examples of Packaging Concerns for Common Classes of Drug Products			
Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Components – Dosage Form Interactions		
	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 Suspensions and Solutions	-	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules; Topical Powders; Oral Powders

Revision of "Table 1" in USP <1664>,
Originally Included into the FDA Guidance for Industry (1999):
"Container/Closure systems for Packaging Human Drugs and Biologics"

USP <1664>: Revision of Table 1, Originally presented in the FDA Guidance for Industry of 1999 (Container/Closure Systems)

"CONTAINER/CLOSURE SYSTEMS FOR PACKAGING HUMAN DRUGS AND BIOLOGICS" (1999)



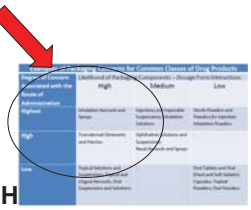
LIKELIHOOD OF INTERACTION = LOW
Packaging Component - Dosage Form

DEGREE OF CONCERN
FOR **ROUTE OF ADMINISTRATION = LOW**

THEN: CERTIFICATE OF ANALYSIS
- COMPENDIAL testing
- ROUTINE QC testing

e.g. Oral solutions/suspensions, Oral Tablets/Capsules/Powders…

USP <1664>: Revision of Table 1, Originally presented in the FDA Guidance for Industry of 1999 (Container/Closure Systems)



LIKELIHOOD OF INTERACTION = HIGH
Packaging Component - Dosage Form

DEGREE OF CONCERN
FOR **ROUTE OF ADMINISTRATION = HIGH**

THEN: 1. CERTIFICATE OF ANALYSIS
- COMPENDIAL testing
- ROUTINE QC testing

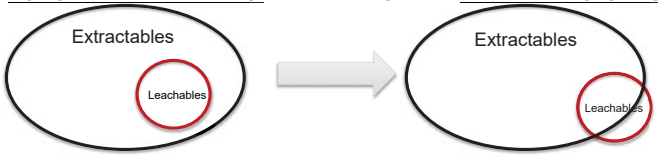
2. ADDITIONAL EXTRACTABLES/LEACHABLES DATA

e.g. Inhalation Aerosols (MDI, DPI, Nasal Sprays), Injections, Injectable suspensions (Parenterals : Pre-filled syringes, IV bags…), Ophtalmic solutions/suspensions…

3. REGULATORY REQUIREMENTS: **WHAT?**

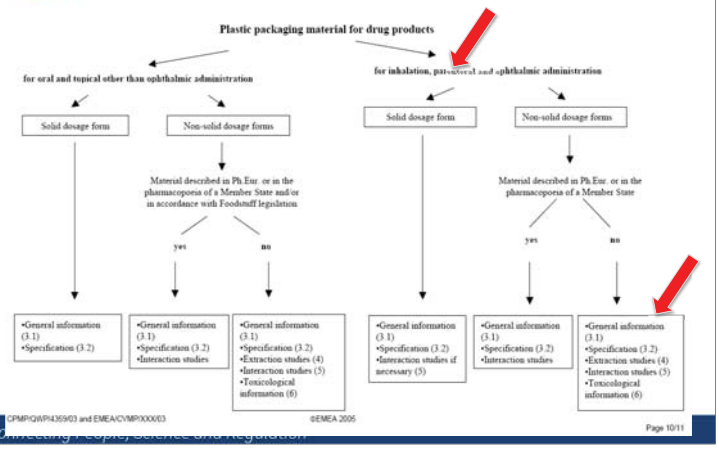
The **"HOW"** in the FDA Guidance Document
"*Container Closure Systems for Packaging Human Drugs and Biologics*" of **1999**
may NOT reflect the current (2015) FDA requirements
for E/L Testing and Documentation:

- **NOT ONLY EXTRACTABLES** evaluation => Consider **LEACHABLE STUDIES**!



3. REGULATORY REQUIREMENTS: **WHAT?**

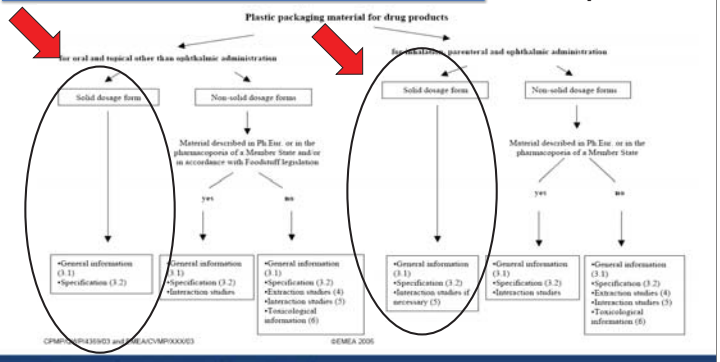
The EM(E)A Guideline on "*Plastic Immediate Packaging Materials*" of 2005



2005: "GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS" (EMEA Guideline)

SOLID DOSAGE FORMS:

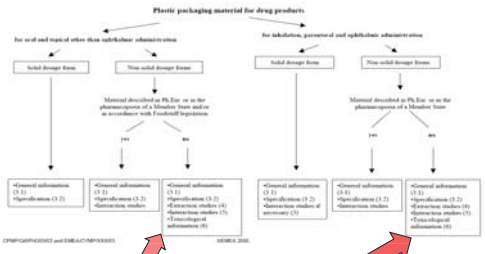
LIKELIHOOD OF **INTERACTION** IS **LOW:** **LOW requirements**



"GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS" (2005)

"OTHER" DOSAGE FORMS:

LIKELIHOOD OF **INTERACTION** IS **HIGH**



E.P. COMPENDIAL TESTING IS REQUIRED BUT **NOT SUFFICIENT**.

ADDITIONAL REQUIREMENTS

1. **EUROPEAN PHARMACOPOEIA TESTS**
2. **EXTRACTION STUDIES**
3. **INTERACTION STUDIES (INCLUDING § 5.1 MIGRATION STUDIES)**

3. REGULATORY REQUIREMENTS: **WHAT?**

Some Side Notes to the EMA Immediate Packaging Guideline (2005)

- Not for Elastomers (?) = > In reality: **ALSO** fo rubbers
- If a Material is described in the E.P. And if it complies with the specifications therein, no Extractable testing may be needed.
  NOT THE ACTUAL POSITION OF EUROPEAN REGULATORS
- If Extractable Testing shows only compounds with low risk (at low concentrations) no leachable study is necessary.
  NOT THE ACTUAL POSITION OF EUROPEAN REGULATORS

MANUFACTURING EQUIPMENT

REGULATORY ASPECTS – PRODUCTION COMPONENTS - MATERIALS

U.S.
Title 21 of the Code of Federal Regulations (CFR) 211.65 (1)
"...Equipment shall be constructed so *that **surfaces** that contact components*, in-process materials or drug products ***shall not be reactive, additive or adsorptive so as to alter safety, identity, strength, quality or purity*** *of the drug product beyond the official or other established requirements*..."

EUROPE
ICH Q7 – GMP Practice Guide
"...Equipment should not be constructed so that *surfaces that contact raw materials, intermediates or API's **do not alter the quality of the intermediates and API's** beyond the official or other established specifications..."*

EU – Good Manufacturing Practices
"...Production Equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive... That it will affect the Quality of the Product..."

REGULATORY ASPECTS – PRODUCTION COMPONENTS - MATERIALS

OBSERVATIONS

The CFR 211.65 and GMP's do ***not only*** refer to the ***impact on Safety***, but also on:
- **Quality**
- Purity
- Strength (e.g. Adsorptive behavior)
- Reactive behavior
- Additive behavior

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

Disposable Production is fairly new, may trigger additional questions

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

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 and 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*

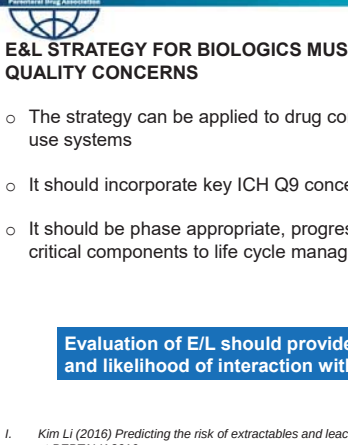
3. REGULATORY REQUIREMENTS: **HOW?**

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

- The strategy can be applied to drug containers, drug delivery systems and 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*


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)

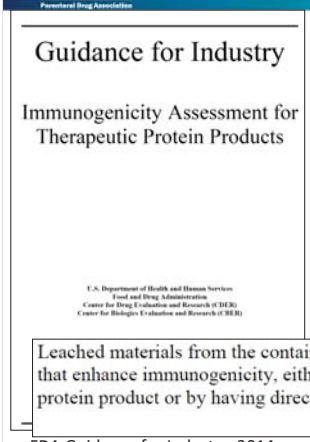
Consequences for EFFICACY – some of the concerns:

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


Guidance for Industry

Immunogenicity Assessment for Therapeutic Protein Products

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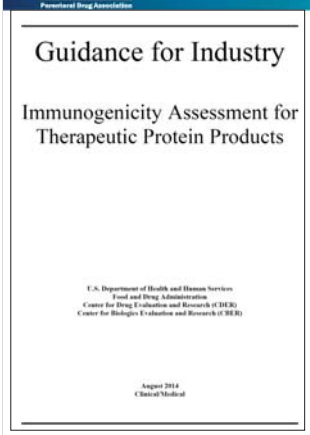
Center for Biologics Evaluation and Research (CBER)

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

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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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2014
Clinical/Medical

Immunogenicity, **not only** a concern for **Single Use Systems**, used in Bioproduction.

Also for **Primary Packaging** of Therapeutic Protein Drug Products, such as
- Pre-Filled Syringes System
- Lyo Vial Systems

This will be adressed later in the Training Course

FDA Guidance for Industry, 2014

REGULATORY REQUIREMENTS & RECOMMENDATIONS:

HOW?

HOW can an adequate testing strategy – to qualify a container / closure system from an E/L perspactive - be put together?

REGULATORY REQUIREMENTS & RECOMMENDATIONS: HOW?

