INTRODUCTION TO EXTRACTABLES AND LEACHABLES

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES
BASEL
27 - 28 FEBRUARY 2020

Dr. Piet Christiaens

Setting the stage

What is expected from packaging materials for drug products?

Working towards a definition of E&L

Do we need to be worried about packaging materials?

Potential suspects and case studies

What does an E&L study look like?

Analytical chemistry and toxicology in tandem

What are the regulatory requirements for safety of a CCS and mfg equipment?

Browsing through the regulatory landscape

What is expected from packaging materials for drug products?

- Working towards a definiton of E&L

What is expected from Container/Closure Systems?

Guidance for Industry – CCS for packaging human drugs and biologics
May 1999!

The selected Container / Closure system must be

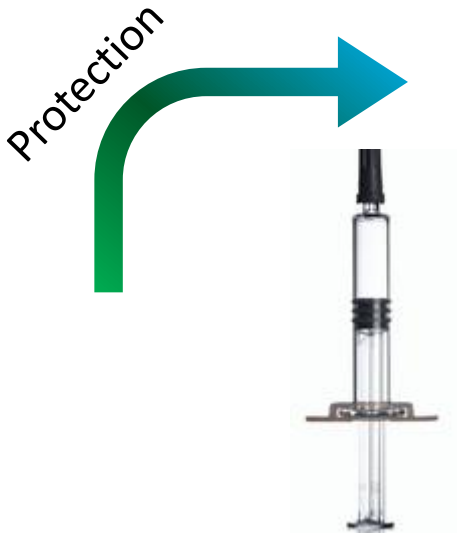
“suitable for its intended use”

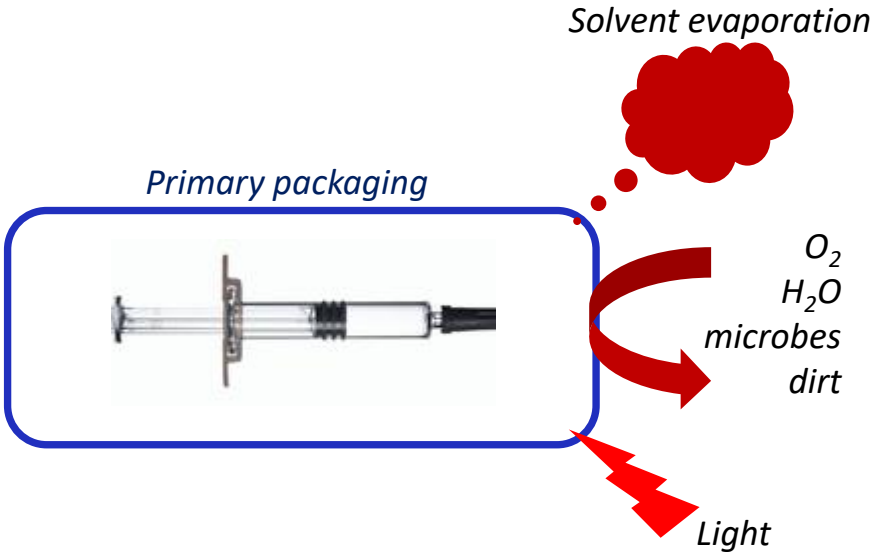
Protection Compatibility Performance Safety

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?

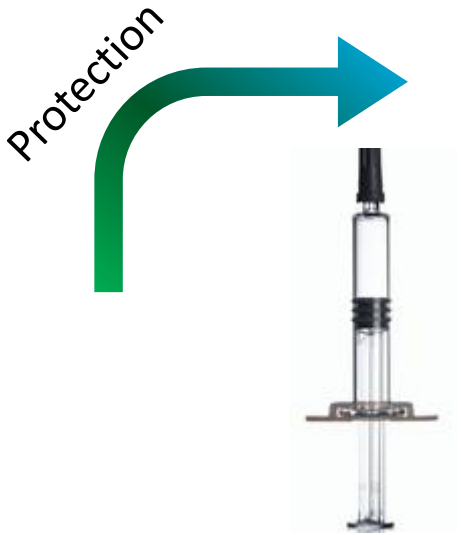
- CCS should protect DP from factors that can cause degradation

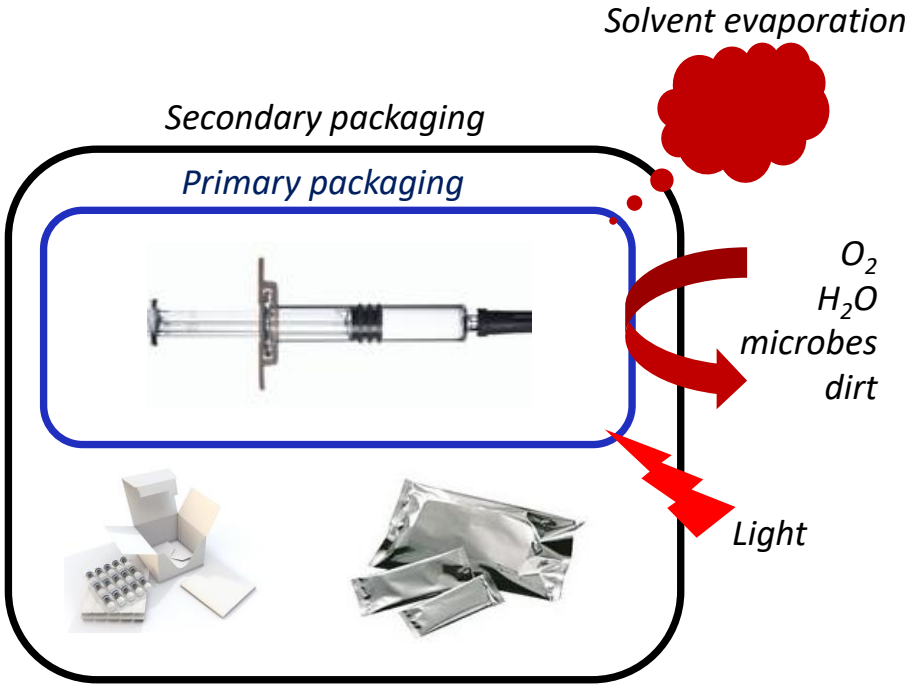




What is expected from Container/Closure Systems?

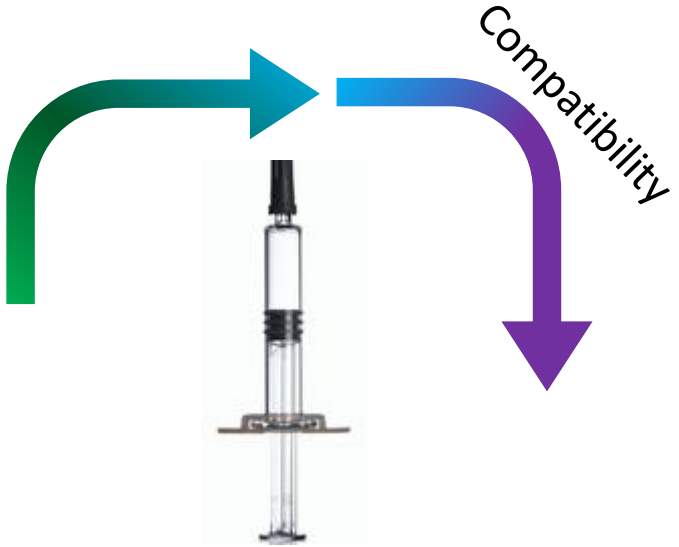
- CCS should protect DP from factors that can cause degradation
  - Secondary packaging!

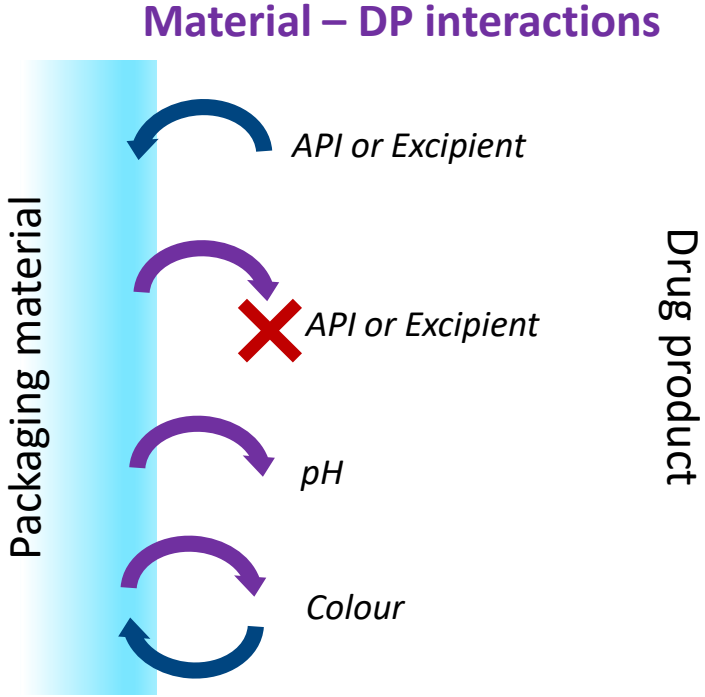




What is expected from Container/Closure Systems?

