REGULATORY REQUIREMENTS

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES

Rome
01 – 02 March, 2018

Dr. Piet Christiaens

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

2. **Are Material-Drug Product Interactions for Real?**

3. **Regulatory requirements for the Pharmaceutical Containers**

4. **Basic Definitions: Extractables, Leachables and Simulation Studies**

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!

What is expected from Container/Closure Systems

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

What is expected from Container/Closure Systems

Protection of the Drug Product from:

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

What is expected from Container/Closure Systems

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

What is expected from Container/Closure Systems

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
- ...

What is expected from Container/Closure Systems

2. Are Material-DP interaction concerns for real?

Focus on Safety/Quality issues

2. Are interaction concerns for real?

The New England Journal of Medicine

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., BÉATRICE 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.)

2. Are interaction concerns for real?

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.

2. Are interaction concerns for real?

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)*

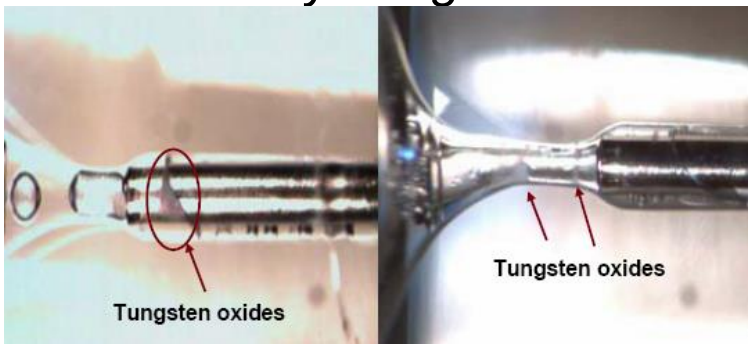
- **PolyNuclear Aromatics (PNA's, carcinogenic)** released from rubbers *(when Carbon Black is used as a colorant (Black)*

- **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*

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!

3. Regulatory Requirements

REGULATORY REQUIREMENTS

WHAT?

What kind of information should be provided?

- US Guidances
- EU Guidelines

- Code of Federal Regulations (CFR)
- ICH Q7 – GMP Practice Guide
- EU – Good Manufacturing Practices

HOW?

How can the testing be performed?

- Pharmacopoeias
- Standards Organizations
- Recommendations of Workgroups
- Consortia

REGULATORY REQUIREMENTS:

WHAT?

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

3. REGULATORY REQUIREMENTS: **WHAT?**

PRIMARY PACKAGING

3. REGULATORY REQUIREMENTS: WHAT?

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

3. REGULATORY REQUIREMENTS: WHAT?

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

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

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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

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**

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		
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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

