PDA Training Course Extractables & Leachables

23-24 October 2025

# Introduction to Extractables & Leachables

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PDA Parenteral Drug Association

Nelson Labs A Sotera Health company

CONNECTING PEOPLE SCIENCE AND REGULATION®

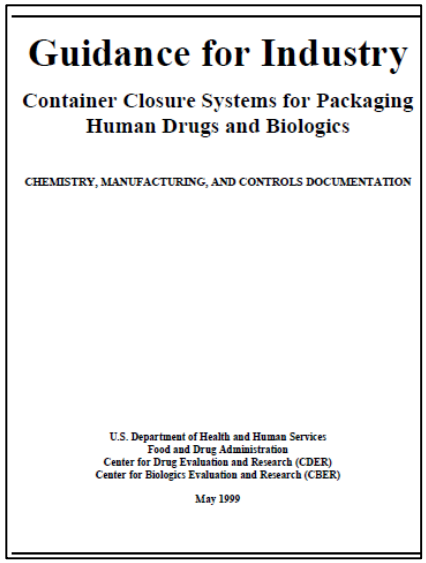
# Setting the stage

1. What is expected from packaging materials for drug products?
   *Working towards a definition of E&L*
2. Do we need to be worried about packaging materials?
   *Potential suspects and case studies*
3. How does an E&L study look like?
   *Analytical chemistry and toxicology in tandem*
4. What are the regulatory requirements for safety of a container/ closure system and manufacturing 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