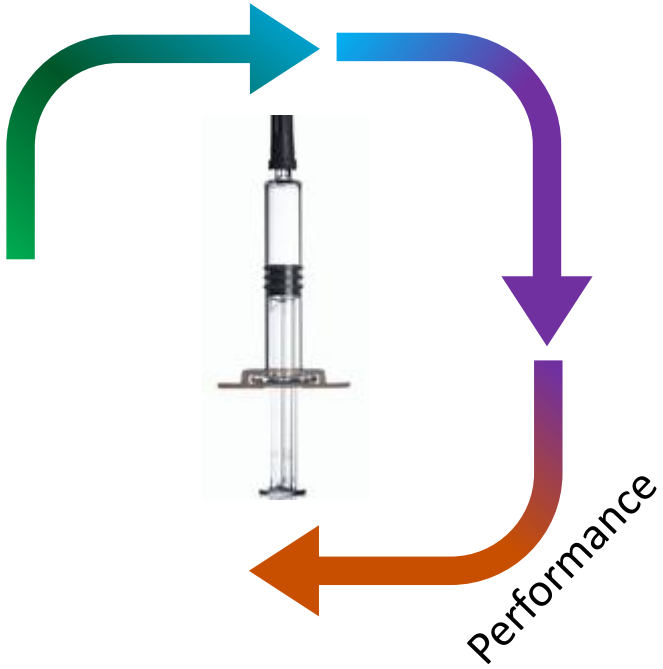
- CCS should be compatible with the DP
  - No interactions that cause detoriation of quality of DP or CCS!





What is expected from Container/Closure Systems?

- CCS is often designed to do more than just store the DP
  - Functionality and Drug Delivery



Facilitating drug delivery

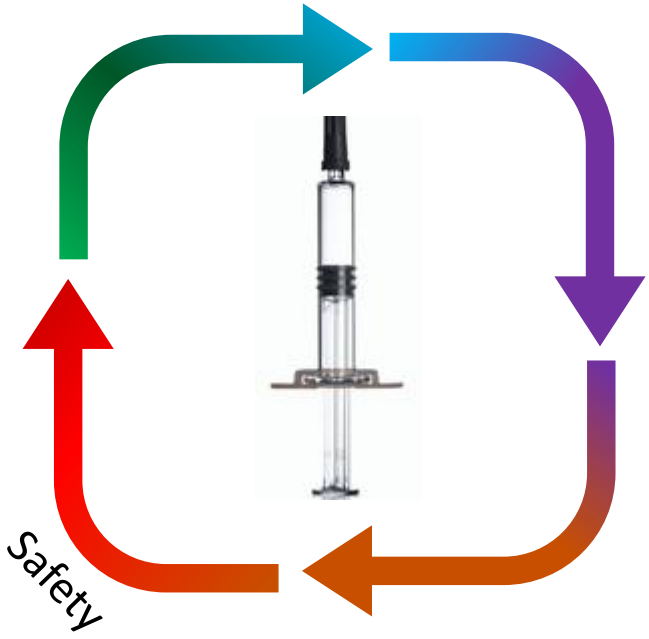
Minimizing waste | *Patient compliance* | *Ease of use*

Many CCS are combination products!

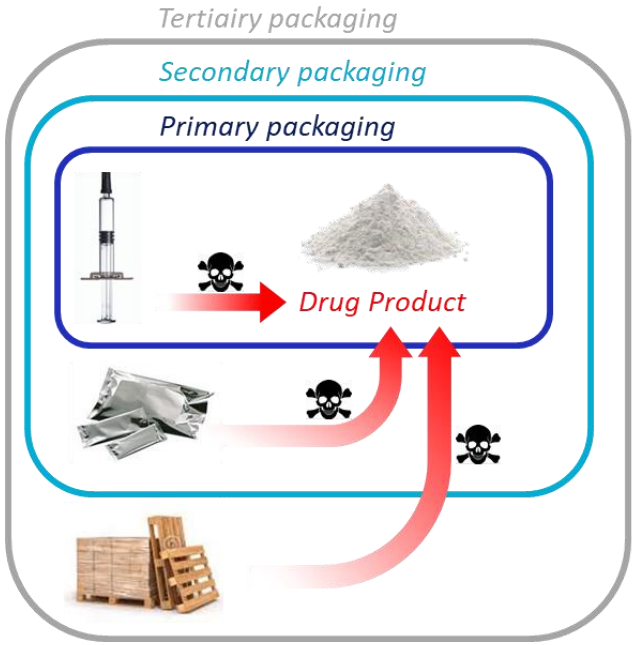
What is expected from Container/Closure Systems?

CCS should be constructed from materials that do not leach harmful substances

- Migration of impurities!

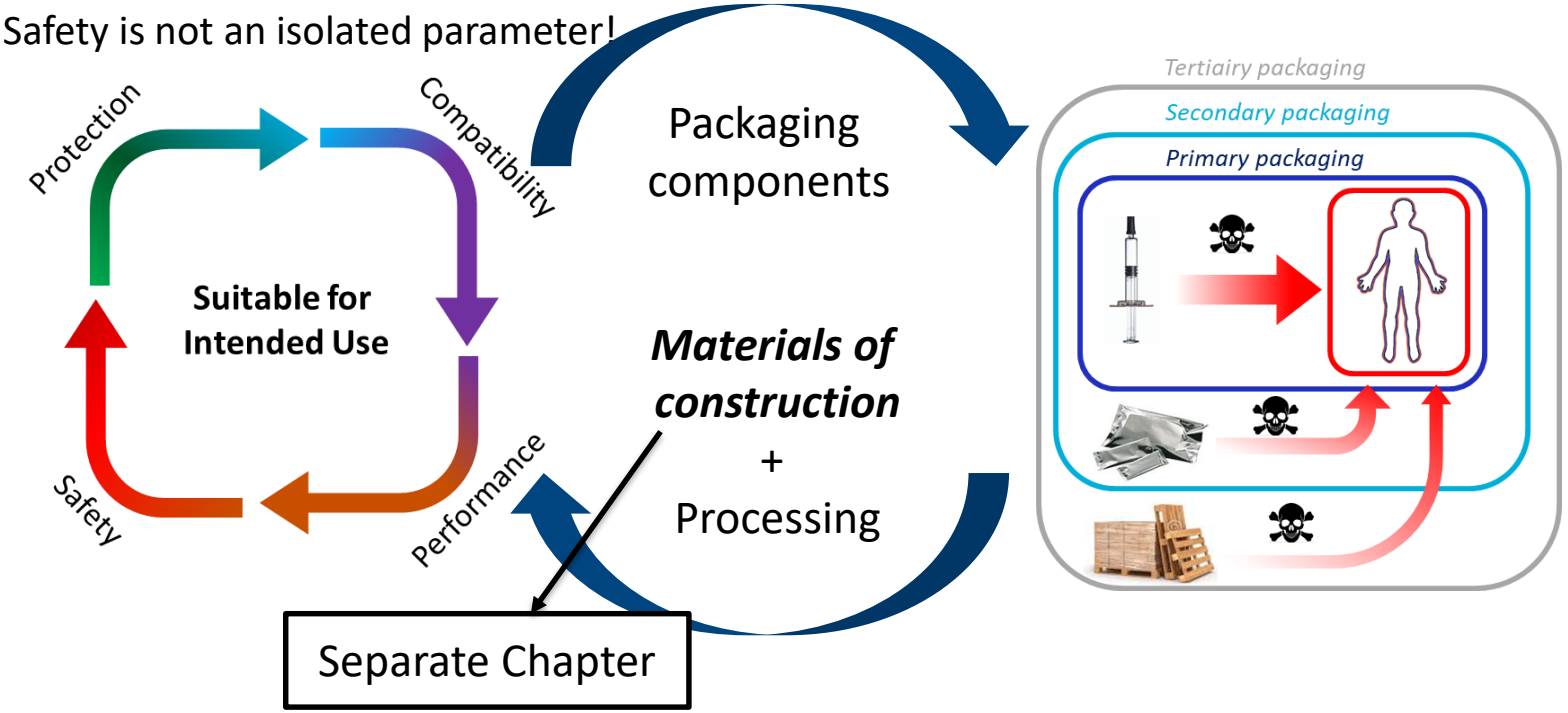


Material – DP interactions



What is expected from Container/Closure Systems?