- US Pharmacopoeia (USP)
- European Pharmacopoeia (EP)
- ISO 10993 Standards (Biocompatibility - Medical Devices)
- PQRI – Product Quality Research Institute
  - OINDP Orally Inhaled and Nasal Drug Products
  - PDP/ODP: Parenteral Drug Products/Ophthalmic Drug Products
- BPSA Bio-Process Systems Alliance (SU Systems)
- BPOG Biophorum Operations Group (SU Systems)

US PHARMACOPOEIA: USP 39

SOME MANDATORY TESTS (<1000)

<381> Elastomeric Closures for Injections

<661> Containers (still partially under revision)

<661.1> Plastic Material of Construction (FINAL)
COP/COC, PA 6, PC, PE, PET/PETG, EVA, PP, PVC
<661.2> Plastic Packaging Systems for Pharmaceutical Use (FINAL)
<661.3> = > **<665>** Manufacturing Systems (UNDER REVIEW)
<661.4> Devices (UNDER DEVELOPMENT)

<87> Biological Reactivity Tests, In Vitro (Cytotox tests)

<88> Biological Reactivity Testing, In Vivo (Class Tests)

US PHARMACOPOEIA: USP 39

SOME USP "GUIDANCE" MONOGRAPHS (>1000)

<1661> **Evaluation of Plastic Packaging** – and Manufacturing Systems and their Materials of Construction with respect to their Safety Impact

<1663> Assessment of **Extractables** Associated with Pharmaceutical Packaging/Delivery Systems

<1664> Assessment of Drug Product **Leachables** Associated with Pharmaceutical Packaging/Delivery Systems

<1665> **Toxicological Assessment** of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems

European Pharmacopoeia :
3.1 *Materials* used in the manufacture of containers

3.1.1.1 **PVC** for human blood (components) containers
3.1.1.2 **PVC** for human blood (components) tubing sets
3.1.3 **Polyolefines**
3.1.4 **PE without additives** containers for parenteral/ophthalmic preps
3.1.5 **PE with additives** containers for parenteral/ophthalmic preps
3.1.6 **PP** containers for parenteral/ophthalmic preps
3.1.7 **EVA** for containers and tubing for parenteral/ophthalmic preps
3.1.9 **Silicone elastomer** for Closures and Tubing
3.1.10 & 11 **non-plasticized PVC**
3.1.14 **Plasticized PVC**
3.1.15 **PET**

European Pharmacopoeia :
3.2 *Containers*

3.2.1 **GLASS** containers for pharmaceutical Use
3.2.2 **Plastic** Containers/Closures for Pharmaceutical Use
3.2.2.1 **Plastic** Containers for aq. solutions for parenteral infusion
3.2.3 **Sterile plastic** containers for human blood (components)
3.2.4 Empty Sterile **containers of plasticized PVC** for human blood
3.2.5 Sterile **containers of plasticized PVC** for human blood, containing anticoagulant
3.2.6 **Sets for the transfusion** of Blood and Blood components
3.2.8 Sterile single-use **plastic syringe**
3.2.9 **Rubber** Closures

TYPICAL for Physico Chemical Compendial tests:

Well Defined Analytical Approach:

- Sample Preparation (Extraction Method, Time, Temperatures...)
- **"GROUP PARAMETER"** Analyses (Acidity/Alkalinity, Residues, Reducing Substances, Absorbance, Turbidity...)
- In some cases: Individual Compound Analyses (Polymer Additives, Extractable/Total Metals...)
- Sometimes: Identification (e.g. FTIR)

PASS / FAIL Criteria!!

Compendial tests follow a **"COOK BOOK"** Approach!!

STRENGHTS of Pharmacopoeial Compendial Tests

- Provide **Basic Information** on the **Quality of Materials**
- Clear **PASS / FAIL** Criteria
- Can be used in the development of a new MATERIAL formulation
- Can be **used to monitor the quality in production** (e.g. In combination with physical tests)
- Assists in the initial safety assessment of a material *(eg. Additives may define which compounds may be encountered as leachables)*

EP/USP Compendial Tests: **No replacement** for Extractable St.

- **Sample preparation**: not always relevant!
  - e.g. Rinsing procedure: loss of potential impurities (extractables)
    WFI is not always to most relevant extraction Vehicle
- **Group Parameters are not usable for Extractables Interpretation**
  - e.g. E.P. Absorbance: Which compounds are Causing absorbance?
    What is the concentration of these compounds?
- **Limited information on individual compounds**
  - e.g. E.P.: Polymer additives, Extractable total metals
- **No detailed information on** process impurities, polymer degradation compounds, additive degradation compounds, oligomers, solvent residues...
- THESE COMPOUNDS ➔ TARGETS FOR LEACHABLE STUDIES!!

3. REGULATORY REQUIREMENTS: **HOW?**

REGULATORY REQUIREMENTS & RECOMMENDATIONS: HOW?

- US Pharmacopoeia (USP)
- European Pharmacopoeia (EP)
- ISO 10993 Standard (Biocompatibility - Medical Dev.)
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  - PDP/ODP: Parenteral Drug Products/Ophthalmic
- BPSA Bio-Process Systems Alliance (SU Systems)
- BPOG Biophorum Operations Group (SU Systems)

Will be addressed in other parts of the workshop

3. REGULATORY REQUIREMENTS: **HOW?**

OTHER GUIDANCE DOCUMENTS...

- Guidance for Industry: Nasal Spray and Inhalation Solutions, Suspension and Spray Drug Products – Chemistry Manufacuring and Controls Documentation, CDER (2002)
- Guidance for Industry: Pharmaceutical Quality of Inhalation and Nasal Products, Health Canada (2006)
- Guidelines on the Pharmaceutical Quality of Inhalation and Nasal Products, EMA (2006)
- Draft Guidance for Industry: Metered Dose Inhalers (MDI) and Dry Powder Inhaler (DPI) Drug Products. Chemistry, Manufacturing and Controls Documentation, CDER (1998)

3. REGULATORY REQUIREMENTS: **HOW?**

APPLICABLE ICH Guidances:

- **ICH Q3D**: Elemental Impurities (2014; Step 4)
- **ICH Q6B**: test procedures and acceptance criteria for biotechnological/biological products (1999)
- **ICH Q5C**: Quality of Biotechnology Products Stability of biotechnological/biological products (1996)
- **ICH Q5E**: Comparability of biotechnology/biological products subject to changes in their manufacturing process (2005)
- **ICH Q7A**: GMP of APIs
- **ICH Q8**: Pharmaceutical Development (2006)
- **ICH Q9**: Quality Riks Management (2006)
- **ICH Q10**: Pharmaceutical Quality Systems (2008)
- **ICH Q3C**: Impurities: Residual Solvents (although no specific reference to C/C impurities)

NON-APPLICABLE ICH Guidances:

- **ICH Q3A**: Chemical Impurities in New Drug Substances
- **ICH Q3B**: Impurities in New Drug Products

ICH Q3D: ELEMENTAL IMPURITIES

during the shelf-life of the product. Studies to understand potential extractables and leachables from the final/actual container closure system (after washing sterilization, irradiation) should be performed.

- Elemental impurities that are known or suspected of being leached into the drug substance and drug product from container closure systems.

Elemental impurities leached from container closure systems: Identifying the potential elemental impurities extracted from container closure systems should be based on a scientific understanding of likely interactions between a particular drug product type and its packaging. When a review of the materials of construction demonstrates that the container closure system does not contain elemental impurities, no additional assessment needs to be performed. It is recognized that the probability of elemental leaching into solid dosage forms is minimal and does not require further consideration in the assessment. For liquid and semi-solid dosage forms there is a higher probability that elemental impurities could leach from the container closure system into the drug product during the shelf-life of the product. Studies to understand potential extractables and leachables from the final/actual container closure system (after washing sterilization, irradiation) should be performed.

ICH Q6B: test procedures and acceptance criteria for biotechnological/biological products (1999)

c) Downstream-derived impurities include, but are not limited to, enzymes, chemical and biochemical processing reagents (e.g., cyanogen bromide, guanidine, oxidising and reducing agents), inorganic salts (e.g., heavy metals, arsenic, non metallic ion), solvents, carriers, ligands (e.g., monoclonal antibodies), and other leachables.

Process-Related Impurities:

Impurities that are derived from the manufacturing process. They may be derived from cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g., inducers, antibiotics, or media components), or downstream processing (e.g., processing reagents or column leachables).

The quality of the excipients used in the drug product formulation (and in some cases, in the drug substance), as well as the container/closure systems, should meet pharmacopoeial standards, where available and appropriate. Otherwise, suitable acceptance criteria should be established for the non-pharmacopoeial excipients.

Degradation Products:

Molecular variants resulting from changes in the desired product or product-related substances brought about over time and/or by the action of, e.g., light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Such changes may occur as a result of manufacture and/or storage (e.g., deamidation, oxidation, aggregation, proteolysis). Degradation products may be either product-related substances, or product-related impurities.

ICH Q5C: Quality of Biotechnology Products Stability of biotechnological/biological products (1996)

6.5. Container/Closure

Changes in the quality of the product may occur due to the interactions between the formulated biotechnological/biological product and container/closure. Where the lack of interactions cannot be excluded in liquid products (other than sealed ampoules), stability studies should include samples maintained in the inverted or horizontal position (i.e., in contact with the closure), as well as in the upright position, to determine the effects of the closure on product quality. Data should be supplied for all different container/closure combinations that will be marketed.

Impurity

Any component of the drug substance (bulk material) or drug product (final container product) which is not the chemical entity defined as the drug substance, an excipient, or other additives to the drug product.

ICH Q5E: Comparability of biotechnology/biological products subject to changes in their manufacturing process (2005)

protease might only be detected by product degradation that occurs over an extended time period; or, in some cases, divalent ions leached from the container closure system might change the stability profile because of the activation of trace proteases not detected in stability studies of the pre-change product. Therefore, real-time/real temperature stability studies on the product potentially affected by the change should be initiated, as appropriate.

ICH Q7A: GMP of APIs

9.2 Packaging Materials

9.20 Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.

9.21 Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.

ICH Q8: Pharmaceutical Development (2006)

2.4 Container Closure System

The choice and rationale for selection of the container closure system for the commercial product (described in 3.2.P.7) should be discussed. Consideration should be given to the intended use of the drug product and the suitability of the container closure system for storage and transportation (shipping), including the storage and shipping container for bulk drug product, where appropriate.

The choice of materials for primary packaging should be justified. The discussion should describe studies performed to demonstrate the integrity of the container and closure. A possible interaction between product and container or label should be considered.

The choice of primary packaging materials should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching), and safety of materials of construction. Justification for secondary packaging materials should be included, when relevant.

ICH Q9: Quality Riks Management (2006)

Selection of container closure system

To determine the critical parameters of the container closure system.

ICH Q10: Pharmaceutical Quality Systems (2008)

- Pharmaceutical Development
  - Drug substance development
  - Formulation development (including container/closure system)
  - Manufacture of investigational products
  - Delivery system development (where relevant)
  - Manufacturing process development and scale-up
  - Analytical method development

Impurities arising from excipients present in a new drug product or extracted or leached from the container closure system are not covered by this guidance. This guidance also does not apply to

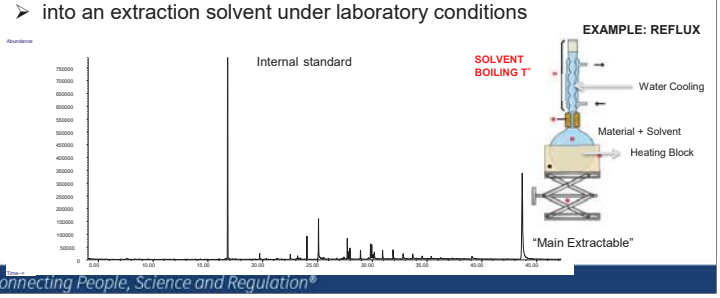
4. What are Extractable Studies, Simulation Studies and Leachable Studies?

EXTRACTABLE STUDIES

DEFINITIONS

EXTRACTABLES (from USP <1663>):

- Organic & Inorganic Chemical Entities
- released from
  - *a pharmaceutical packaging/delivery system*
  - *packaging component*
  - *packaging material of construction*
- into an extraction solvent under laboratory conditions



What is the **PURPOSE** of an Extraction Study?

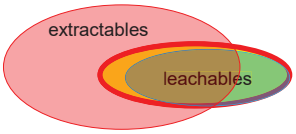
- Material Characterization of the Packaging Components
- "Impurities Profiling" of the Materials
  - Identify as Many Compounds as Possible
  - Identify "Bad Actors" in the Materials
- Early Risk Evaluation
- Allows to Compare the Supplier Information with Actual Data
- Allows a QbD Approach
- Use of Extraction solutions which are "Compatible" with Screening techniques: CLEAN SOLVENTS
- Identify Compounds that may need to be Monitored as Leachable
  - Toxicity
  - Concentration in the Materials
  - Risk for Migration
- Not as a Final Step in the Safety Assessment!

SIMULATION STUDY

» Purpose of Simulation Study

- Find + identify extractables which are **probable leachables**
- Establish which extractables must be targeted in a migration study
  - **Screening**
  - **mimic circumstances of final drug product:** acceleration, moderate exaggeration
  - **worst case:** sufficient amounts to identify
  - **safety/ toxicological risk assessment** to define target leachables

CLOSING THE GAP!!