Container Closure Systems for Packaging Human Drugs and Biologics

CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION

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

May 1999

The selected Container/Closure System (CCS) must be

**“suitable for its intended use”**

Protection

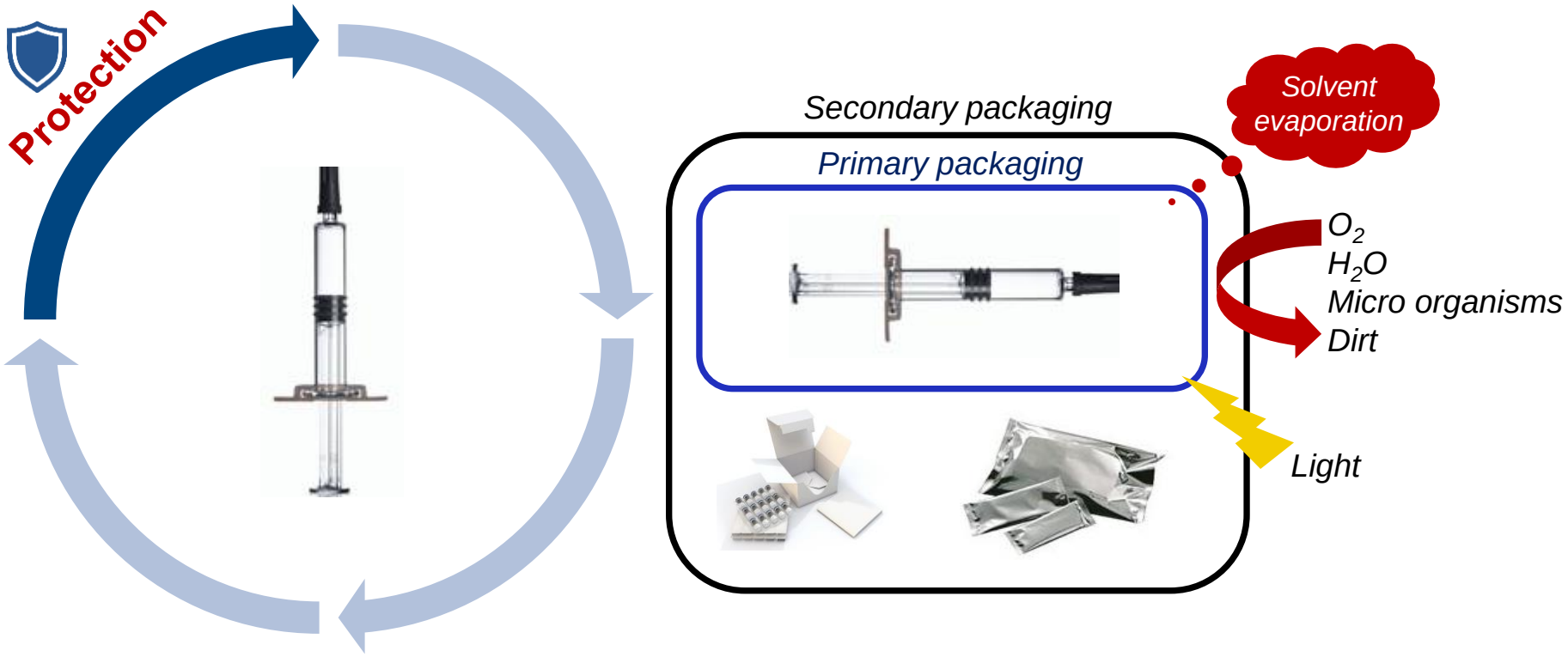
Compatibility

Performance

Safety

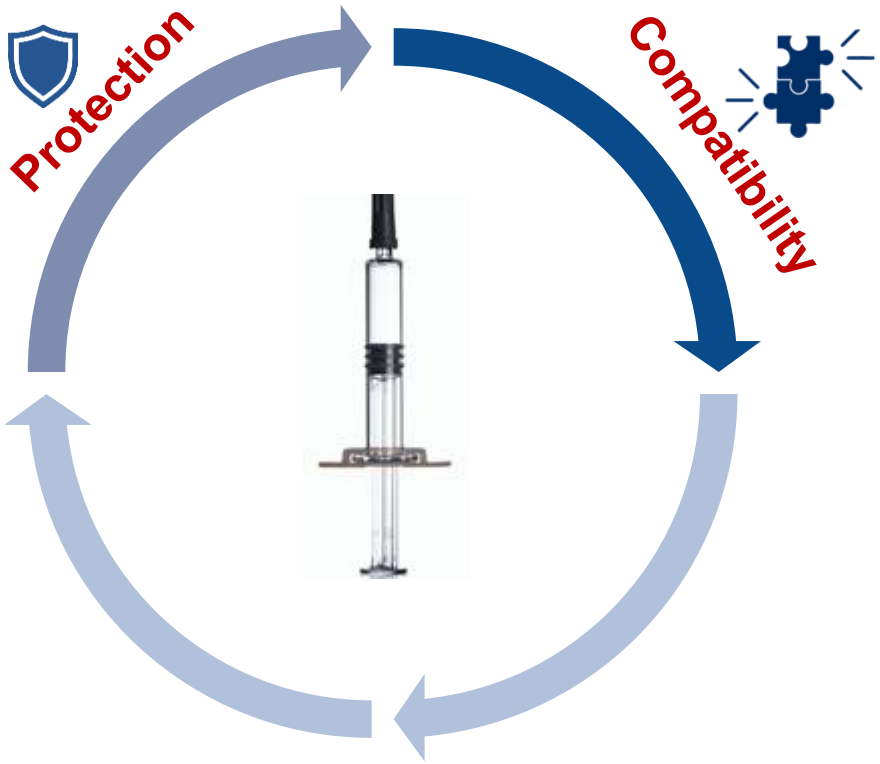

*A CCS that is suitable for a particular drug product, may not be suitable for another drug product!*

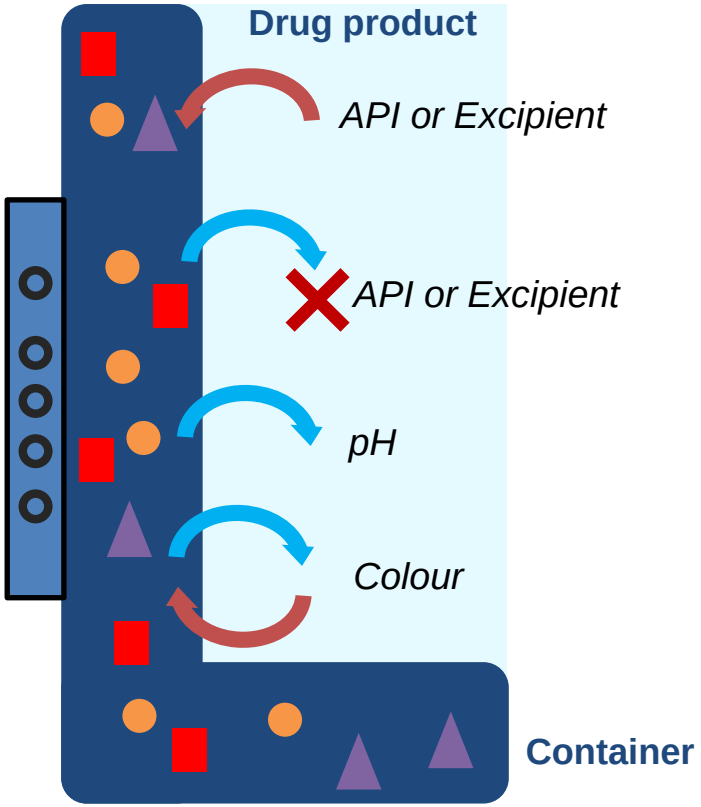
# What is expected from Container/Closure Systems?