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

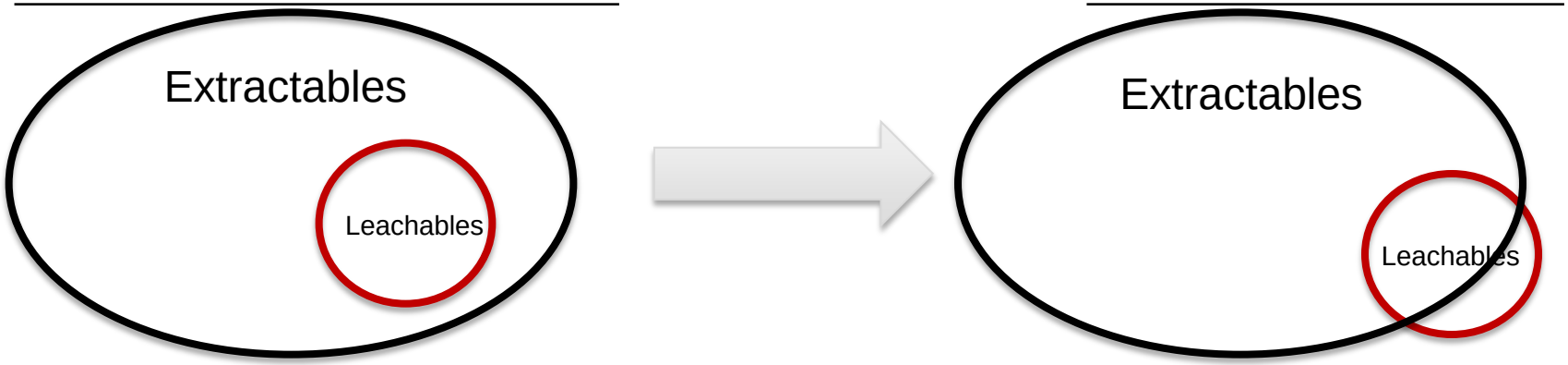
2. ADDITIONAL EXTRACTABLES/LEACHABLES DATA

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

3. REGULATORY REQUIREMENTS: **WHAT?**

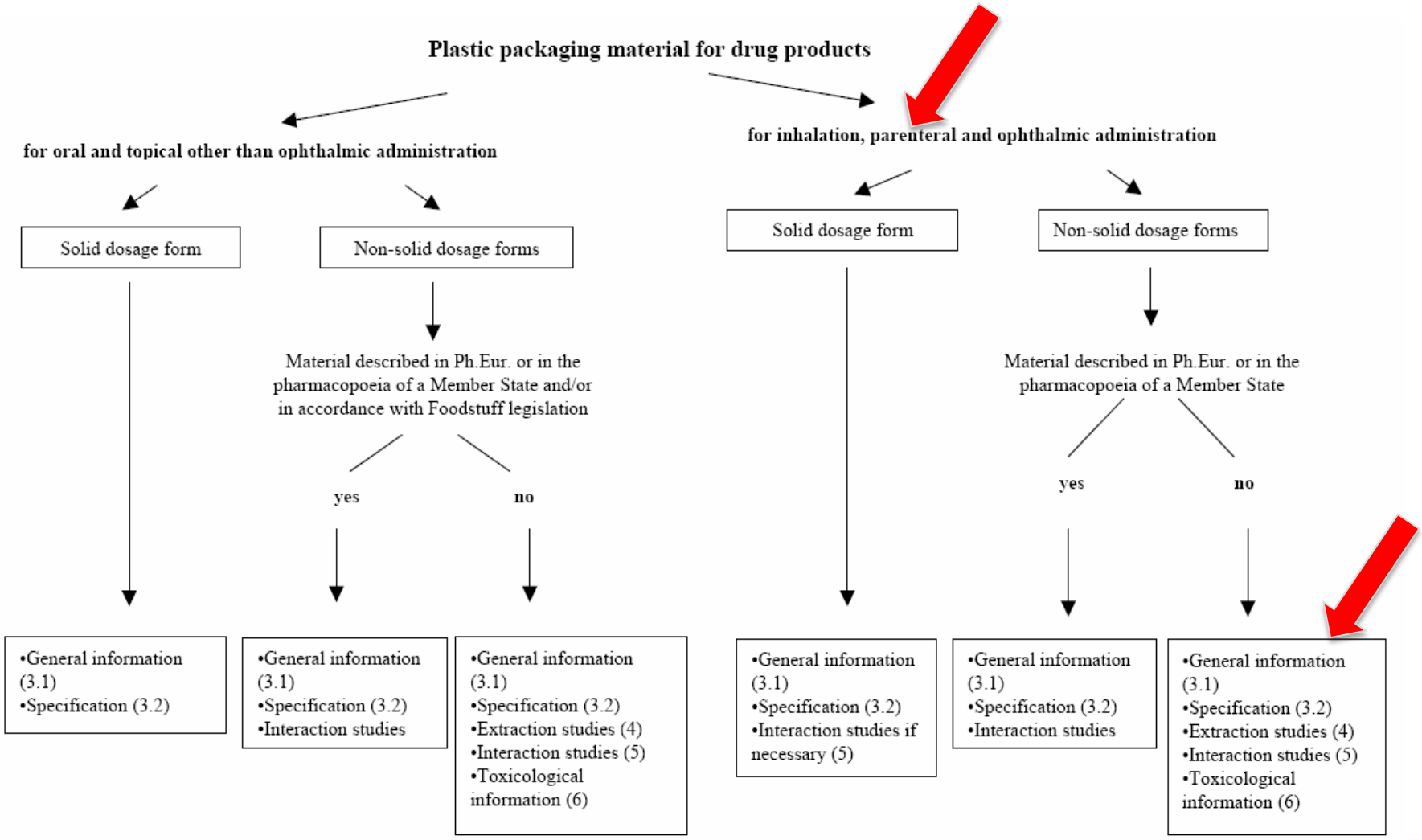
The **"HOW"** in the FDA Guidance Document "*Container Closure Systems for Packaging Human Drugs and Biologics*" of **1999** may NOT reflect the current (2015) FDA requirements for E/L Testing and Documentation:

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



3 REGULATORY REQUIREMENTS: **WHAT?**

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



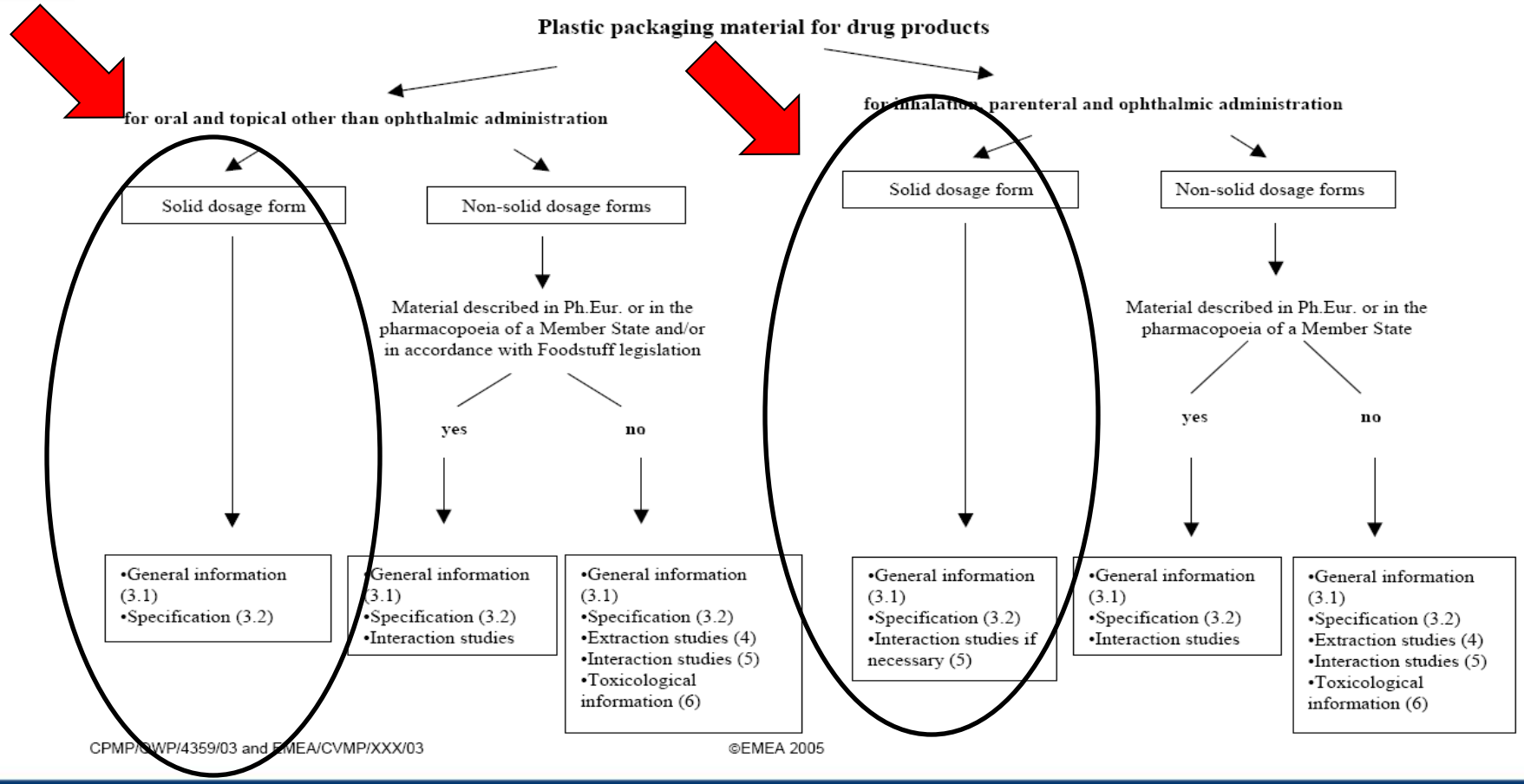
CPMP/QWP/4359/03 and EMEA/CVMP/XXX/03 ©EMEA 2005