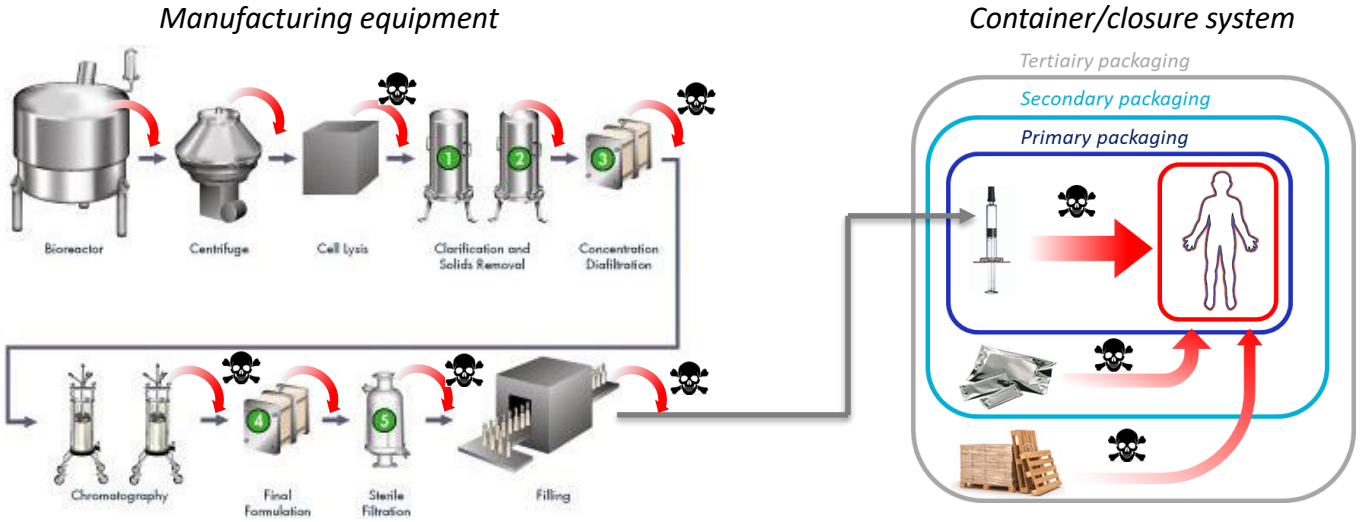
- Each aspect of the design of a CCS has a potential impact on its safety!
  - Safety is not an isolated parameter!



What is expected from Container/Closure Systems?

E&L study is a qualitative and quantitative investigation of migrating compounds from contact materials into DP

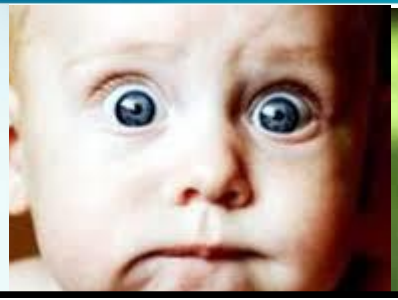
- Contact materials: CCS + manufacturing equipment
- Impact on safety and quality



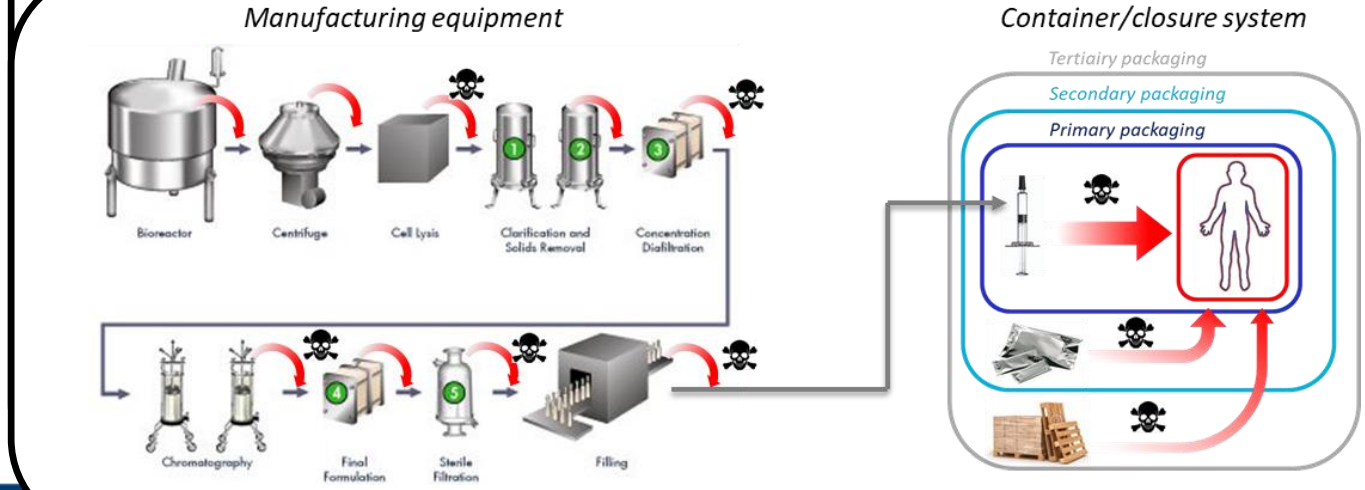
Do we need to be worried?

- Case Studies and potential suspects

Do we need to be worried?

Extractables and leachables



Are interaction concerns for real?

Degree of concern depends on composition DP and route of administration

Degree of concern

Separate Chapter

Separate Chapter

Drug tablets and capsules

Solid drug product
Weak interaction with CCS
Oral administration

Parenteral drug products

Liquid drug product (aqueous)
Intermediate interaction with CCS
Administration to bloodstream

OINDPS

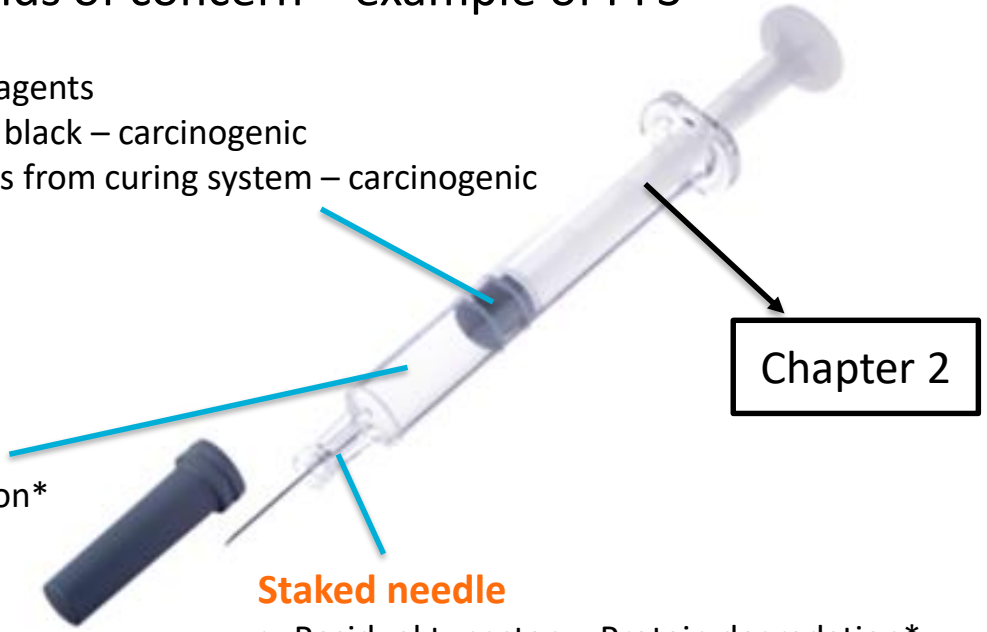
Aerosol (driving gas)
Strong interaction with CCS
Chronic administration to target organ

What is expected from Container/Closure Systems?

- Potential compounds of concern – example of PFS

Rubber stopper

- Halogenated rubber oligomers – alkylating agents
- PolyNuclear Aromatics (PNA's) from carbon black – carcinogenic
- Nitrosamines and sulfur-holding compounds from curing system – carcinogenic
- Iron – oxidative degradation of proteins*
- Aromatic antioxidants – toxic



Glass barrel

- Barium and Aluminum – particle formation*
- Silicon oil – protein aggregation*

Staked needle

- Residual tungsten – Protein degradation*
- Acrylates from incomplete curing – reactive and toxic*

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

What is expected from Container/Closure Systems?

Bisphenol A and DEHP – (in)famous examples of impurities from plastic

Leaching of the plasticizer di(2-ethylhexyl)phthalate (DEHP) from plastic containers and the question of human exposure.