**CCS must protect the drug product from the environment (i.e. from factors causing degradation) and from losing ingredients to the**

# What is expected from Container/Closure Systems?

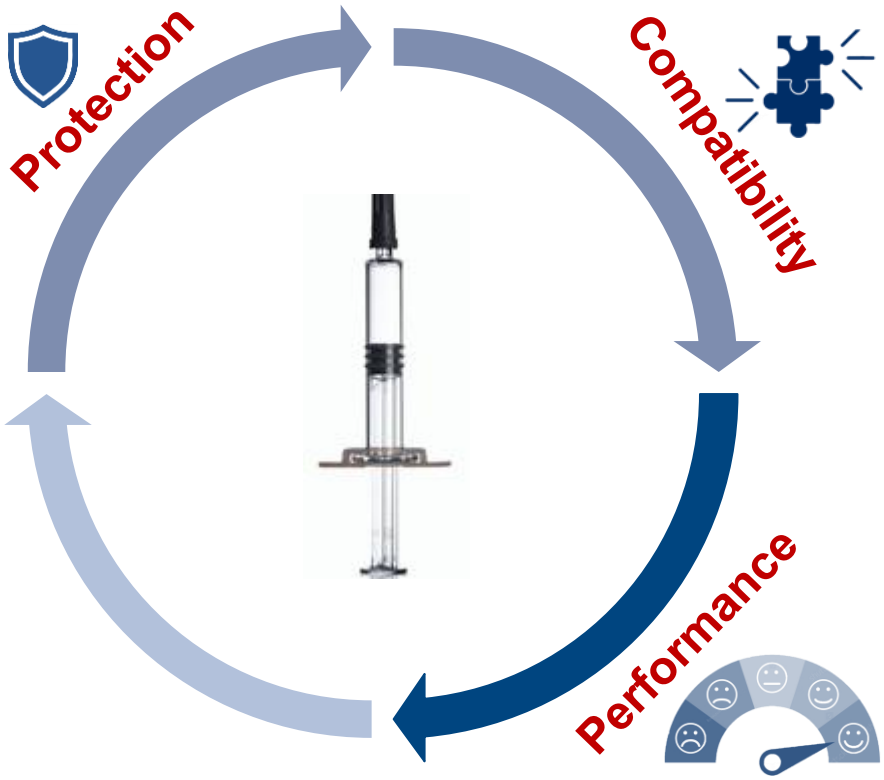



**Material – DP interactions**

**There should be no interactions that cause deterioration of quality of the drug product or CCS**

# What is expected from Container/Closure Systems?




1. **Storage**
2. **Facilitate drug delivery**

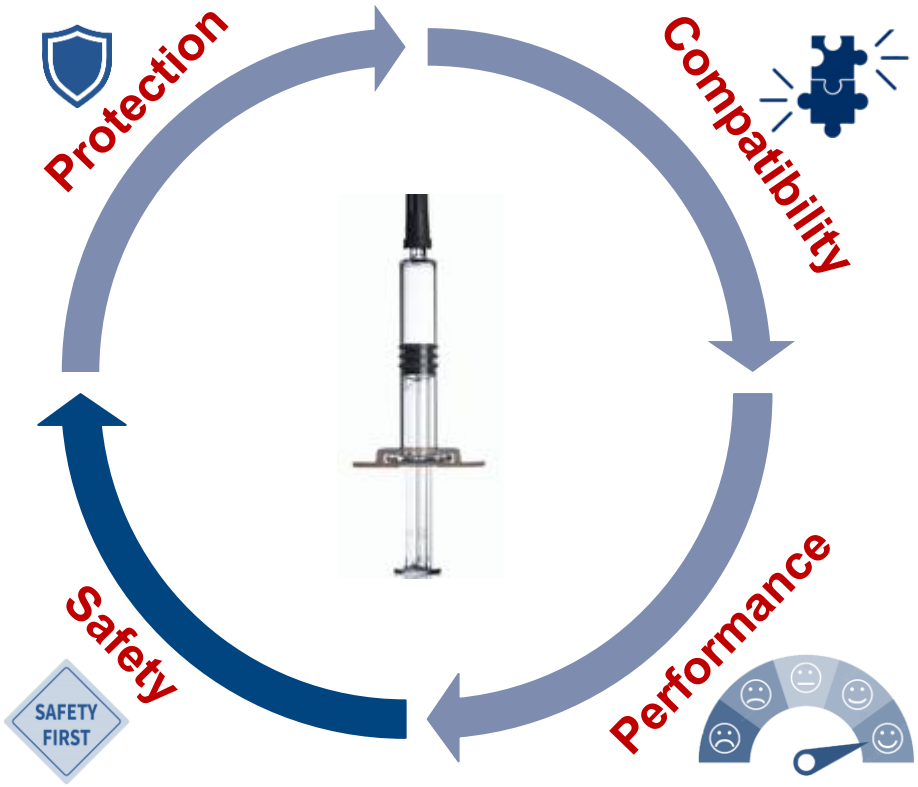
3. **Functionality**

*Ease of use* *Minimizing Patient compliance waste*

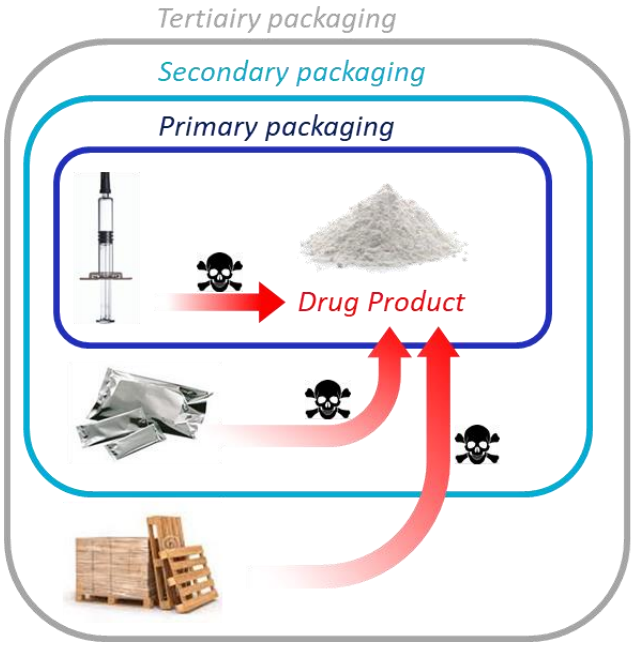