Additional Study Design: SIMULATION STUDY

Conditions of a Simulation Study:

1. Exaggerated & Accelerated Conditions:
   - Exaggerated: Composition of the Simulant
     Increased Surface area
     Underfilling (e.g. Bags)
   - Accelerated: temperature of Storage – Accelerated Ageing
2. Study the Complete Packaging System, not only the individual parts
3. Or, Study some parts of the Packaging System which are of Particular Interest

Example Novo Nordisk:

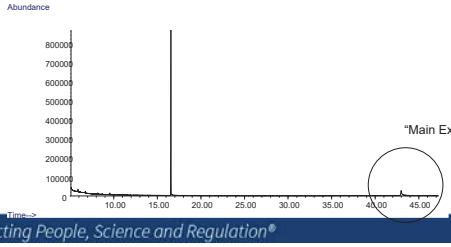
Carsten Worsoe, PDA Pre-Filled Syringes Conference

Exaggerated Exposure: Exposed Surface Area of Plungers 10x compared to reality
Accelerated: 3 Months at 40° C
Using the DP

MIGRATION / LEACHABLE STUDY

LEACHABLES (from USP <1664>):

- Foreign Organic and Inorganic Chemical Entities
- present in a packaged drug product because they have leached into the packaged drug product from
  - *the packaging/delivery system*
  - *packaging component*
  - *packaging material of construction*
- under normal conditions of storage and use
- or during accelerated drug product stability studies



- TRYING TO ASSESS THE LEACHING BEHAVIOUR
- ASSESS POTENTIAL TOXIC CONSEQUENCES = **SAFETY**
- ASSESS IMPACT ON **DRUG PRODUCT QUALITY**
- FOCUS ON QUANTIFICATION OF **"TARGET" COMPOUNDS**
  KNOWN POLYMER ADDITIVES USED
  VALIDATION PACKAGE OF CONTAINER SUPPLIERS
  EXTRACTABLES STUDY INFORMATION
- **"SIMULATED USE"** CONDITIONS
  STORAGE TIME / TEMPERATURE / HUMIDITY
  CONDITIONS: SIMILAR TO STABILITY STUDIES
  PHARMACEUTICAL FORMULATION AS CONTACT SOLUTION
- **VALIDATED METHODS** (ICH Q2(R1))

The terms **extractable** and **leachable** provide clarity in terms of:

1.The **potential** versus the **actual** impact of the product on its user.

* **Extractable** = potential impact: *what "could" come out*
* **Leachable** = actual impact: *what "will" come out*

2.The object on which the testing is performed.

* **Extractable** = test the material
  Leachable = test the finished product

D. Jenke (presentation at SmithersRapra, Providence, May 2013)

Where do these compounds come from?
- POLYMERS 101 / GLASS 101 / THE MECHANISM OF POYMER LEACHING

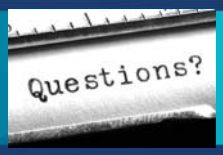
Regulatory Guidance/Recommendations how to design such a study?
- REGULATORY UPDATE
  - PQRI
  - USP
  - ISO 10993

What kind of Analytical Tools can you use?
- ANALYTICAL APPROACH IN E/L TESTING

How to assess the results from an E/L study?
- FROM THRESHOLD APPROACH (PQRI) TO IN-DEPTH TOXICOLOGICAL REVIEW

How to put the theory into practice, how to design an E/L approach for different parenteral applications?
- SETTING UP E/L STUDIES
  - INJECTABLES
  - LVP
  - SUS

Introduction – Regulatory Aspects



POLYMERS 101 – GLASS 101

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

Dr. Piet Christiaens

CONTENT

Content

1. What is a Polymer?
2. Classification of Polymers
3. Types of Polymers – Examples in Medical Use
4. Properties of polymers
5. Understanding the Composition of Polymers

WHAT IS A POLYMER?

Polymers 101

1. What is a "Polymer"?

*A **polymer** is a chemical compound or mixture of compounds consisting of repeating structural units created through a process of polymerization*

Greek words:
πολύς (polus, meaning "many, much")
μέρος (meros, meaning "parts")

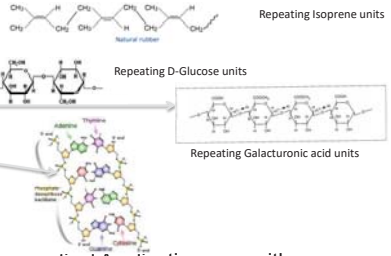
Refers to a molecule

- whose structure is composed of **multiple repeating units**
- As a consequence:
  - *a characteristic of high relative molecular mass and*
  - *associated properties*.

NATURAL VS SYNTHETIC POLYMERS

Classification of Polymers

- Polymers also exist in Nature: **NATURAL POLYMERS**
  - Latex / Natural Rubber
  - Starch
  - Cellulose
  - Pectin
  - DNA
  - Silk / Wool
  - ....

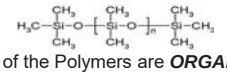


- However, most of the Pharmaceutical Applications are with **SYNTHETIC POLYMERS**

SYNTHETIC Polymers

a small fraction are ***INORGANIC POLYMERS***

Example: Siloxanes (PolyDiMethylSiloxanes; PDMS) *(SILICONE)*

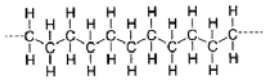


However, most of the Polymers are ***ORGANIC POLYMERS***

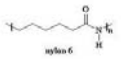
Examples: **see next slide**

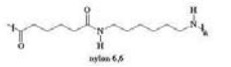
SYNTHETIC Polymers

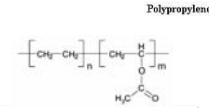
Some Examples of ***ORGANIC POLYMERS***



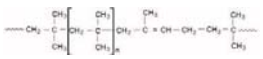
Polyethylene (PE)





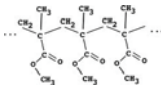


Ethylene Vinyl Acetate



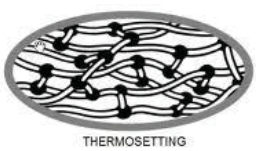
IIR Rubber

Isobutyl **I**sopropenyl **R**ubber



THERMOPLASTIC VS THERMOSET POLYMERS

THERMOPLASTIC



THERMOSETTING

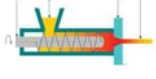
"Entangled" Polymer Chains

Crosslinked Polymer Chains

THERMOPLAST VERSUS THERMOSET

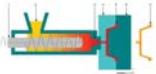
THERMOPLAST :
Polymers that soften when heated and become firm again when cooled

Giving the **final form to a container/component** is based upon this principle:
Molding, Extrusion...



Extrusion

Examples: LDPE, HDPE, PP, PC, EVA,...



Injection Molding

THERMOPLAST VERSUS THERMOSET

THERMOSET :

Polymers that soften when heated and molded subsequently

BUT

Decompose when Reheated

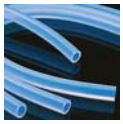
Thermoset polymers are typically "**cross linked**"

Example: Bakelite

Fenol Formaldehyde Resin

Rubbers

Silicone tubings



TYPES OF POLYMERS

TYPES OF POLYMERS - **HOMOPOLYMERS**

A-A-A-A-A-A-A-A-A-A-A-A-A-A-A-A-A-A-A-A

A homopolymer is a **polymer** built from a **sequence of identical monomers**

EXAMPLES:

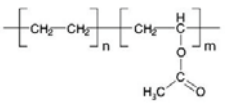
- Polyethylene
- Polypropylene
- PVC

TYPES OF POLYMERS – **COPOLYMERS**

When *two or more different monomers* unite together to polymerize, their result is called a **copolymer**

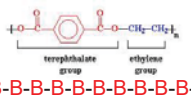
Random Copolymer A-B-A-A-B-B-B-A-B-A-A-A-B-A-B-B-A-B-A

Examples: Poly EVA



Regular Copolymer A-B-A-B-A-B-A-B-A-B-A-B-A-B-A-B-A-B-A

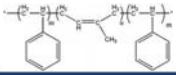
Examples:PET



Block Copolymer A-A-A-A-B-B-B-B-B-B-B-B-B-B-B-B-A-A-A-A

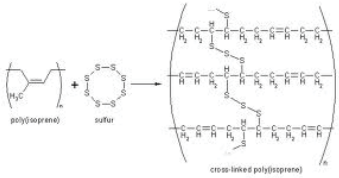
Examples

SIS Elastomer

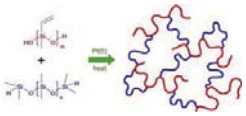


TYPES OF POLYMERS – **CROSS-LINKED Polymers**

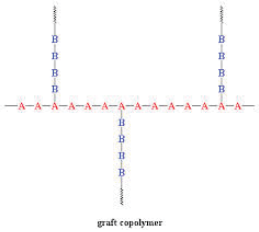
Isoprene/ Butadiene RUBBERS



Silicone rubbers (Pt-cured)



TYPES OF POLYMERS – **GRAFT COPOLYMERS**

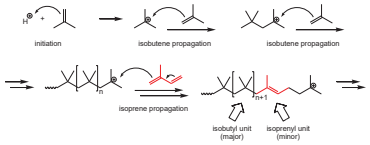


CLASSIFICATION BASED UPON POLYMERISATION MECHANISM

CHAIN GROWTH

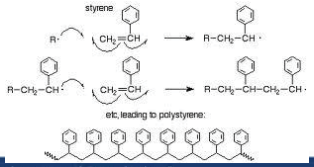
Example 1: Cationic Polymerization of “Butyl Elastomer”

Lewis Acid

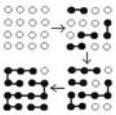


Understanding Polymerization of Butyl Elastomer helps to understand the formation and presence of rubber oligomers (see presentation E/L for Parenterals – Day 2)

Example 2: Radical Polymerization of Polystyrene



STEP GROWTH (definition)



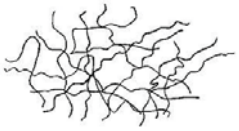
Examples: Polyaddition, polycondensation – Nylon 6,6

Seen as an Extractable /Leachable

POLYMER PROPERTIES

1. MORPHOLOGY

1. **AMORPHOUS Polymers**

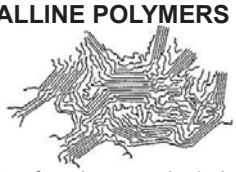


Because of
- Irregularities in Polymer Structure
- The Nature of the Polymer
- Cross-linking (for certain Polymers)

Nº intermolecular bonds (e.g. Hydrogen bonds, Van der Waals forces) will lead to an alignment of the polymer chains

Examples: PS, PVC, SAN, ABS, PMMA, PC, PES

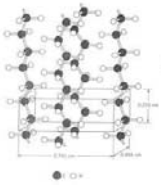
2. (Semi-)CRYSTALLINE POLYMERS

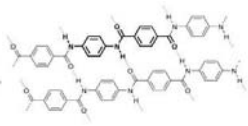


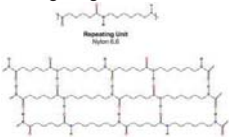
Hydrogen Bonds (e.g. PA)
Van der Waals Forces
(e.g. Polyolefins)

Impact of Stereochemistry of a polymer on physical properties

Bring "alignment" in chains







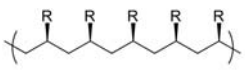
Kevlar

Nylon 6,6

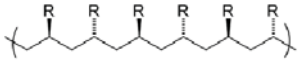
AMORPHOUS versus CRYSTALLINE

AMORPHOUS versus CRYSTALLINE

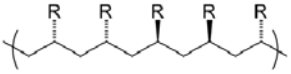
Impact of **StereoChemistry** of a polymer on physical properties



Isotactic
Typically semi-crystalline
(e.g. PP via Ziegler-Natta polymerisation)