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

PDA Parenteral Drug Association

SOLID DOSAGE FORMS:

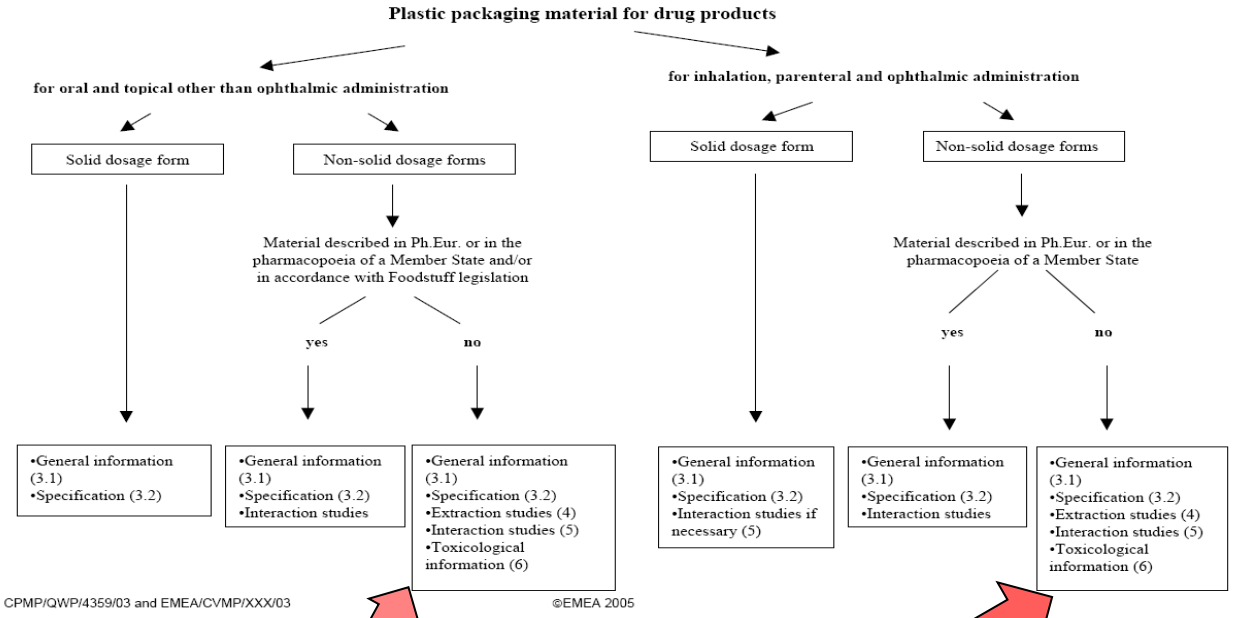
LIKELIHOOD OF INTERACTION IS LOW: LOW requirements



"GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS" (2005)

"OTHER" DOSAGE FORMS:

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



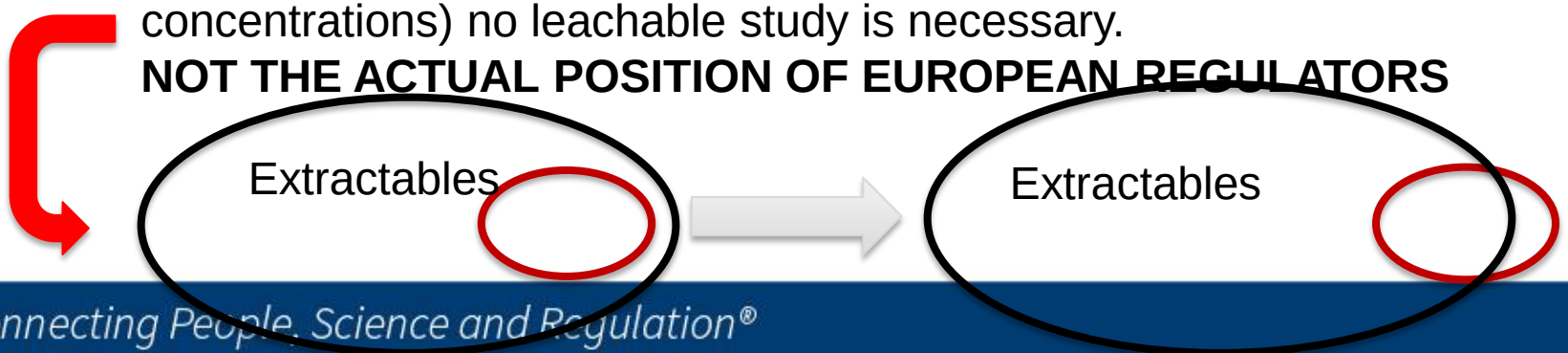
E.P. COMPENDIAL TESTING IS REQUIRED BUT **NOT SUFFICIENT**.

ADDITIONAL REQUIREMENTS

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

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



3. REGULATORY REQUIREMENTS: **WHAT?**

MANUFACTURING EQUIPMENT

3. REGULATORY REQUIREMENTS: **WHAT?**

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..."

3. REGULATORY REQUIREMENTS: HOW?

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

3. REGULATORY REQUIREMENTS: HOW?

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

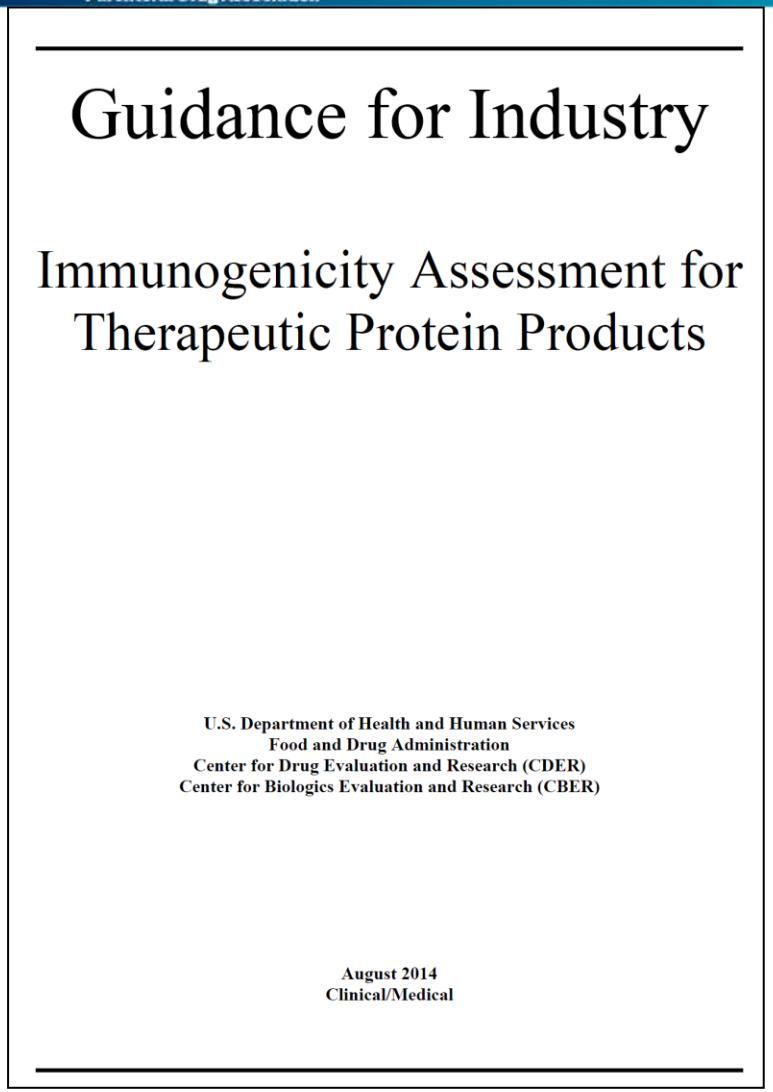
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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



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)

August 2014
Clinical/Medical

FDA Guidance for Industry, 2014

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

REGULATORY REQUIREMENTS & RECOMMENDATIONS:

HOW?