**Many CCS are combination products!**

**A CCS is often designed not only for the storage of the DP, also for its functionality and drug delivery**

# What is expected from Container/Closure Systems?



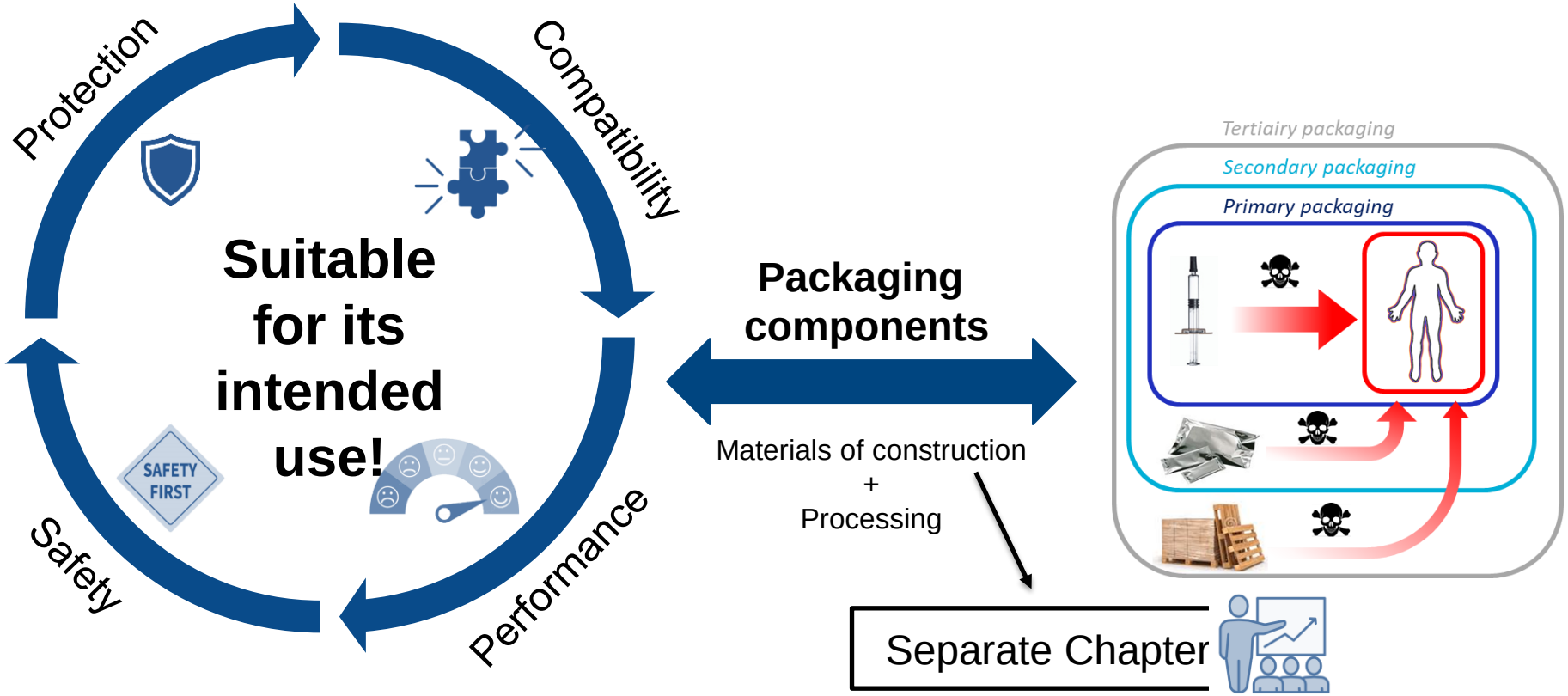

## Material – DP interactions




*Is there anything migrating from the packaging into the drug? And at what levels?*

**Packaging should not leach harmful substances**
**➔ Need for E&L studies!**

# What is expected from Container/Closure Systems?



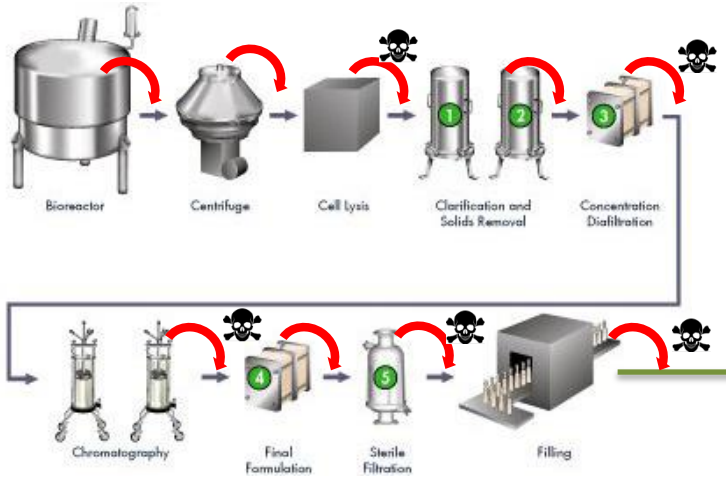

**Each aspect of the design of a CCS has a potential impact on safety!**
**➔ E&L studies are a cornerstone in impurities assessment of a DP**