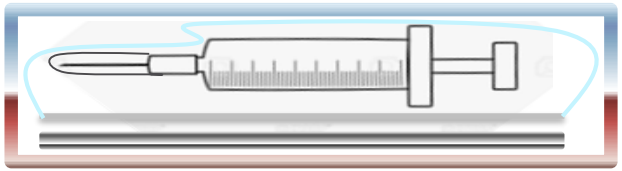
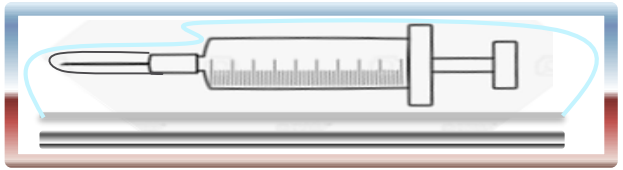
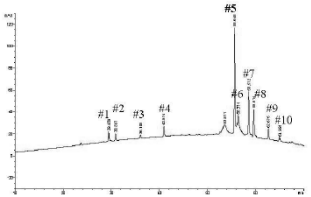
Di(2-ethylhexyl)phthalate (DEHP) is a widely used plasticizer to render poly(vinyl chloride) (PVC) soft and malleable. Plasticized PVC is used in hospital equipment, food wrapping, and numerous other commercial and industrial products. Unfortunately, plasticizers can migrate within the material and leach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

BPA, chemical used to make plastics, found to leach from polycarbonate drinking bottles Into humans - Exposure to BPA May Have Harmful Health Effects

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.

- Eprex = Human Recombinant EPO
- introduced in late ‘80 early ’90 – Janssen Cilag
- Increase Hematocrit (RBC-count) in CKD Patients
- Until ’98: no side effects
- From ‘98 onwards: increased incidence of PRCA
  - *Caused a drop in Hematocrit (instead of an increase)*
  - *Immune response*

Treatment of CKD Patients
SC injection

	< 1998	> 1998
		
FORMULATION *(Protein Stabilizer)*	Serum Albumin	Polysorbate 80
CONTAINER CLOSURE SYSTEM		Incompatible 

Leachables are Formulation Dependent

Leachables from the rubber plunger

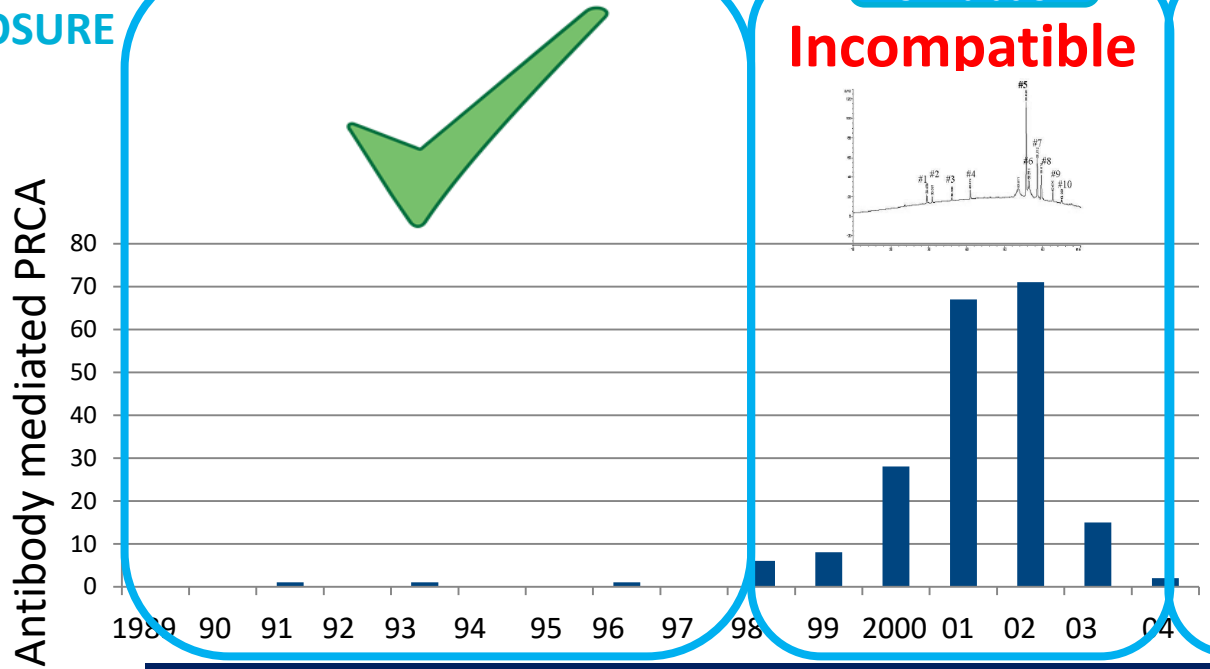
Eprex case: Incidents of AB-mediated Pure Red Cell Aplasia

CONTAINER CLOSURE SYSTEM

Changes in Formulation

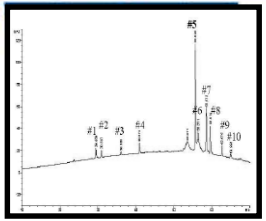
Incompatible

Coated Plungers



Red Blood Cell levels substantially reduced because of an Anti-body mediated immune response

Basant Sharma[1], PhD; Fred Bader[1], PhD; Tom Templeman[1], PhD; Peter Lisi[2], PhD; Mary Ryan[3], PhD; George A. Heavner[4], PhD



QUESTION: Who could have **predicted an anti-body mediated immune response**, based upon those analytical data?

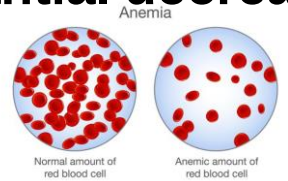
Peak[a]	Compound	Average concentration[b]
1	Unknown	Unknown
2	Bisphenol A	0.070
3	4-*tert*-amylphenol	0.046
4	2-chloro-4-*tert*-amylphenol	0.037
5	Vultac® 2 disulfide	0.778
6	2,2'-methylene-bis-4-*tert*-amylphenol	0.243
7	Vultac® 2 trisulfide	0.235
8	Vultac® 2 tetrasulfide	0.142
9	Vultac® 2 pentasulfide	0.063
10	Vultac® 2 hexasulfide	0.024

Basant Sharma[1], PhD; Fred Bader[1], PhD; Tom Templeman[1], PhD; Peter Lisi[2], PhD; Mary Ryan[3], PhD; George A. Heavner[4], PhD

Mode of action - Hypothesis in the early work:

Leachables (one or more) could **cause adjuvant-like properties**, "boosting" an immune response, which is **causing ADA's (Anti-Drug-Antibodies) to be formed**

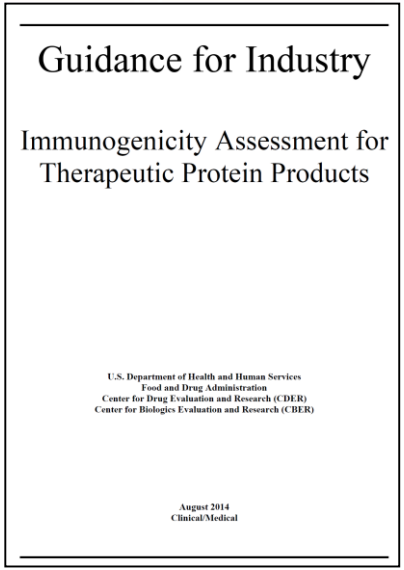
ADA's attacked both endogenous & exogenous EPO
ultimately resulting in **a substantial decrease of Red Blood Cells (PRCA/Anemia)**



However, the **"adjuvant like properties"** of the detected compounds were studied in **animal models**, but **no ADA's were observed**.

FDA Guidance for Industry (2014) Immunogenicity –

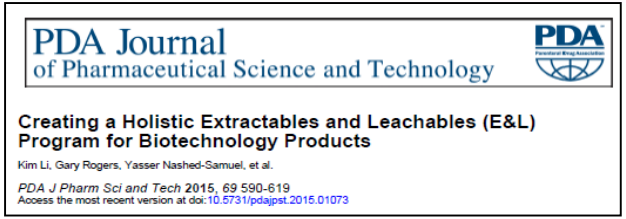
Mode of Action -
New Line of Thinking:


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


PDA Journal of Pharmaceutical Science and Technology

Creating a Holistic Extractables and Leachables (E&L) Program for Biotechnology Products

Kim Li, Gary Rogers, Yasser Nashed-Samuel, et al.

PDA J Pharm Sci and Tech 2015, *69* 590-619
Access the most recent version at doi:10.5731/pdajpst.2015.01073


PQRI
Product Quality Research Institute

Reactive Leachables may form **covalent bonds** with Biologics and may lead to **Immuno Responses**

What is expected from Container/Closure Systems?