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

3. REGULATORY REQUIREMENTS: HOW?

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

3. REGULATORY REQUIREMENTS: **HOW?**

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**

3. REGULATORY REQUIREMENTS: **HOW?**

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

3. REGULATORY REQUIREMENTS: **HOW?**

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!!

3. REGULATORY REQUIREMENTS: **HOW?**

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.)
- PQRI – Product Quality Research Institute
  - OINDP Orally Inhaled and Nasal Drug Products
  - 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.

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

ICH Q3B: Impurities in New Drug Products

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

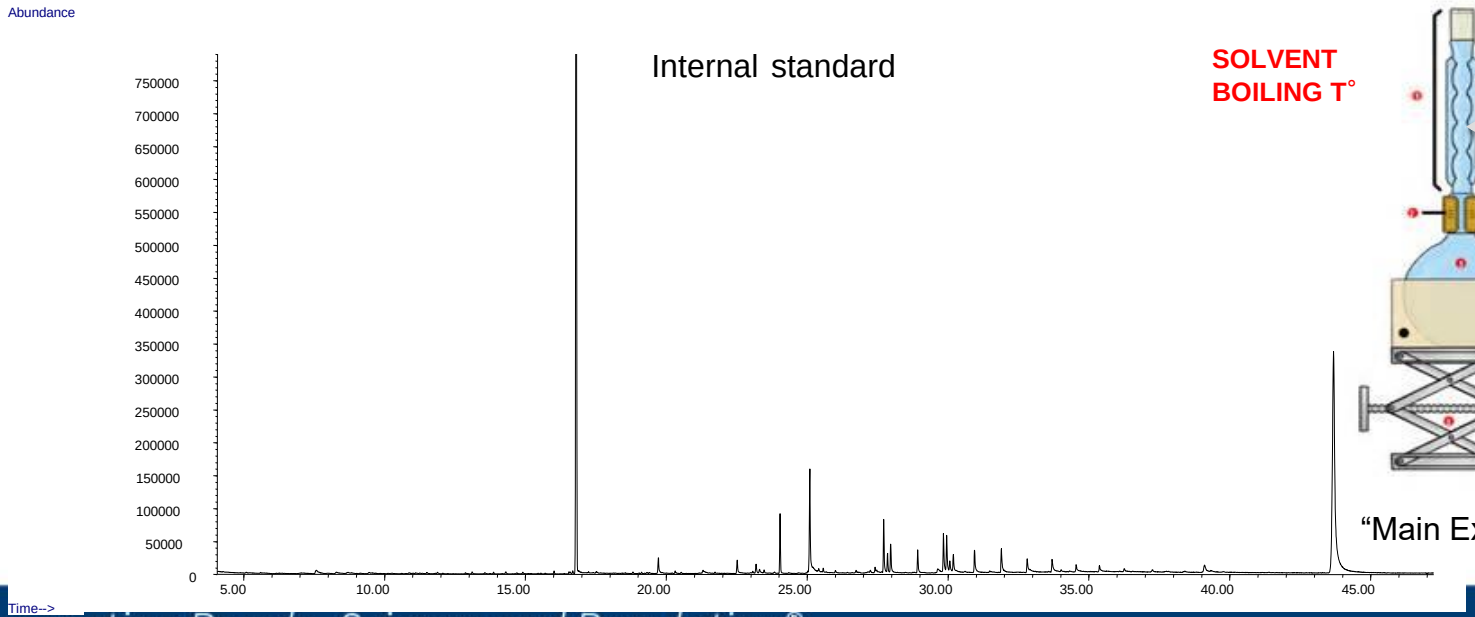
4. What are Extractable Studies, Simulation Studies and Leachable Studies?