# What is expected from Container/Closure Systems?

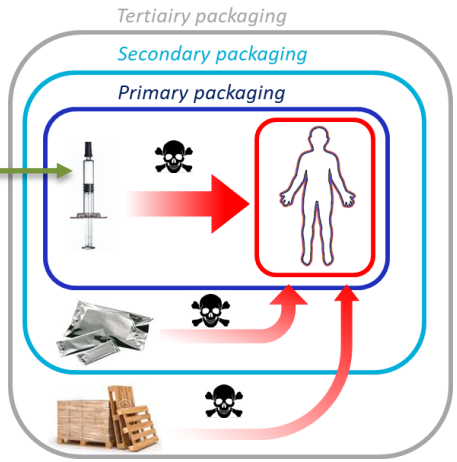
**E&L studies are a qualitative and quantitative investigation of compounds migrating from contact materials into DP**

Impact on safety and quality!

**Manufacturing equipment**




**Container/closure system**



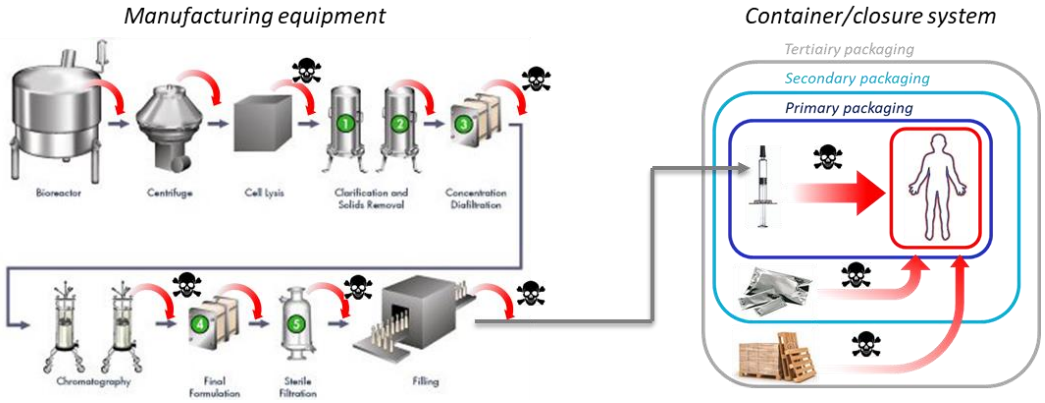
# Do we need to be worried?

*Case Studies and Potential Suspects*

# Do we need to be worried?

**ARE INTERACTION CONCERNS FOR REAL?**


## Extractables and leachables



# Are interaction concerns for real?


**Drug tablets and capsules**

- Solid drug product
- **Weak interaction** with CCS
- Oral administration

**Parenteral drug**

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

**OINDPS**

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

**DEGREE OF CONCERN**

**Degree of concern depends on:**
- **dosage form**
- **route of administration**

*SVP: small volume parenteral*
*LVP: large volume parenteral*
*OINDP: Orally inhaled and nasal drug product*