Syndiotactic
PS: Syndiotactic PS is semi-crystalline



Atactic
Typically amorphous polymers
PS: Atactic PS is amorphous

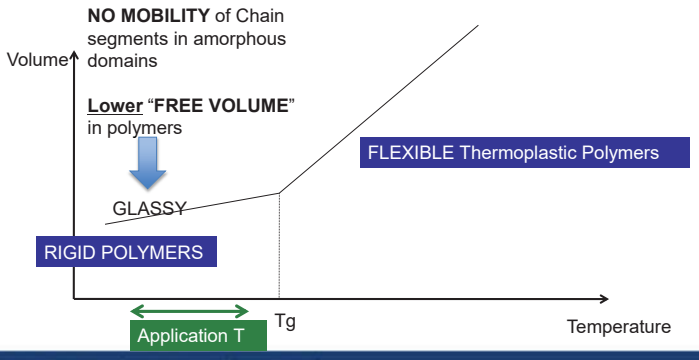
TACTICITY MODULATORS, SOMETIMES FOUND AS EXTRACTABLES

2. GLASS TRANSITION T° (T_g)

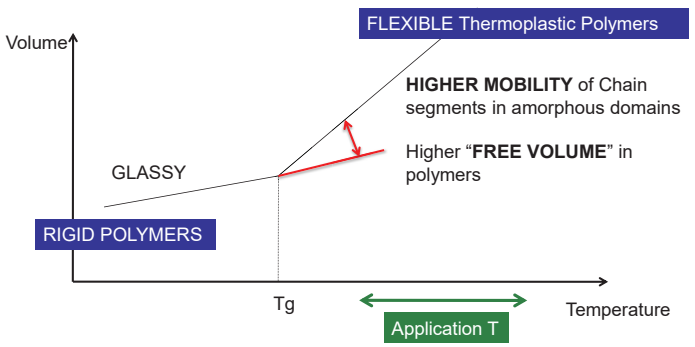
DEFINITION

GLASS TRANSITION TEMPERATURE (T_g):
Temperature when a Polymer goes
from a "glassy" state (< T_g) to a "rubber" state (> T_g)

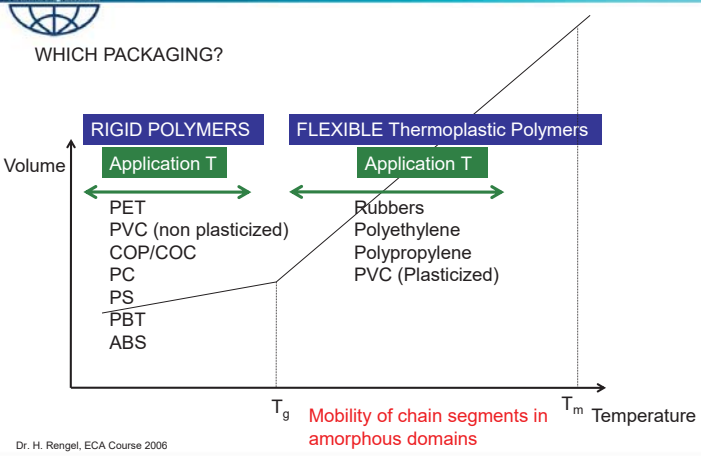
WHAT IS **RIGID** PACKAGING?



WHAT IS **FLEXIBLE** PACKAGING?



WHICH PACKAGING?



Dr. H. Rengel, ECA Course 2006

Examples of T_g for different materials

LDPE	T_g = -125°C
POM	T_g = -50°C
PP	T_g = -25°C
PBT	T_g = +70°C
PVC	T_g = +81°C (non plasticized)
ABS	T_g = +110°C
PC	T_g = +150°C

The T_g of a material will also have an impact on the migration behavior of a material!

COMPOSITION OF COMMERCIAL POLYMERS

COMPOSITION OF **COMMERCIAL POLYMERS**

- Additives
- Residues
- Catalysts
- Oligomers
- Degradation Compounds from Polymers
- Degradation Compounds from Polymer Additives

1. ADDITIVES

Anti-Oxidants
Plasticizers
Photostabilizers
Slip Agents
Antiozonants
Coupling Agents
Lubricants
Acid Scavengers
Peroxides / Crosslinkers

Blowing Agents
Pigments/Colorants
Antistatic Agents
Metal Chelators
Adhesives
Catalysts
Clarifying Agents
Antifogging agents
Fillers

(Red: coming with some examples)

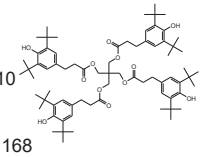
Anti-Oxidants

Function: assuring protection against thermal and oxidative degradation during processing and during shelf life of polymer
(*Sterically Hindered Phenols & Organic Phosphites/Phosphonates are mostly used*)

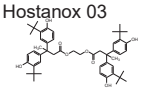
European Pharmacopoeia lists a.o. the following Anti-Oxidants:

BHT

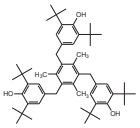
Irganox 1010



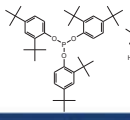
Hostanox 03



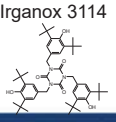
Irganox 1330



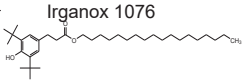
Irgafos 168



Irganox 3114



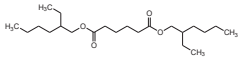
Irganox 1076



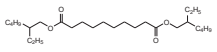
Plasticizers

Function: Gives the plastic flexibility and durability
Plasticizer requirements:
- Low Water solubility (low extractibility)
- Stability to heat and light
- Low Odor, taste and toxicity

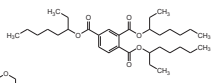
Diethylhexyladipate



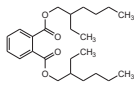
Diethylhexylsebacate



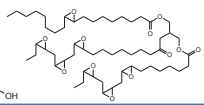
TOTM



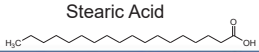
Diethylhexylphthalate (DEHP)



ESBO



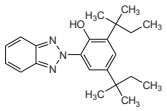
Stearic Acid



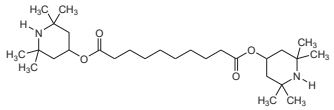
Photostabilizers

Function: Protects the Polymer from UV-Degradation (exposure to sunlight)

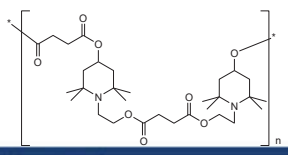
Tinuvin 328



Tinuvin 770



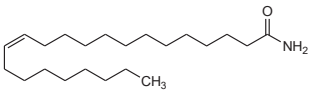
Tinuvin 622



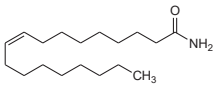
Slip Agents

Function: reduce the “friction” or “film adherence”, important when producing bags from films

Erucamide



Oleamide



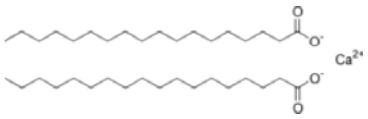
Remark:
because of their specific properties, Slip agents will be widely detected as Leachables!

Acid Scavengers

Function: Protects the polymer from “acid attacks” through conversion of strong acids (high degradation impact) to weak acids (low degradation impact)

Examples: $Ca(Stearate)_2 + 2HCl \rightarrow CaCl_2 + Stearic\ acid$

strong acid *weak acid*



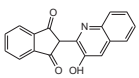
Pigments / Colorants

Function: Gives the polymer/rubber the desired color (cosmetic)

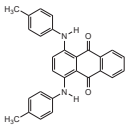
Examples: Carbon Black (PNA’s!), TiO_2 (white), Fe_2O_3 (red), Pigment Green 07

Solvent Red

Solvent yellow 114



Solvent Green 03

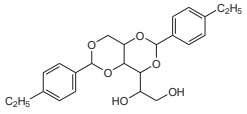


Remarks: beware of the composition of the Masterbatch!

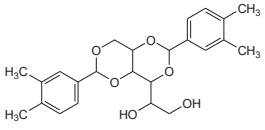
Clarifying Agents (Nucleating Agents)

Function: by controlling the crystallisation (nucleation) when cooling off PP, it becomes transparent.

NC-4



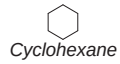
Millad 3988



2. RESIDUES

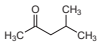
Residues from the production process (non-limitative)

Solvents


Cyclohexane

Hexane


DHN

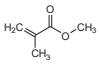

MIBK


IPA

Monomers


Styrene


Caprolactam


Methyl methacrylate


Isoprene

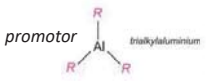
Catalysts

Titanium
Zirkonium
Cobalt
Aluminum
Iron
Hafnium
...

Catalysts

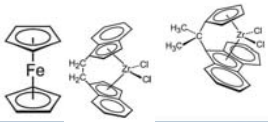
Function: assists in a very efficient polymerization process.

EXAMPLES:

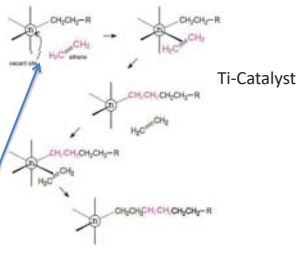


Ziegler-Natta Catalyst

Metallocenes
(stereospecific catalysts)

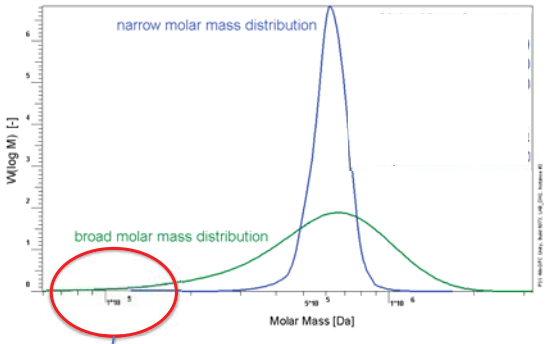


Ti-Catalyst



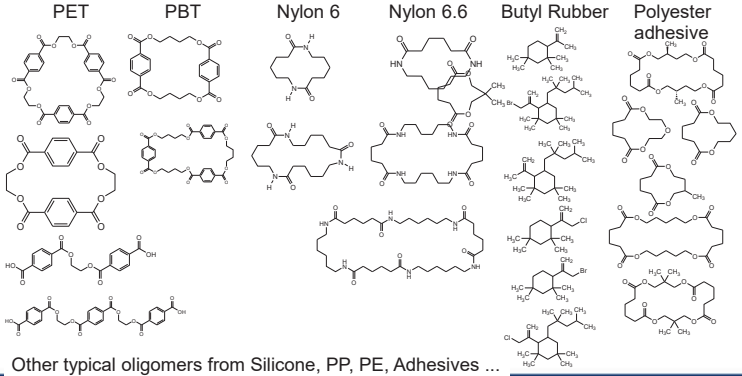
The alkene monomer attaches itself to an empty coordination site on the titanium atom and this alkene molecule then inserts itself into the carbon-titanium bond to extend the alkyl chain. This process then continues, thereby forming a linear polymer

3. OLIGOMERS



OLIGOMERS: Examples

PET PBT Nylon 6 Nylon 6.6 Butyl Rubber Polyester adhesive



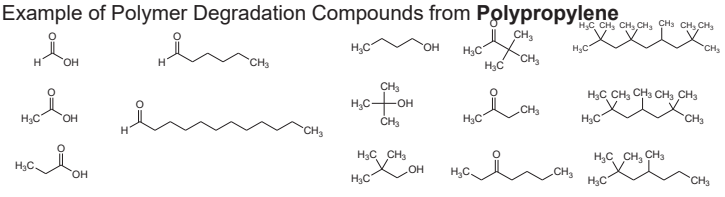
Other typical oligomers from Silicone, PP, PE, Adhesives ...