EXTRACTABLE STUDIES

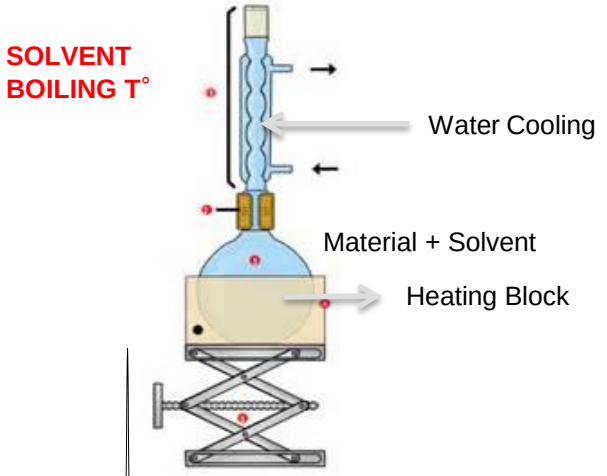
DEFINITIONS

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



EXAMPLE: REFLUX



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!

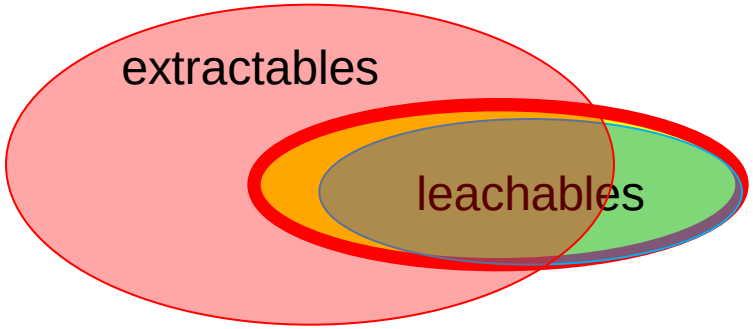
SIMULATION STUDY

» 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

4. EXTRACTION, **SIMULATION** AND LEACHABLE STUDIES

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

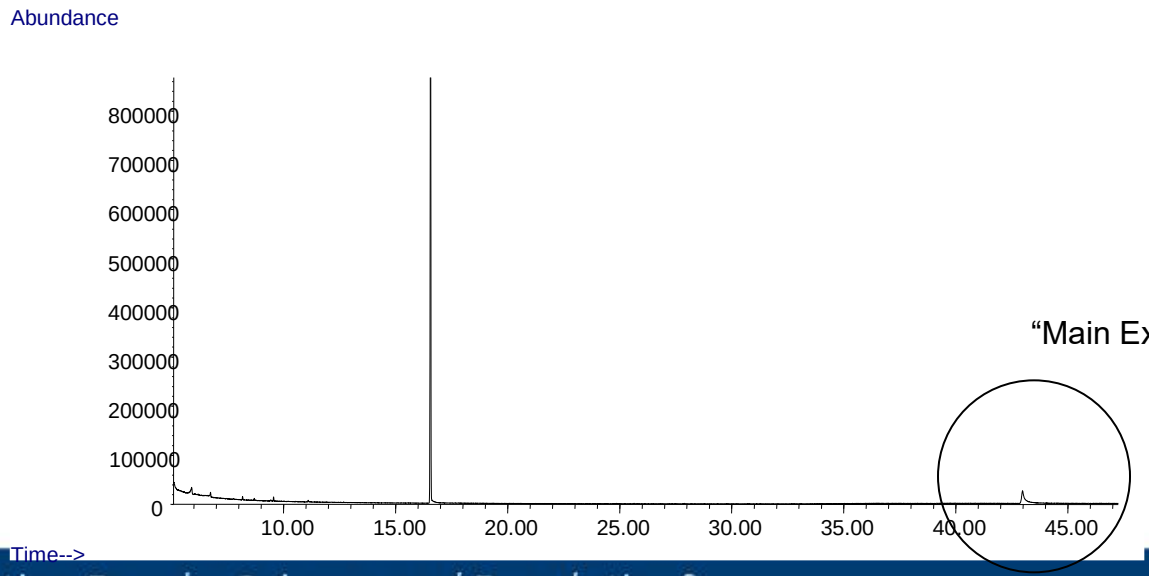
Accelerated: 3 Months at 40˚C

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



"Main Extractable" becomes a leachable!!

4. EXTRACTION, **SIMULATION** AND LEACHABLE 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)

4. EXTRACTION SIMULATION AND LEACHABLE STUDIES

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