- Tribromoanisole case – tertiary packaing affects quality of DP

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."*

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….

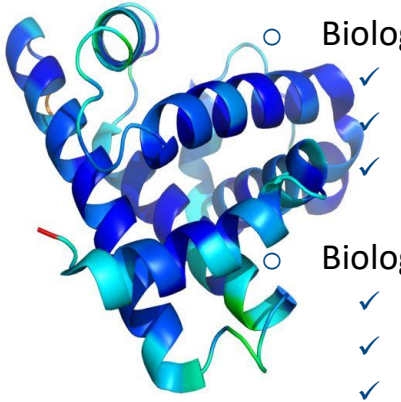
Glumetza Recall: 52 Lots of Diabetes Drug May Have Chemical Contamination

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.

2,4,6-Tribromoanisole (a wood preservative) contamination of DP due to lack of good barrier properties of primary packaging

What is expected from Container/Closure Systems?

- Protein drug products require special care
  - 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)



How does an E&L study looks like?

- Analytical Chemistry and Toxicology in Tandem

The flow of an E&L study

Analytical chemistry and toxicology in tandem

Assessing the risk to the patient through 4 basic questions:

EXT

- What are the chemical **impurities of the packaging**?
  - Extractables study – focus on identification

TOX

- What are the **targets of concern?**
  - Comparison of EXT concentrations with safety concern thresholds

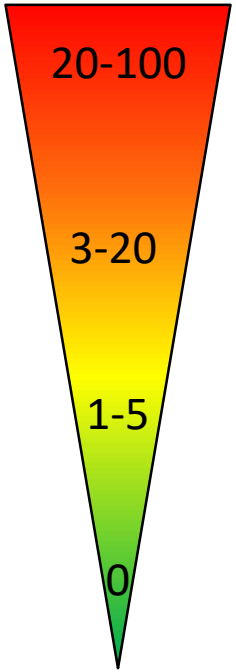
LEA

- Which compounds are **migrating into the drug product**?
  - Leachables study – focus on quantitation

TOX

- What is the **risk to the patient**?
  - Toxicological evaluation of leachables

N° of compounds involved



The flow of an E&L study

EXT

TOX

LEA

TOX

What are the chemical impurities of the packaging?

Extractables study = analytical study of the packaging

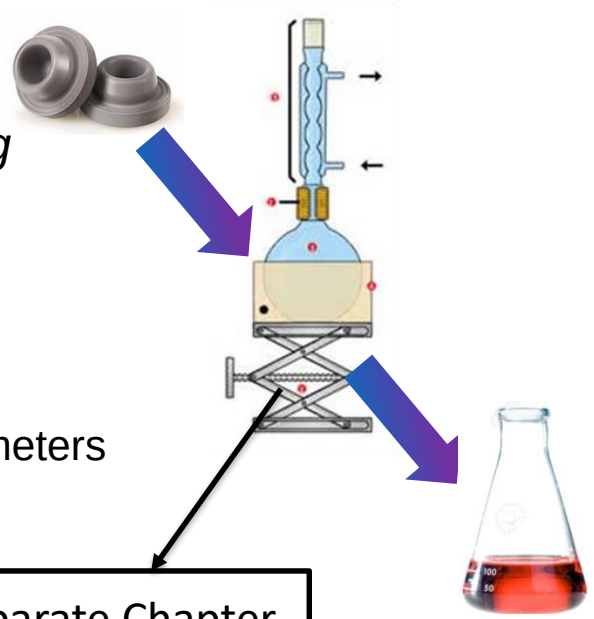
Generating the extract

Packaging components in final form

- ETO, steam, X-ray, washed, siliconized, ...

Worst-case approximation of DP-CCS interaction in 3 parameters

- Solvents (pH and polarity) or DP vehicle
- Temperature and time
- Extraction stoichiometry



Separate Chapter

The flow of an E&L study

What are the chemical impurities of the packaging?

Extractables study = analytical study of the packaging

EXT

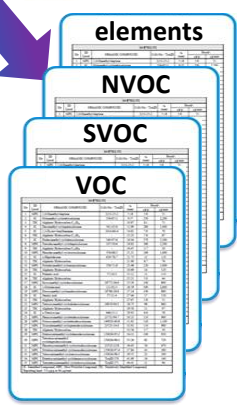
TOX

LEA

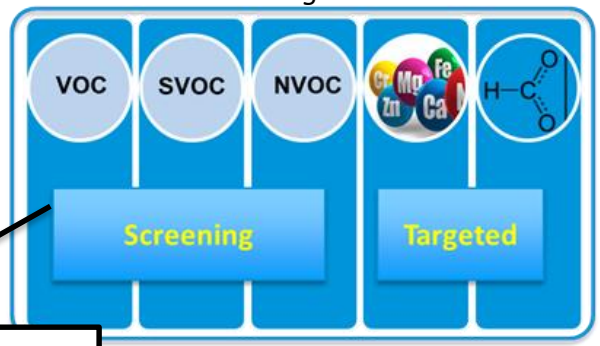
TOX

Analyzing the extract - Screening

- Methods designed for the detection of as many compounds as possible
- Semi-quantitative results
- Supplemented with targeted techniques based on processing and MOC



orthogonal



screening

Separate Chapter

Main purpose of an EXT study is **Identification** of migrating compounds!

The flow of an E&L study

Classification and Comparison of concentrations with thresholds

EXT

TOX

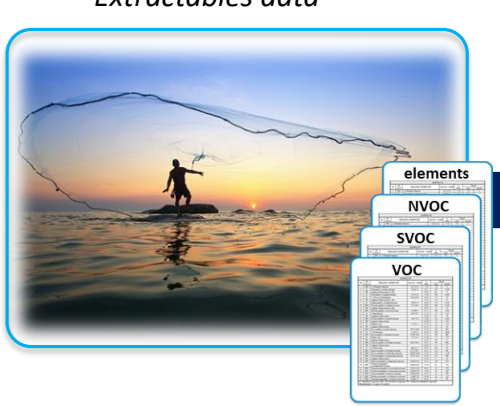
LEA

TOX

What are the compounds of concern?

In silico evaluation of extractables data

Extractables data



QSAR software

General toxicity
Highest treshold

Sensitizers, irritants

Carcinogens, mutagens
Lowest threshold

Compounds > class-specific threshold → **target compounds** for leachable study!

The flow of an E&L study

Which chemical impurities are migrating into the drug product?

Leachables study

Analyis of the drug product

EXT

TOX

LEA

TOX

Separate Chapter

targeted

Target compounds

Quantitative

Compound-specific tresholds

screening

Unexpected leachables

Semi-Quantitative

Safety Concern Threshold / Qualification Threshold

Main purpose of a LEA study is **Quantitation** of migrating compounds!

The flow of an E&L study

What is the risk to the patient?

Toxicological evaluation of leachables

Toxicological assessment of LEA data

EXT

TOX

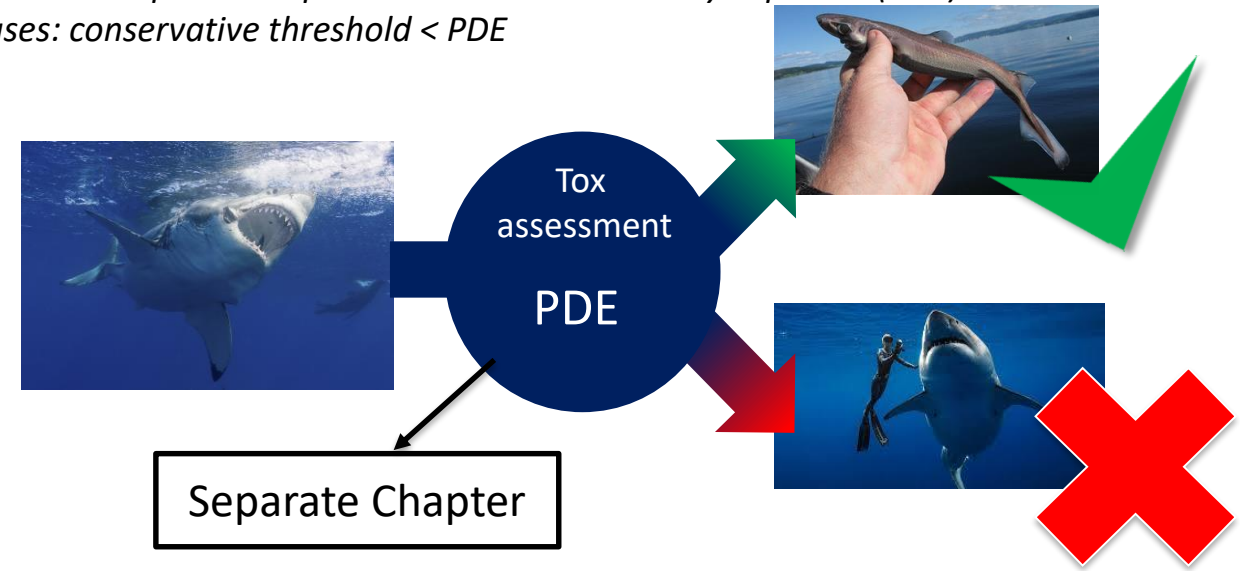
LEA

TOX

All leachables > conservative treshold should be subjected to toxicological assessment