4. POLYMER DEGRADATION COMPOUNDS

Polymer degradation Compounds

Origin: Oxidative degradation of the polymers
(when the polymer is not properly stabilized via anti-oxidants)

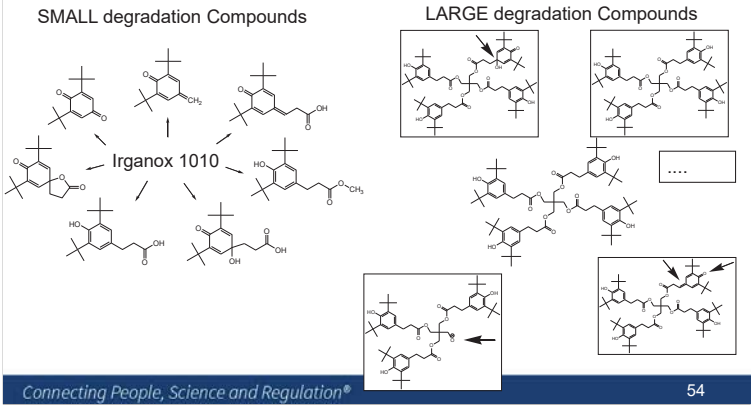
Example of Polymer Degradation Compounds from **Polypropylene**



Acids Aldehydes Alcohols Ketones Polymer Fragments

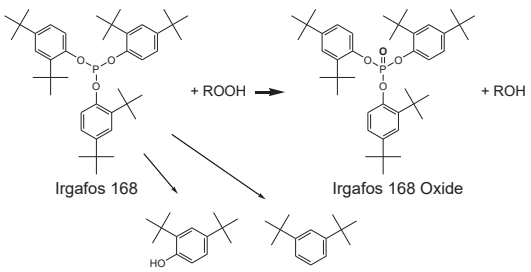
5. POLYMER ADDITIVE DEGRADATION COMPOUNDS

Example Degradation of **Irganox 1010**



EXAMPLE: Degradation of Irgafos 168

(also other degradation compounds for Irgafos 168 are known)



PROCESSING OF POLYMERS

Name(s)	Formula	Monomer	Examples of Uses
Polyethylene low density (LDPE)	$-(CH_2\text{-}CH_2)_n-$	ethylene $CH_2=CH_2$	Films for bags, multilayer contact film
Polyethylene high density (HDPE)	$-(CH_2\text{-}CH_2)_n-$	ethylene $CH_2=CH_2$	Bottles, Caps
Polypropylene (PP) different grades	$-[CH_2\text{-}CH(CH_3)]_n-$	propylene $CH_2=CHCH_3$	Bottles, Caps
Poly(vinyl chloride) (PVC)	$-(CH_2\text{-}CHCl)_n-$	vinyl chloride $CH_2=CHCl$	Bags, tubings
Polystyrene (PS)	$-[CH_2\text{-}CH(C_6H_5)]_n-$	styrene $CH_2=CHC_6H_5$	Secondary Packaging (Tubs)
Polytetrafluoroethylene (PTFE, Teflon)	$-(CF_2\text{-}CF_2)_n-$	tetrafluoroethylene $CF_2=CF_2$	Containers, seals, tubes, tubings, "inert"coatings…
Poly(methyl methacrylate) (PMMA)	$-[CH_2\text{-}C(CH_3)CO_2CH_3]_n-$	methyl methacrylate $CH_2=C(CH_3)CO_2CH_3$	Implantable Lenses (IOL)
Poly(vinyl acetate) (PVAc)	$-(CH_2\text{-}CHOCOCH_3)_n-$	vinyl acetate $CH_2=CHOCOCH_3$	Multilayer films
cis-Polyisoprene natural rubber	$-[CH_2\text{-}CH=C(CH_3)\text{-}CH_2]_n-$	isoprene $CH_2=CH\text{-}C(CH_3)=CH_2$	rubbers

GLASS 101

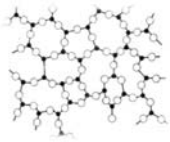
WORKSHOP
EXTRACTABLES - LEACHABLES

Dr. Piet Christiaens

What is Glass?

An inorganic fused substance that has been cooled to a rigid condition without crystallization (e.g. Supercooled amorphous substance)

Why Glass as packaging material?



- Well-known material
- Transparent
- Heat resistant
- Good barrier properties: gas & vapour tight
- Chemically and physically (quite) inert.

Glass in Pharmaceutical Packaging

- Ampoules
- Injection Vials
- Infusion Bottles
- Syringes
- Carpules
- Bottles for oral drug products
- Bottles for solid preparations

Composition of Glass – Function of Ingredients

- SiO_2 : Backbone structure
- CaO : Increasing hardness & Chemical resistance
- Al_2O_3 : Increasing Chemical Resistance
- Na_2O & B_2O_3 : Lowering the melting point
- Fe_2O_3, TiO_2 : Amber Glass
- CuO : Blue Glass
- Mn^{3+} : Violet Glass

J. Zuercher, ECA Course E/L, Prague 2010

Glass Types

Glass Type	General Description	Uses
I	High resistant Borosilicate	Parenteral Preparations
II	Treated Soda-Lime	Acidic and Neutral Parenteral Preparations
III	Soda Lime	Not for Parenteral Preparations
NP	Soda-Lime	Oral / Topical

Glass Composition for different Glass Types:

Component	Type I (Borosilicate)	Type II, III, NP (Soda-Lime)
SiO_2	70 - 73%	69 - 73%
B_2O_3	10%	0 - 1%
Na_2O	2 - 9%	13 - 14%
Al_2O_3	6 - 7%	2 - 4%
BaO	0,1 - 2,0%	0 - 2%
K_2O	1 - 2%	0 - 3%
CaO	0,7 - 1,0%	5 - 7%
MgO	0 - 0,5%	3 - 4%
ZnO	0 - 0,5%	-

Metal Profile of a Type I - Clear Glass Vial (ICP-MS)

Main Metals	Amount (%)	**Trace Metals (> 1µg/g)**	Amount (µg/g)
Si	>30%	Mg	61
Al	2%	Ba	21
Na	2,40%	Ce	8,8
B	5,50%	Ti	6,7
K	0,1%	Hf	6
Ca	0,036%	Mo	4,8
Fe	0,7 - 1,0%	Y	2,8
Zr	0 - 0,5%	La	2,5
		Sr	1,7
		Pd	1,6
		Ga	1,2
		Pb	1

Zuccarello et. Al., PDA, J Parm Sci technol 63, 339-352, 2009

GLASS 101

Examples for Extractables / Leachables

- **High heating** during molding process leads to an **increasing release of alkali ions** from the glass surface => Delamination
- During the process, **components of the heated glass vaporize and deposit** on the surface
- **Heating promotes migration of alkali oxides** within the silica matrix to the glass surface
- Relevant for **glass containers** made from **tubular glass**
- **Small volume** containers are **more impacted** than larger containers

GLASS 101

Parameters, impacting the Glass Leachables

- **Filling Volume**: *smaller filling volumes show higher leachable concentrations*
- **Storage time**: *leachable concentrations increase over time*
- **Sterilization / Sterilization time**: *longer autoclaving cycles, higher concentrations*
- **Sterilization Temperature**: *higher temperatures, higher concentrations*
- **Type of contact solution**:
  [Si]: Lactic acid < acetic acid < ascorbic acid < malic acid < tartaric acid < oxalic acid < citric acid
  ***Complexing agents**, such as EDTA may also impact the metal release from Glass*
- **Impact of pH**: *higher pH, higher [Si] release.*
  In general, more metals are leaching out of glass at pH>9

GLASS 101

Risk of Glass Leachables

- **Most observed Metal Leachables from Glass:**
  Si and **Na** as MAJOR leachables, **K, B, Ca & Al** as MINOR LEA, **Fe**: traces
- **Alkali release:** pH shift of unbuffered solutions
- **Silicon (Si) release**:increased particle load, delamination!
- **Aluminum release**:
  Aluminum can accumulate in patients with reduced renal function, causing e.g. neurological diseases
- Potential **Arsenic (As) release**:
  glass can contain arsenic oxide (III) as a fining agent to improve glass tranparency. Arsenic is toxic!
- **Release of metals**, causing precipitation with some salts, present in the DP
  Ba => $BaSO_4$, Al => $Al(OH)_3$

GLASS 101

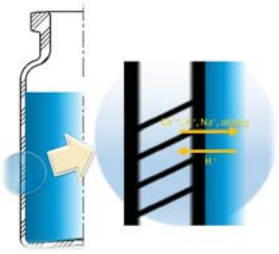
How to (try to) prevent Glass Leaching

1. Chemical surface treatment

$(NH_4)SO_4$ is injected before annealing

$(NH_4)SO_4$ ➔ $(NH_4)HSO_4 + NH_3$

$2Na^+ + (NH_4)HSO_4$ ➔ $Na_2SO_4 + NH_3 + 2H^+$



Afterwards, rinsing with Water to remove soluble $NaSO_4$

Result: lower pH shift because lower amounts of Na will leach

GLASS 101

How to (try to) prevent Glass Leaching

2. Put a Coating on the Glass

Deposition of SiO_x layer as an inert glass layer

e.g. Schott Type I Plus

GLASS 101

How to (try to) prevent Glass Leaching

3. Siliconization

Siliconized surfaces are hydrophobic, **reducing the wettability** of the container surface

Thus siliconized glass surfaces are **reducing the potential of interactions** with aqueous fillings

The **release of alkali ions is reduced**, compared to non-siliconized containers

However, Siliconized surface may then release organic compounds! (e.g. Siloxanes)

THE MECHANISM OF POLYMER MIGRATION
A DESCRIPTIVE APPROACH

PDA WORKSHOP
EXTRACTABLES – LEACHABLES
Berlin
28 – 29 September, 2017

Ir. John Iannone

Physics of Leachables Migration from Polymeric Materials

Perhaps **FABES MODEL** could make our lives easier…

General Formula for Modeling the Migration of Leachables

$$\frac{m_{F(t)}}{A} = 0.1\, c_{p,0}\, \rho_p\, d_p \left(\frac{\alpha}{\alpha+1}\right)\left[1 - \sum_{n=1}^{\infty} \frac{2\alpha\,(1+\alpha)}{1+\alpha+\alpha^2 q_n^2} \exp\left(-D_p t \frac{q_n^2}{dp^2}\right)\right]$$

OOPS… not that easy after all!