Comparison of worst-case patient exposure with Permitted Daily Exposure (PDE)

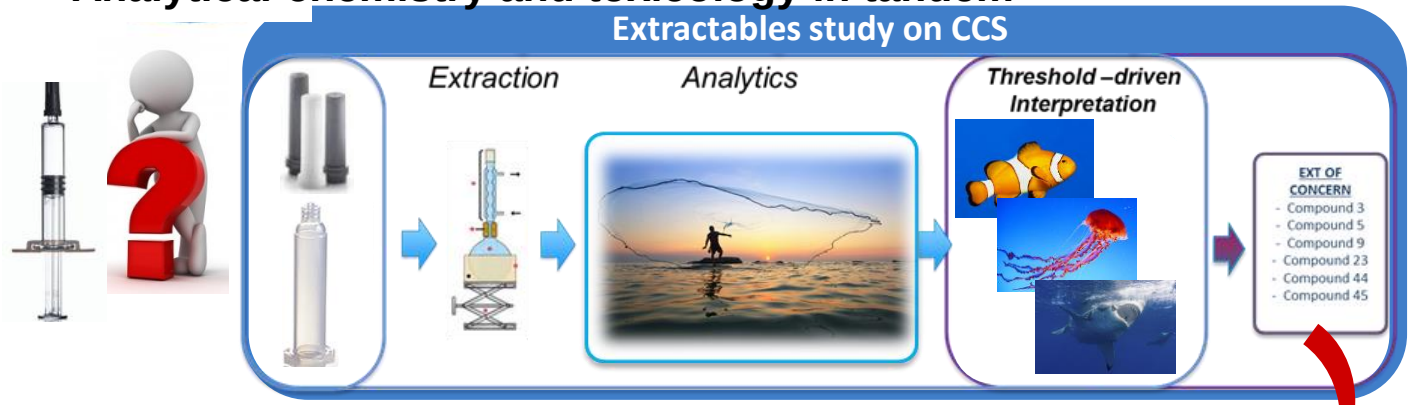
In most cases: conservative threshold < PDE



The flow of an E&L study

Analytical chemistry and toxicology in tandem

Let's recap!



What are the regulatory requirements for safety of a CCS?

- Browsing through the Regulatory Landscape

Regulatory Requirements

- Two types of Regulatory Requirements

What kind of information should be provided?

US guidances

EU guidelines - GMP

Code of Federal Regulations

ICH

How can the testing be performed?

Pharmacopeias (USP, JP, EP, ...)

Standard Organizations (ISO)

Recommendations of Workgroups (PQRI

Consortia

Regulatory Requirements

What kind of information should be provided?

PRIMARY PACKAGING







Regulatory Requirements - What

- The **What Requirements** for 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 Requirements - What

PRIMARY PACKAGING

- The **What Requirements** for Primary Packaging

REGULATORY ASPECTS – PARENTERALS – NON-LIMITATIVE LIST

<1999: 21CFR 211.94(a) "DRUG PRODUCT CONTAINERS AND CLOSURES"

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

Regulatory Requirements - What

The **What Requirements** for Primary Packaging - **FDA**

- Required information depends on route of administration and CCS-DP interaction
- From FDA guidance (1999) to USP <1664>

Separate Chapter

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

Regulatory Requirements - What

The **What Requirements** for Primary Packaging - **FDA**

- Going through the FDA/USP matrix

Examples of Packaging Concerns for Common Classes of Drug Products			
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LIKELIHOOD OF INTERACTION = LOW
Packaging Component - Dosage Form

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

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

CERTIFICATE OF ANALYSIS may be sufficient

- COMPENDIAL testing
- ROUTINE QC testing

Regulatory Requirements - What

The **What Requirements** for Primary Packaging - **FDA**

- Going through the FDA/USP matrix

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

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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

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

CERTIFICATE OF ANALYSIS (compendial and routine testing)

+

EXTRACTABLES and/or LEACHABLES testing required

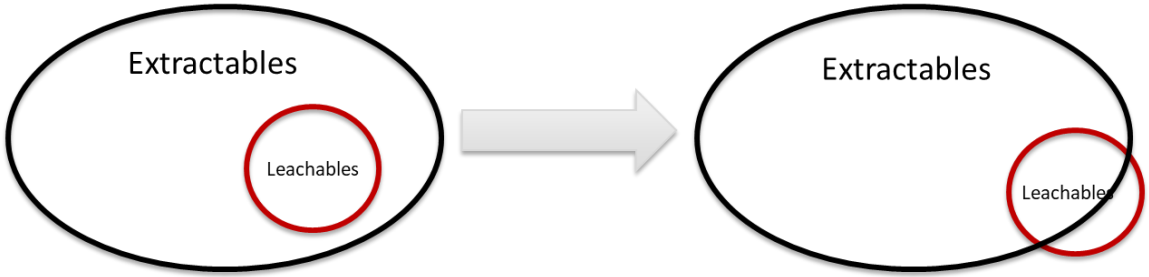
Regulatory Requirements - What

The **What Requirements** for Primary Packaging - **FDA**

- **Important remark on FDA guidance**

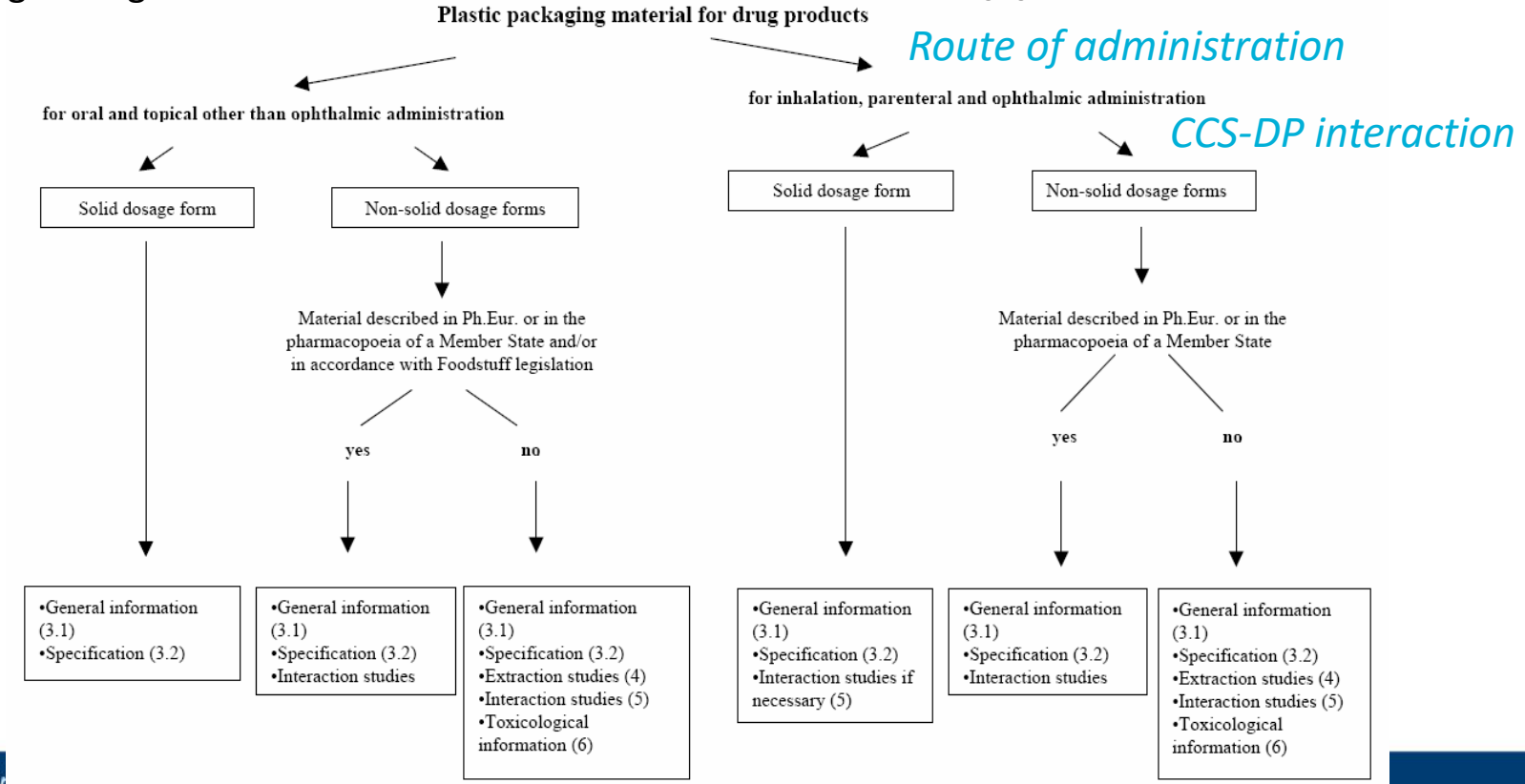
The requirements in the FDA Guidance Document
"*Container Closure Systems for Packaging Human Drugs and Biologics*" of **1999**
do NOT reflect the current (2015) FDA/USP requirements
for E/L Testing and Documentation

NOT ONLY EXTRACTABLES evaluation => Consider **LEACHABLES STUDIES**!