Leaching Will Depend Upon:

1. **Solubility** of LEACHABLE IN Polymer
2. **Diffusion** of LEACHABLE THROUGH Polymer

Solubility of LEACHABLE IN Polymer

Is Impacted By

A. **Polymer Morphology**
B. **Temperature**
C. **Age/Sterilization**
D. **Structure & Molecular Weight of LEACHABLE**

Solubility of LEACHABLE IN Polymer

Is Impacted By

A. POLYMER MORPHOLOGY

B. Temperature

C. Age/Sterilization

D. Structure & Molecular Weight of LEACHABLE

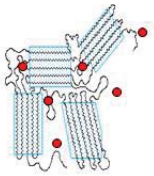
Solubility of LEACHABLE IN Polymer

A. POLYMER MORPHOLOGY

AMORPHOUS **SEMI-CRYSTALLINE**

Polymer Additive/Impurity

- Dissolves in Amorphous Phase
- Insoluble in Crystalline Phase



PC, PVC, PS, PU

CRYSTALLINE SITES: BARRIER FOR MIGRATION

PE, PP, PET, EVA, PEEK, PA

Solubility of LEACHABLE IN Polymer

Is impacted by

A. Polymer Morphology

B. TEMPERATURE

C. Age/Sterilization

D. Structure & Molecular Weight of LEACHABLE

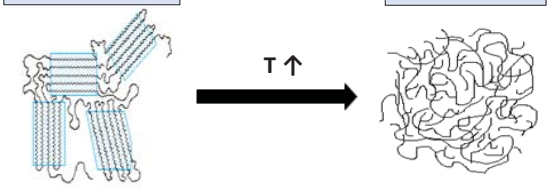
Solubility of LEACHABLE IN Polymer

B. TEMPERATURE

As Temperature Increase, Solubility Increases

Room Temperature

Melt Temperature



RESULT: **BETTER SOLUBILITY** at higher T
LESS "CRYSTAL **BARRIER**" FOR MIGRATION

Solubility of LEACHABLE IN Polymer

Is impacted by

A. Polymer Morphology

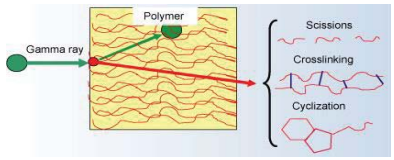
B. Temperature

C. AGE/STERILIZATION

D. Structure & Molecular Weight of LEACHABLE

Solubility of LEACHABLE IN Polymer

C. AGE/STERILIZATION



Polymer Degradation
Polymer Additive Degradation
Changes in Polymer Crystallinity

This will **impact** the: LEACHABLES **SOLUBILITY**
LEACHABLES **MIGRATION**

CONCLUSION:
» **Perform E&L Testing on Final STERILIZED SYSTEMS**

Solubility of LEACHABLE IN Polymer

Is Impacted By

A. Polymer Morphology

B. Temperature

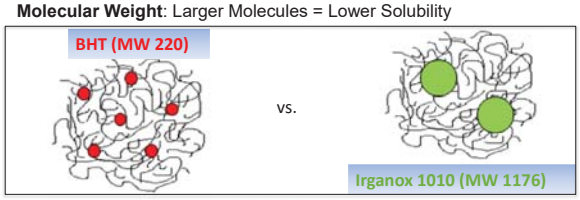
C. Age/Sterilization

D. STRUCTURE & MOLECUALR WEIGHT of Leachable

Solubility of LEACHABLE IN Polymer

D. Structure & Molecular Weight of LEACHABLE

» **Molecular Weight**: Larger Molecules = Lower Solubility



» **Polarity "Match":** Structurally ALIKE

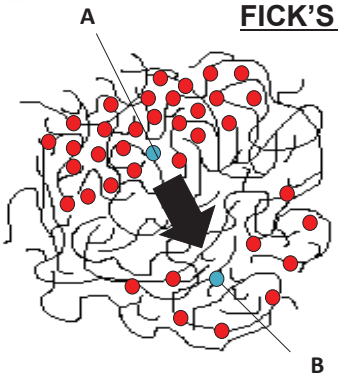
» **MELTING POINT**: higher T_{melt} - lower solubility
impacted by: - molecular symmetry
- crystallinity

Leaching Will Depend Upon:

1. **Solubility** of LEACHABLE IN Polymer
2. **Diffusion** of LEACHABLE THROUGH Polymer

Diffusion of LEACHABLE THROUGH the Polymer

FICK'S LAW



$$\frac{dC}{dt} = D\frac{d^2C}{dx^2}$$

With D = Diffusion coefficient

$D = D_0 \exp(-E/RT)$

Diffusion of LEACHABLE THROUGH the Polymer

Is Impacted By

A. **Polymer Morphology**
B. **Temperature**
C. **Polymer Type (T_g)**
D. **Molecular Weight of LEACHABLE**
E. **Contact Fluid/Environment**

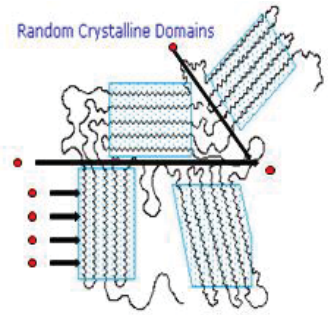
Diffusion of LEACHABLE THROUGH the Polymer

Is Impacted By

A. **POLYMER MORPHOLOGY**
B. Temperature
C. Polymer Type (T_g)
D. Molecular Weight of LEACHABLE
E. Contact Fluid/Environment

Diffusion of LEACHABLE THROUGH the Polymer

A. Polymer Morphology



- **Crystalline Sites:** Impermeable Barrier for Polymer Additives
- **Filler Particles:** Diffusion Barriers for Polymer Additives
- **Less Diffusion in:** SEMI-CRYSTALLINE POLYMERS

Diffusion of LEACHABLE THROUGH the Polymer

Is Impacted By

A. Polymer Morphology

B. TEMPERATURE

C. Polymer Type (T_g)

D. Molecular Weight of LEACHABLE

E. Contact Fluid/Environment

Diffusion of LEACHABLE THROUGH the Polymer

B. Temperature

Remember:

$$D = D_0 e^{(-E/RT)}$$

Therefore:

If T ↑, then D ↑

DIFFUSION of impurities/polymer additives will **Increase Exponentially** when **Temperature Increases**

Diffusion of LEACHABLE THROUGH the Polymer

Is Impacted By

A. Polymer Morphology

B. Temperature

C. POLYMER TYPE (T_g)

D. Molecular Weight of LEACHABLE

E. Contact Fluid/Environment

C. Polymer Type

Glass Transition Temperature (T_g)

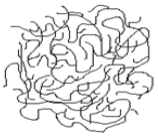
Polymer transitions from **GLASSY** ($t < T_g$)
to **RUBBERY** ($t > T_g$)

EXAMPLES

LDPE	T_g = -125 ºC	PBT	T_g = 70 ºC
POM	T_g = -50 ºC	PVC	T_g = 81 ºC
PP	T_g = -25 ºC	ABS	T_g = 110 ºC
		PC	T_g = 150 ºC

DIFFUSION IN APOLAR > DIFFUSION POLAR POLYMERS

C. Polymer Type



FREE VOLUME

Ratio of:

$$\frac{\text{Interstitial space (between polymer chains)}}{\text{Total Volume of the Polymer}}$$

Polymers in a **Rubber State** ($T_g < t$)
Typically have **HIGHER** Free Volume

More Free Volume PROMOTES Diffusion

Is impacted by

A. Polymer Morphology

B. Temperature

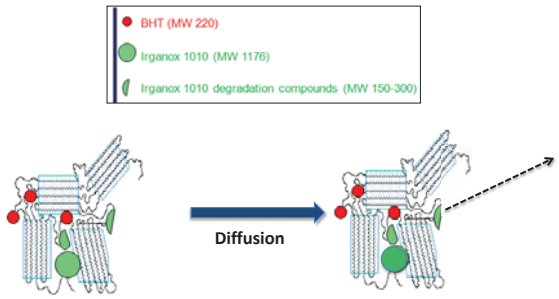
C. Polymer Type (T_g)

D. MOLECULAR WEIGHT OF LEACHABLE

E. Contact Fluid/Environment

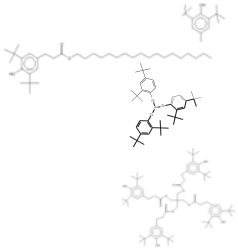
D. Molecular Weight of LEACHABLE

Diffusion Increases with Decrease in M.W.



Diffusion of LEACHABLE THROUGH the Polymer

OLIGOMERIC ADDITIVES → REDUCING DIFFUSION



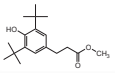
BHT: M.W. 220: HIGH DIFFUSION

Irganox 1076: M.W. 530

Irgafos 168: M.W. 646

Irganox 1010: M.W. 1176: LOW DIFFUSION

Polymer Additive DEGRADATION INTO SMALLER MOLECULES → FASTER DIFFUSION OF DEGRADANTS

Example: 

3,5-Di-*tert*-butyl-4-hydroxyphenyl propionic acid methyl ester

Degradation product of Irganox 1010 /Irganox 1076

Diffusion of LEACHABLE THROUGH the Polymer

Is Impacted By

A. Polymer Morphology

B. Temperature

C. Polymer Type (T_g)

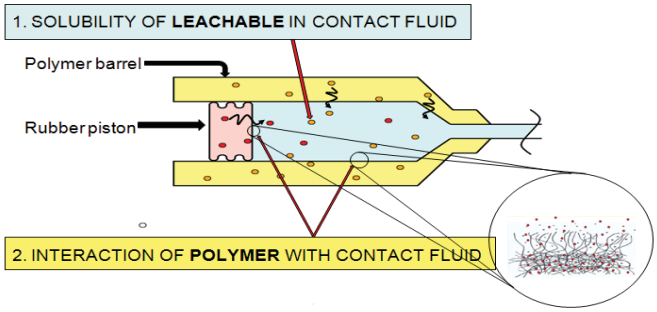
D. Molecular Weight of LEACHABLE

E. CONTACT FLUID/ENVIRONMENT

Diffusion of LEACHABLE THROUGH the Polymer

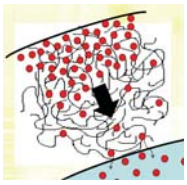
E. Contact Fluid/Environment

Two Important Aspects



E. CONTACT FLUID

1. INTERACTION CONTACT FLUID - LEACHABLE



IN GENERAL:

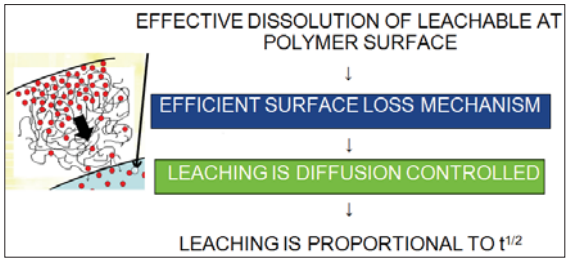
For most Organic Compounds:

ORGANIC/HYDROPHOBIC CONTACT FLUIDS = **HIGH SOLUBILITY** SOLVENTS

WFI/**HYDROPHILIC** CONTACT FLUIDS = **LOW SOLUBILITY** SOLVENTS

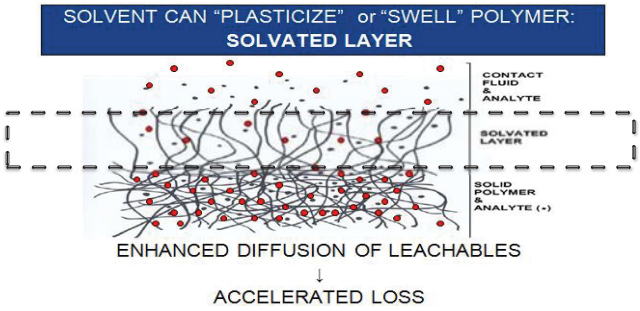
E. Contact Fluid/Environment

1. Solubility of the Leachable in the Contact Fluid



E. Contact Fluid/Environment

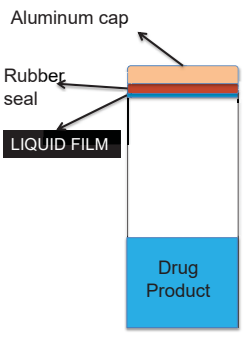
2. Interaction of the Contact Fluid with the Polymer



Application Specific Effects

1. **Super Saturation**
2. **Outgassing**
3. **Blooming**

SUPERSATURATION



LIQUID FILM is formed via
- Evaporation during storage
- Transportation

Film may be different in composition than the DP

Diffusion of Rubber Compounds into small volume
- Metals
- Organic

Can cause **Aggregation, Particle Formation**

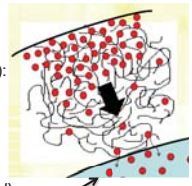
May be **irriversible**
- Particles do not dissolve anymore when in contact with the total DP volume

LIQUID FILM may also act as **"barrier"**
- for migration
- for outgassing (see next slide)

OUTGASSING

Material (e.g.):
Film
(Overwrap)

Rubber
(Lyo Vial, Needle Shield)



Solvent: air, gas phase

No "Liquid Film" barrier on rubber
(see previous slide)

Lyo Cake
= adsorbent

OUTGASSING of RUBBER CLOSURE

Outgassing is mainly an issue for:
- Volatile Organic Compounds
- Semi-Volatile Organic Compounds

BLOOMING

What is it?