PDA Regulatory Requirements - What

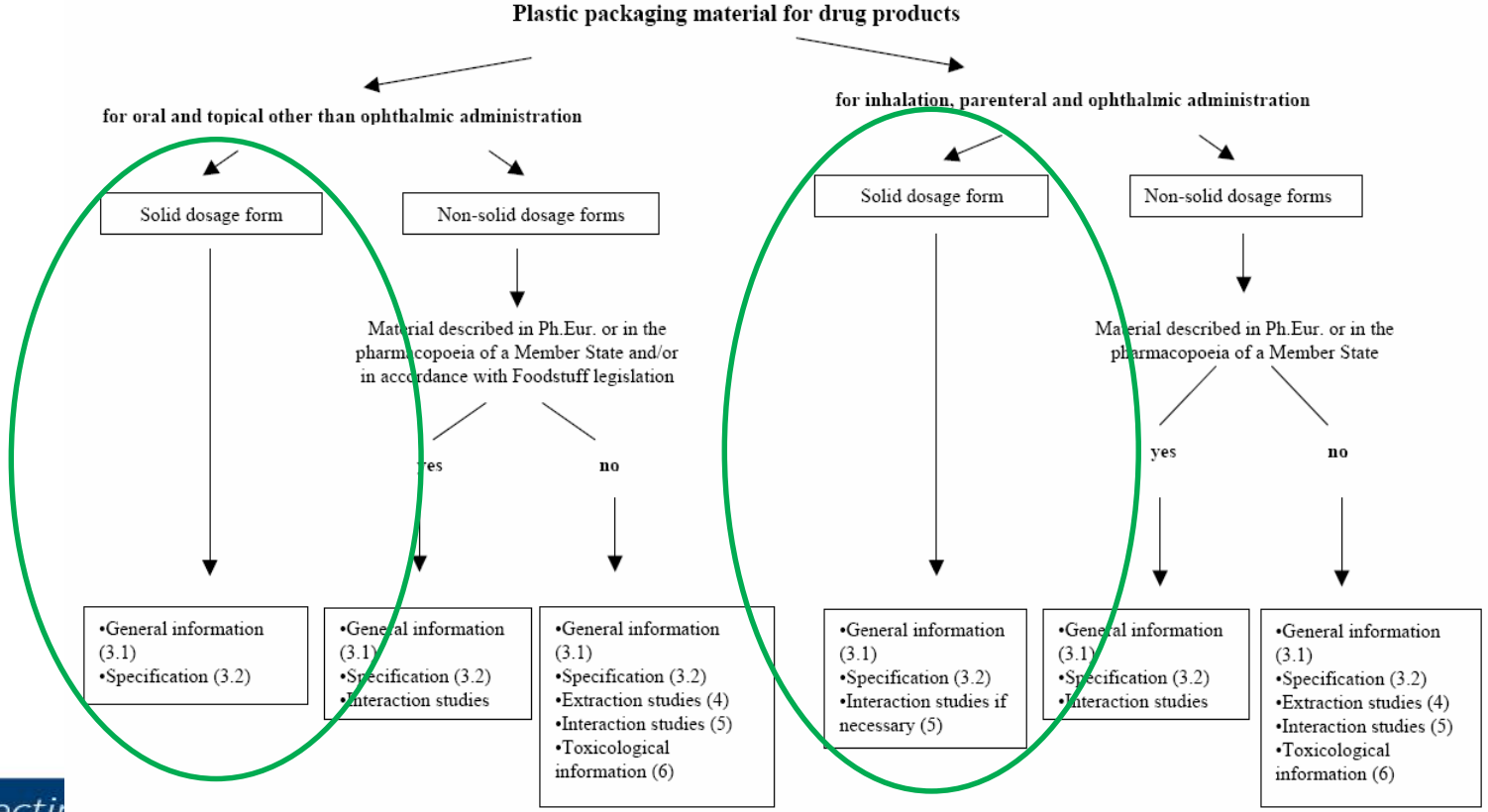
- The **What Requirements** for Primary Packaging - **EMEA**
  - Going through the decision tree (EM(E)A Guideline on "Plastic Immediate Packaging Materials" of 2005)



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

Regulatory Requirements - What

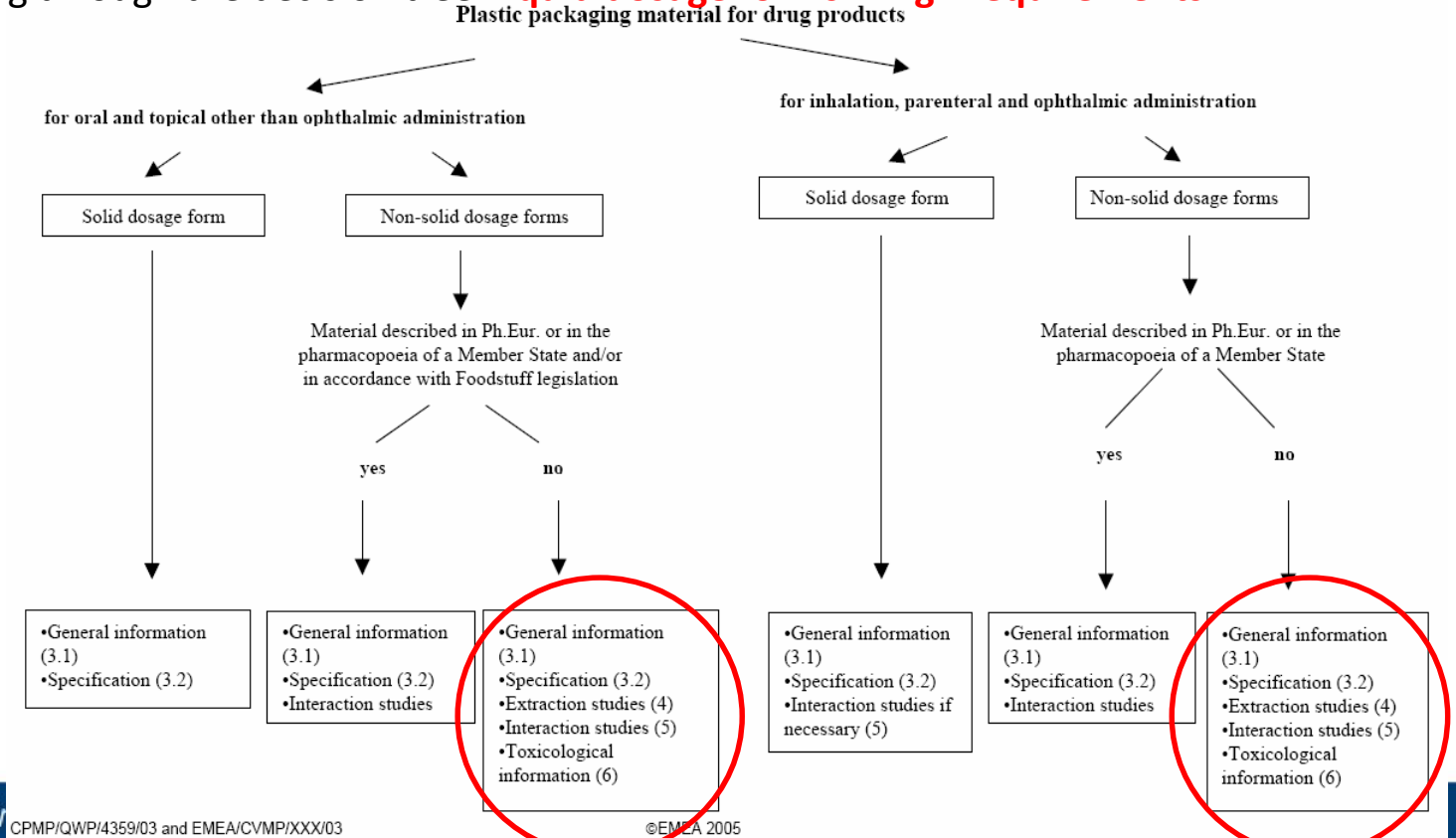
- The **What Requirements** for Primary Packaging - **EMEA**
  - Going through the decision tree: **solid dosage forms – low requirements**



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

Regulatory Requirements - What

- The **What Requirements** for Primary Packaging - **EMEA**
  - Going through the decision tree: **liquid dosage forms – high requirements**

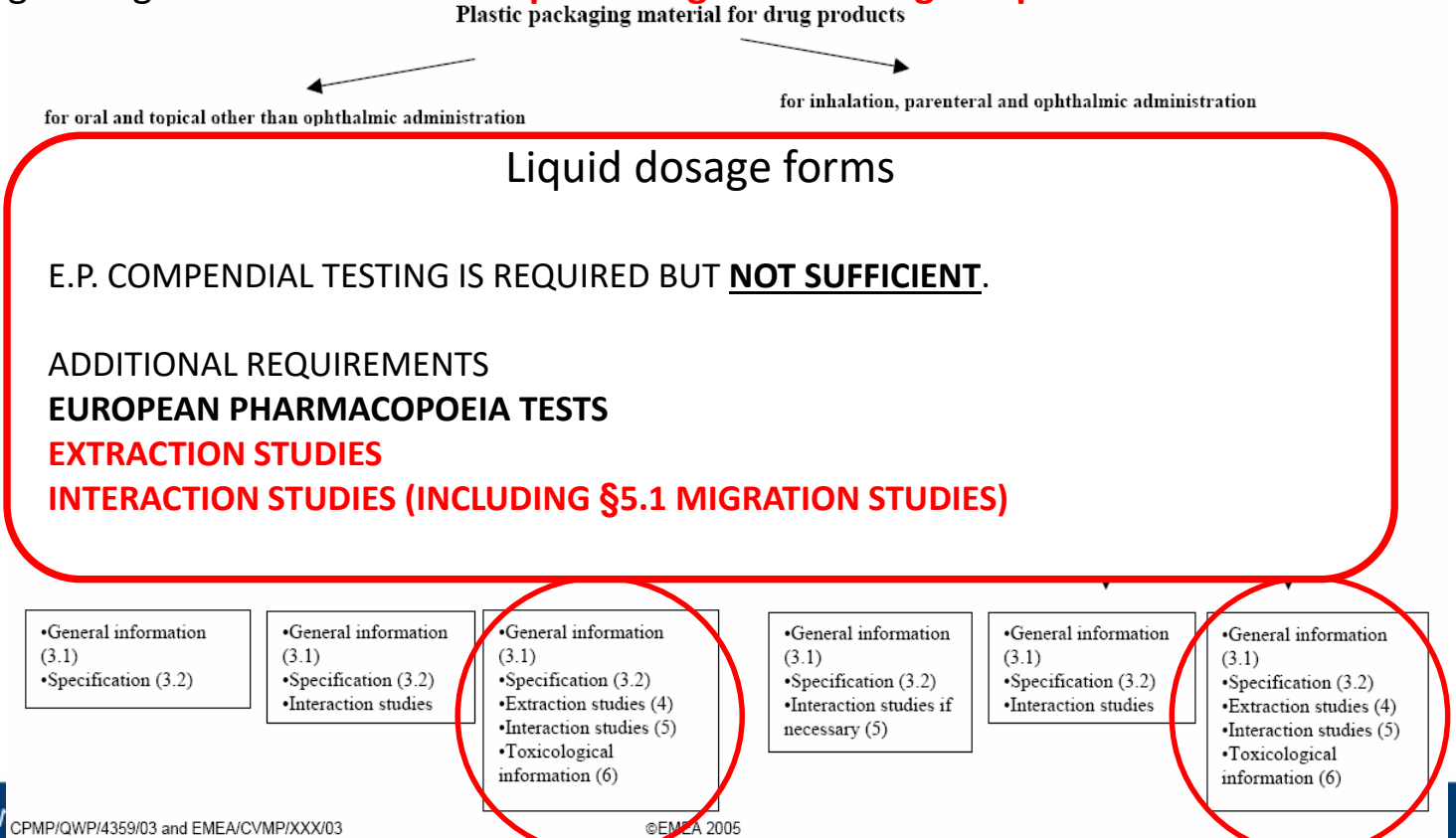


CPMP/QWP/4359/03 and EMEA/CVMP/XXX/03 ©EMEA 2005

Regulatory Requirements - What

PRIMARY PACKAGING

- The **What Requirements** for Primary Packaging - **EMEA**
  - Going through the decision tree: **liquid dosage forms – high requirements**



Regulatory Requirements - What

- The **What Requirements** for Primary Packaging - **FDA**
  - Important remarks on EMA packaging guideline

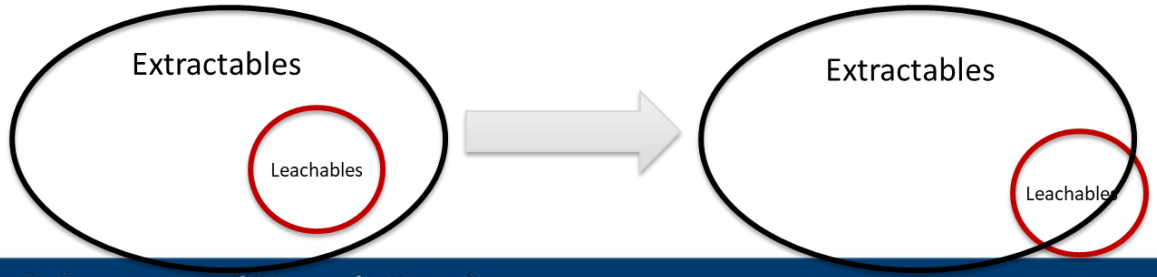
Not for Elastomers (?) = > In reality: **ALSO** fo rubbers

If a Material is described in the E.P. and if it complies with the specifications therein, no Extractable testing may be needed.

≠ THE ACTUAL POSITION OF EUROPEAN REGULATORS

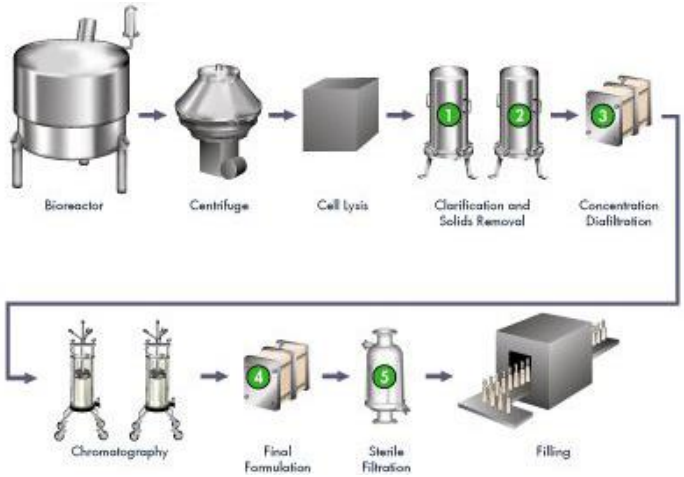
If Extractable Testing shows only compounds with low risk (at low concentrations) no leachable study is necessary.

≠ THE ACTUAL POSITION OF EUROPEAN REGULATORS



Regulatory Requirements - What

What kind of information should be provided?



Manufacturing equipment

Regulatory Requirements - What

Manufacturing equipment

- The **What Requirements** for Manufacturing Equipment

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 Requirements - What

Manufacturing equipment

- The **What Requirements** for Manufacturing Equipment

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

How should the test be performed?

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

Regulatory Requirements – HOW?

“HOW” requirements:

- 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)

Regulatory Requirements – HOW?

US Pharmacopoeia (USP) → Separate Chapter

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)

Regulatory Requirements – HOW?

European Pharmacopoeia (EP)

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**

Regulatory Requirements – HOW?

European Pharmacopoeia (EP)

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

Regulatory Requirements – HOW?

Compendial testing (USP and EP)

CHARACTERISTICS of Physicochemical 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!!

Regulatory Requirements – HOW?

Compendial testing (USP and EP)

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)

Regulatory Requirements – HOW?

Compendial testing (USP and EP)

LIMITATIONS of Pharmacopoeial Compendial Tests

- **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 their concentration?

- **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...

Compendial testsing ≠ substitute for Extractables testing

Regulatory Requirements – HOW?

USP guidances monographs (>1000) → Separate Chapter

<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 PharmaceuticalPackaging/Delivery Systems

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

*<1665> **Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products (Draft)***

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)

Regulatory Requirements – HOW?

Other guidance documents

- 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)**
- 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)

Dr. Dan Mellon – FDA - youtube

Thank you!

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.

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.

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