- Blooming is a physical phenomenon
- Observed in polymers which are (super)saturated with additives
- A process of **diffusion controlled migration** of additives from the **polymer**
- Typical for additives with **low solubility** & **high diffusion rate**

Typical Conditions when blooming occurs

» **Low solubility** of the additive in the polymer
» **High diffusion** of the additive through the polymer
» **Dosing** of the additive into the polymer **close to the solubility** of the additive in polymer
» **Low temperature applications** may accelerate blooming process (lower solubility, *but also lower diffusion...*)

LUNCH TIME ;-)

…finally!

The PODP Best Demonstrated Practice Recommendations – Chemistry and Toxicology

Dennis Jenke,

Chair, PQRI PODP Chemistry Working Team

PODP Best Demonstrated Practice Recommendations – Chemistry: Background

2006: The Product Quality Research Institute (PQRI) issued a Recommendation entitled "Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products"[1]. The recommendation provided a scientific rationale and process to identify, quantify and establish the biological safety of leachables and/or extractables in OINDP. Included were Best Demonstrated Practices for performing Controlled Extraction Studies specifically for the OINDP dosage forms.

2008: The PQRI initiated an effort to extend the OINDP Recommendations to a second dosage form, Parenteral and Ophthalmic Drug Products (PODP). That organization's Chemistry Team hypothesizes that the "good science" best demonstrated practices that were established for the OINDP pharmaceutical development process can be extrapolated to container closure systems for PODP.[2]

2013: The PQRI PODP Chemistry Team is ready to talk about some of its Best Demonstrated Practice Recommendations.[3]

2016: The PQRI PODP Chemistry Team publishes the results of a simulation (migration) study.[4]

2017: The PQRI PODP Best Demonstrated Practice Recommendations will be published.

PODP Best Demonstrated Practice Recommendations – Chemistry: What is a Best Demonstrated Practice Recommendation?

Best Demonstrated Practice: a technique or methodology that, through experience and research, has proven to reliably lead to a desired result. A best practice is a method or technique that has consistently shown results superior to those achieved with other means, and that is used as a benchmark. A commitment to using the best practices in any field is a commitment to using all the knowledge and technology at one's disposal to ensure success.

Recommendation: a suggestion or proposal as to the best course of action, esp. one put forward by an authoritative body.

A **Best Demonstrated Practice Recommendation** is a guide, made by recognized authorities in a relevant field of practice and proposed by an organization with a recognized and validated authority to do so, whose purpose is to direct and enable the practice of good science by competent practioneers in an effective, efficient, appropriate, rigorous and necessary manner.

PODP Best Demonstrated Practice Recommendations – Chemistry: What a Best Demonstrated Practice Recommendation is not

1. A Standard
2. A Specification
3. A Compendial Monograph
4. A Regulatory Guidance or Guideline
5. A Rule or Law
6. A Commandment
7. A Cook Book

The Challenge facing the PODP Team

PODP

OINDP

Attributes that OINDP And PODP Do Not Share: Daily Dose

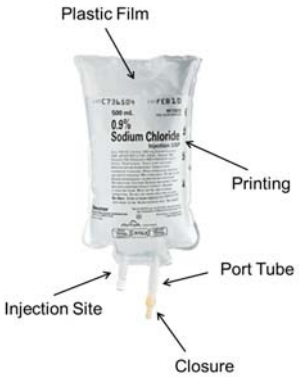
Metered Dose Inhaler (small volume - large number of doses)

Large Volume Parenteral (large volume - small number of doses)

Attributes that OINDP And PODP Do Not Share: Materials of Construction

Metered Dose Inhaler

Parenteral Solution for Infusion



Attributes that OINDP And PODP Do Not Share: Materials of Construction

Prefilled Syringe

Vial Products

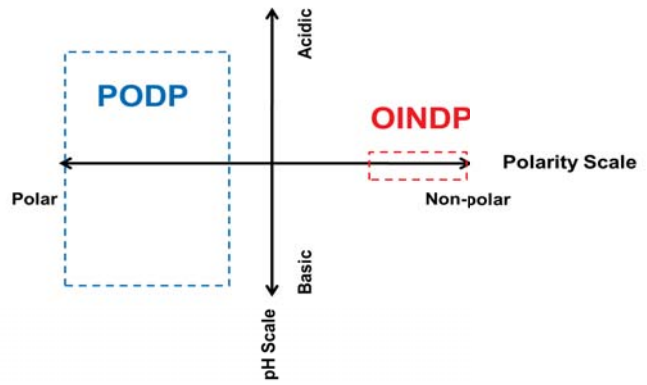
Plungers

Tip Cap

Barrel

Ophthalmic Bottles

Attributes that OINDP And PODP Do Not Share: Diluents and Formulation Components



Attributes that OINDP And PODP Do Not Share: Additional Attributes

1. Dosing Regimen: Acute versus Chronic.
2. Patient Population and Disease State Treated.
3. Heat History.
4. Others???

Bottom Line:

It is not a trivial exercise to extrapolate the OINDP Conclusions and Recommendations to PODPs.

PODP Best Demonstrated Practice Recommendations – Chemistry: Overall Conclusion

It is relevant and appropriate to note that

1. *The data generated and experiences gained in the PODP studies, which were performed on materials relevant for PODP products and with methods appropriate for PODP dosage forms, and*
2. *The accumulated experiences and technical knowledge of the individual members of the PODP Chemistry Working Group*

support the spirit, if not the exact letter, of all the (OINDP) recommendations as they are applied to the PODP situation.

PODP Best Demonstrated Practice Recommendations – Chemistry: An OINDP Definition that is Adopted for PODP with Modification

OINDP Definition:

Controlled Extraction Study (CES) - a laboratory investigation into the qualitative and quantitative nature of extractables profiles of critical components of an OINDP container/closure system.

PODP Definition:

Controlled Extraction Study – a laboratory investigation into the qualitative and quantitative nature of extractables profiles of a container/closure system and/or **its critical components** and materials of construction.

Discussion:

The language in the PODP Recommendation expands the scope of the CES to make it more generally applicable to all dosage forms and to include materials of construction to capture materials characterization studies.

PODP Best Demonstrated Practice Recommendations – Chemistry: OINDP Recommendations that Are Adopted for PODP with Little or No Modification

Controlled Extraction Studies (CES) should:

- Include careful sample preparation based on a knowledge of the analytical techniques used,
- Include a defined and systematic process for the identification of individual extractables,
- Include a re-examination of supplier information describing component formulation.

PODP Best Demonstrated Practice Recommendations – Chemistry: OINDP Recommendations that Are Adopted for PODP with Clarification

OINDP Recommendation:

A Controlled Extraction Study should include multiple analytical techniques.

PODP Recommendation:

A Controlled Extraction Study should utilize an analytical process with thoughtfully chosen **multiple** orthogonal **analytical techniques** for the purpose of discovering, identifying and quantifying relevant and appropriate extractables. Included in the analytical process is a consideration of the completeness of the analytical process.

Discussion:

The language in the PODP Recommendation captures concepts that were included in the OINDP Recommendations document but not specifically captured in the abbreviated OINDP Recommendation statement.

PODP Best Demonstrated Practice Recommendations – Chemistry: OINDP Recommendations that Are Adopted for PODP with Clarification

OINDP Recommendation:

Scientifically justifiable analytical thresholds for extractables and leachables in OINDP can be established.

PODP Recommendation:

Scientifically justifiable analytical thresholds for extractables and leachables in PODP can be established.

However:

The absolute values of the analytical thresholds will differ, OINDP versus PODP, consistent with the inherent differences in these dosage forms, including their dosing and conditions of use.

PODP Best Demonstrated Practice Recommendations – Chemistry: OINDP Recommendations that Are Adopted for PODP with Modification

OINDP Recommendation:

A Controlled Extraction Study should:

1. **Employ vigorous extraction with multiple solvents of varying polarity, and**
2. **Incorporate multiple extraction techniques.**

PODP Recommendation:

Controlled extractions studies should use a combination of **multiple extraction solvents** and **extraction techniques** as appropriate for, and consistent with, the intent and purpose of the controlled extraction study.

Discussion:

The language in the PODP Recommendation captures concepts that were included in the OINDP Recommendations document but not specifically captured in the abbreviated OINDP Recommendation statement.

PODP Best Demonstrated Practice Recommendations – Chemistry: Type of Controlled Extraction Studies

- Material characterization (i.e., identify and quantify the additives and ingredients in a material, as ingredients and additives may be used to forecast extractables),
- Packaging assessment (i.e., identify extractables as a means of forecasting leachables in a specific dosage form, simulation study),
- Quality Control (i.e., exercise control over the quality of incoming materials of construction for a packaging system).
- Change Control (i.e., respond to changes in the materials and/or processes associated with a packaging system.

PODP Best Demonstrated Practice Recommendations – Chemistry: The Simulation Study

In situations of analytically challenging Analytical Evaluation Thresholds (AETs) for certain PODPs (e.g., large volume parenterals), a special type of extraction study termed a "Simulation Study," should be applied in lieu of or to supplement drug product leachables studies. These studies can establish an extractables profile representing the worst-case leachables profile of the packaged drug product that the study simulates.

Table 3.3. Comparison of Key Operational Parameters, Simulation Study Versus Leachables Study

Operational Parameter	Value for Simulation Study	Value for Leachables Study
Test Sample	Simulating solvent (s)	Drug product
Test System	Marketed Packaging System[1]	Marketed Packaging System
Test Conditions	Accelerated clinical use	Clinical Use[2]

Notes: [1]In some situations, a simulation study may use an exaggerated packaging system. For example, if the packaging system has a single port tube and the purpose of the study is to assess leachables derived from the port tube, then the exaggerated packaging system could be constructed with two ports.
[2]It is the case that leachables studies (for example leachables testing performed as part of a stability study) could also include accelerated clinical use conditions.

"since the extractables profile is the same as the leachables profile, then one can safety assess the extractables profile and not perform subsequent leachables testing." The appropriateness of such an answer rests on the rigor of the simulation and its associated **justification**.

PODP Best Demonstrated Practice Recommendations – Chemistry: A New PODP Recommendation

PODP Recommendation:

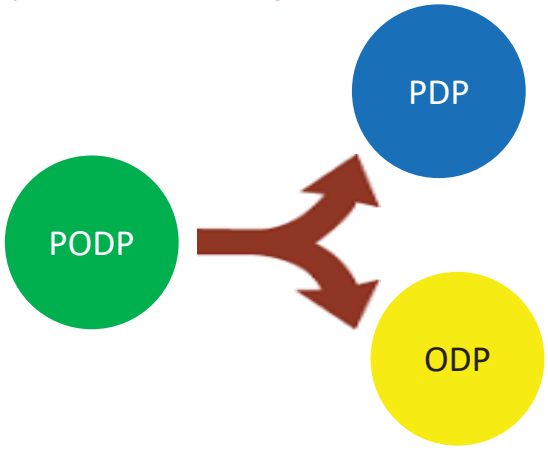
When assessing the potential product impact of leachables, the following factors must be considered:

- The ability of the leachable to directly affect patient safety due to the inherent toxicity of the of the leachable,
- The ability of the leachable to indirectly affect patient safety due to the leachable's interaction with the drug product and its ingredients,
- The ability of the leachable to impact the product's general chemical and physical characteristics (e.g., pH, appearance),
- The ability of the leachable to impact the drug product's efficacy and/or stability, and
- The ability of the leachable to impact drug product quality attributes which are not specified above.

Discussion:

The OINDP Recommendations were primarily focused on patient safety as affected by the inherent toxicity of leachables, although the more general effect of leachables on product quality was discussed in the OINDP Recommendation document. The PODP drug products may, in certain cases, be more generally susceptible to packaging-related quality issues (e.g., protein biologics).

PODP Best Demonstrated Practice Recommendations – Chemistry: At some point, PDPs and ODPs Diverge



PODP Best Demonstrated Practice Recommendations – Chemistry: OINDP Recommendations that Are Adopted for PDP with Modification

OINDP Recommendation:

A Controlled Extraction Study should be guided by an Analytical Evaluation Threshold (AET) that is based on an accepted safety concern threshold.

PDP Recommendation:

A Controlled Extraction Study for a PDP should be guided by an Analytical Evaluation Threshold (AET) that is based on an accepted and relevant safety standard such as the **safety concern threshold.**

Discussion:

The OINDP Recommendation has been modestly expanded to include relevant and appropriate safety standards and thresholds other than the safety concern threshold, as the application of the SCT may not be appropriate for some dosage forms (e.g., ophthalmic). It is noted that use of the AET to guide the Controlled Extraction Study will affect the strategies and tactics used to design and complete the Study.

PODP Best Demonstrated Practice Recommendations – Chemistry: OINDP Recommendations that Are Adopted for ODP with Modification

OINDP Recommendation:

Controlled Extraction Studies should be accomplished on all critical components incorporated into the container/closure systems of every type of OINDP.

ODP Recommendation:

Extractables and leachables assessments of drug products in semipermeable container closure systems (e.g., ODP in LDPE) must include packaging components that do not make direct drug product contact (e.g., labels, product information inserts, unit cartons).

Discussion:

The semipermeable container closure systems that are more typically used with ophthalmic drug products are poor barriers and thus it is more likely that ophthalmic drug products would contain foreign impurities that are associated with secondary, tertiary and/or auxiliary sources.

PODP Best Demonstrated Practice Recommendations – Chemistry

Cited References

[1]Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products. PQRI Leachables and Extractables Working Group, September 9, 2006, available at http://www.pqri.org/pdfs/LE-Recommendations-to-FDA-09-29-06.pdf.
[2]PQRI. Parenteral and Ophthalmic Drug Products Work Plan; Prodcut Quality Research Institute: Arlington, VA, 2008; available at http://www.pqri.org/commworking/minutes/pdfs/dptc/podpwg/Addl/podp_work_plan_schedule.pdf.
[3]D. Jenke, J. Castner, T. Egert, T Feinberg, A. Hendricker, C. Houston, D.G. Hunt, M. Lynch, A. Shaw, K. Nicholas, D.L. Norwood, D. Paskiet, M. Ruberto, E.J. Smith, F. Holcomb. Extractables characterization of five materials of construction representative of packaging systems used for parenteral and ophthalmic drug products. PDA J Pharm Sci Technol. 76(5): 448-511 (2013).
[4]D. Jenke, T. Egert, A. Hendricker, J. Castner, T. Feinberg, C. Houston, D.G. Hunt, M. Lynch, L. Markovic, K. Nicholas, D.L. Norwood, D. Paskiet, M. Ruberto, E.J. Smith, and F. Holcomb. Simulated Leaching (Migration) Study for a Model Container-closure System Applicable to Parenteral and Ophthalmic Drug Products (PODPs). *PDA J Pharm Sci Technol.* **71(2)**: 68-87 (2017).

PDP and ODP Best Demonstrated Practice Recommendations – Toxicology

The issue of safety is not exactly the same for PDP and ODP. Oversimplifying greatly,

- Safety assessment of leachables in ophthalmics requires a greater focus on local topical effects and recognizes the importance of irritation and toxicity as key endpoints.
- Safety assessment of leachables in parenterals requires a greater focus on systemic effects and recognizes cancer risk as a key endpoint.
- As a result, the PDP recommendations around thresholds will differ from those for ODP.

PDP and ODP Best Demonstrated Practice Recommendations – Toxicology, PDP Thresholds

OINDP Thresholds	
Qualification Threshold (QT) = 5 µg/day	Safety Concern Threshold (SCT) = 0.15 µg/day

PDP Thresholds		
Class I, General Toxicity (QT) = 50 µg/day	Class 2, Sensitizers/Irritants = 5 µg/day	Class 3, Mutagens (**SCT**) = 1.5 µg/day

PDP and ODP Best Demonstrated Practice Recommendations – Toxicology, ODP Practices

The primary toxicological endpoints that need to be considered for qualifying leachables for topical ophthalmic products include (i) ocular irritation and toxicity; (ii) sensitization (skin) and (iii) genotoxicity.

Thresholds based on "available data and industry practices" are difficult to establish for ODP as ocular toxicity data is rarely available.

Generally Accepted Practice for Confirmed Leachables:

- Report in ppm concentration units, either mass per volume (µg/mL) or mass per mass (µg/g)
- At levels above 1 ppm, report that the leachable is present
- At levels of 10 ppm and above, identify the leachable
- At levels of 20 ppm and above, qualify the leachable

Thus, thresholds for ODP are concentration based (and not dose based as they are for OINDP and PDP).

PDP and ODP Best Demonstrated Practice Recommendations – A "New" Issue - Compatibility Issues with Biopharmaceuticals

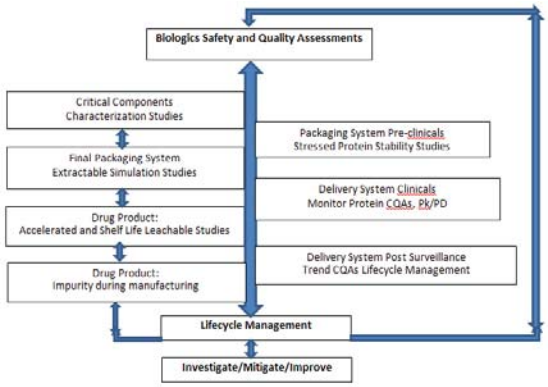
Beyond safety considerations, biotechnology products require additional considerations of the product quality attributes as biotechnology products are more susceptible to structural modifications than are chemically synthesized drug products, primarily due to their:

- large molecular weights,
- complex structures,
- abundance of binding sites on their surfaces

Structural modifications may alter product quality, safety, and/or efficacy.

PDP and ODP Best Demonstrated Practice Recommendations – A "New" Issue - Compatibility Issues with Biopharmaceuticals

Figure 5.1. Evaluation of biologic safety and quality throughout the lifecycle management of a biologic product

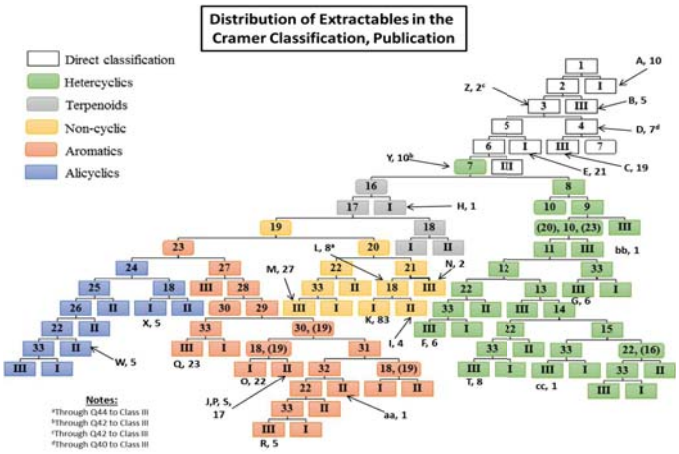


PDP and ODP Best Demonstrated Practice Recommendations – A "New" Issue - Compatibility Issues with Biopharmaceuticals

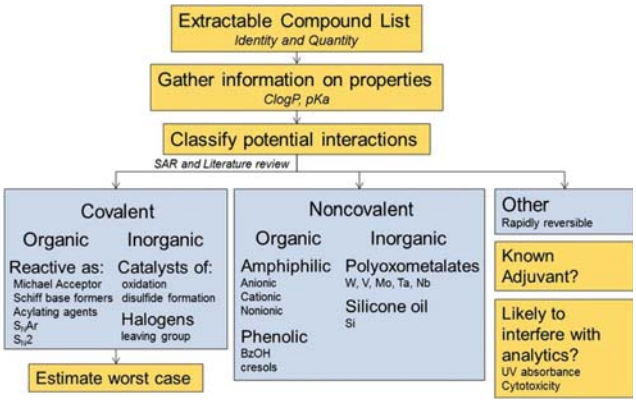
Quality assessments for biotherapeutics would include identifying and mitigating risks related to the following:

- Changes in the dosage form purity, safety, stability
- Changes in the product appearance, physicochemical and molecular structure
- Loss of potency due to absorption or adsorption of the active drug substance
- Degradation of the active drug substance induced by a leachable
- Reduction in the concentration of API or excipient due to absorption or adsorption
- Leachable-induced changes in formulation pH, product degradation, precipitation, aggregation
- Changes in the packaging component or system (discoloration, surface, function, brittleness etc.)

The Cramer Classification for Establishing Safety Levels for Compounds



Schematic representation of the proposed strategy for assessing the potential impact of extractable compounds on product attributes



Source: Kim Li et al. PDA J Pharm Sci and Tech 2015;69:590-619

Considering Extractables which could Induce Protein Modification

"Because of the irreversible nature of the protein modification, covalent binding presents a higher risk of affecting product quality attributes as compared to noncovalent binding"

A Partial List of Extractables that Could Induce Protein Modification via Covalent Binding

Agents or Mechanisms	Compounds
Michael acceptors	(2E,9Z)-Ethyl 12-oxoctadeca-2,9-dienoate 1-{(2-Ethylheptyl)oxy)-1-oxopropan-2-yl (1-{(2-ethylhexyl)oxy)-1-oxopropan-2-yl) maleate 1-{(3-Butyl-4-methylcyclohexa-1,5-dien-1-yl)methoxy)-1-oxopropan-2-yl (1-{(4-ethyl-3-methylbenzyl)oxy)-1-oxopropan-2-yl) maleate 1,6-Hexanedioldiacrylate 13-oxooctadeca-9,11-dienoic acid 1-Hydroxy-2-propyl methacrylate 1-oxo-1-{(2E,5E)-2-{(Z)-prop-1-en-1-yl)octa-2,5-dien-1-yl)oxy)propan-2-yl (1-oxo-1-{{(E)-2-{(Z)-prop-1-en-1-yl)hept-2-en-1-yl)oxy)propan-2-yl) maleate 2,6 Di(tert-butyl)-4-hydroxy-4-methyl-2,5-cyclohexandien-1-one (BHT-OH) 2,6-di-tert-butyl-4-methylene-2,5-cyclohexandienone (BHT-quinone-methide) 2,6-Di-tert-butyl-p-benzoquinone (BHT-quinone) 2-Hydroxypropyl methacrylate 3-tert-Butyl-4-hydroxyanisole 4-ethyl 1-methyl 2-hexanoylsuccinate 7,9-bis(tert-butyl)-1-oxaspiro[4,5]deca-6,9-diene-2,8-dione (BODDD) Acrylic Acid Bis(1-{(2-ethylhexyl)oxy)-1-oxopropan-2-yl) maleate Isomers Dibutylmaleate Dihexyl maleate (Methyl maleate) Isobornyl methacrylate Methacrylic acid (MAA) Tetraethylene glycol dimethacrylate Tetrahydrofurfuryl methacrylate

Source: Kim Li et al. PDA J Pharm Sci and Tech 2015;69:590-619

PDP and ODP Best Demonstrated Practice Recommendations – Questions

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