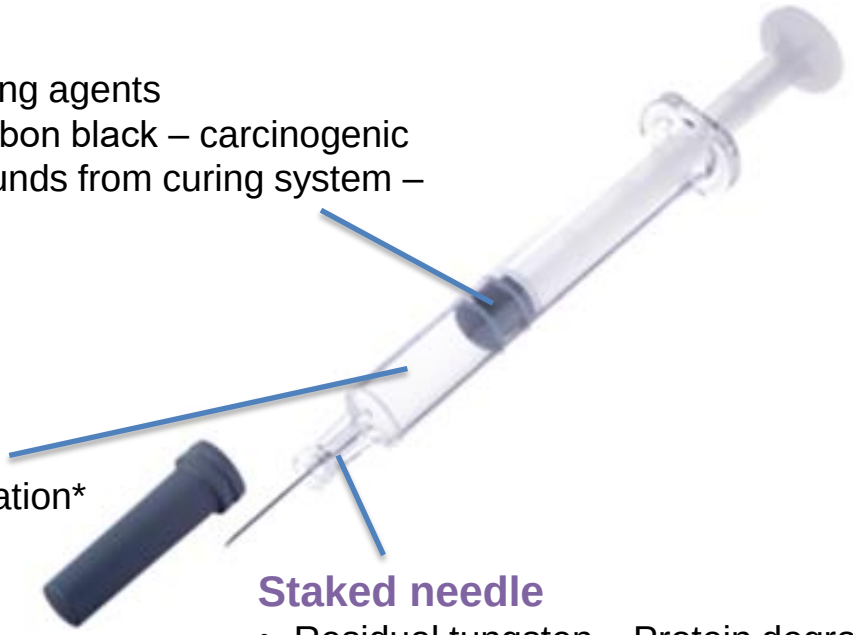
*Separate Chapters

# Are interaction concerns for real?

## 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*

# Are interaction concerns for real?

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

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

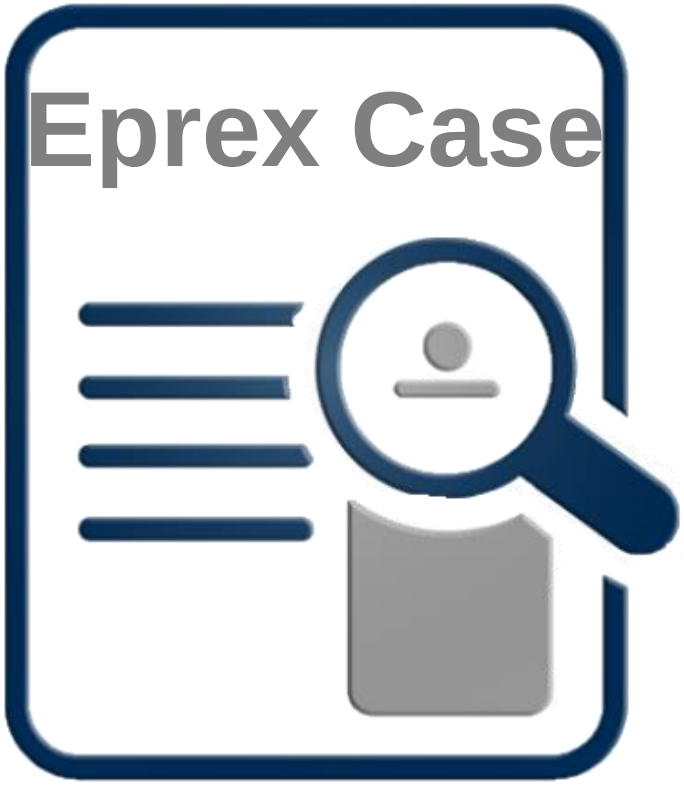
*Boston, MA — A new study from Harvard School of Public Health (HSPH) researchers found that participants who drank for a week from polycarbonate bottles, the popular, hard-plastic drinking bottles and baby bottles, showed a two-thirds increase in their urine of the chemical bisphenol A (BPA). Exposure 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.*

### 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.*

# Are interaction concerns for real?

**Eprex® case (1998) – serious adverse events**




- Eprex® = Human Recombinant EPO
- Introduced in late ’80-early ’90 – Janssen Cilag
- Increase Hematocrit (RBC count) in CKD Patients, SC injection
- Until ’98: no major side effects
- From ‘98 onwards: increased incidence of PRCA
  - *Caused a drop in Hematocrit (instead of an increase)*
  - *Serious impact on health CKD patients*
  - *Immune response*



*EPO=erythropoietin*
*CKD=chronic kidney disease*
*SC=subcutaneous; PRCA=Pure Red Cell Aplasia*

# Are interaction concerns for real?

**Eprex® case (1998) – serious adverse events**

**1998**

Human Serum Albumin

**FORMULATION**

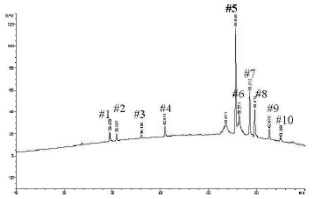
*(Protein Stabilizer)*

Polysorbate 80

Compatible

**CONTAINER/CLOSURE SYSTEM**

Incompatible




*Leachables from the rubber plunger*

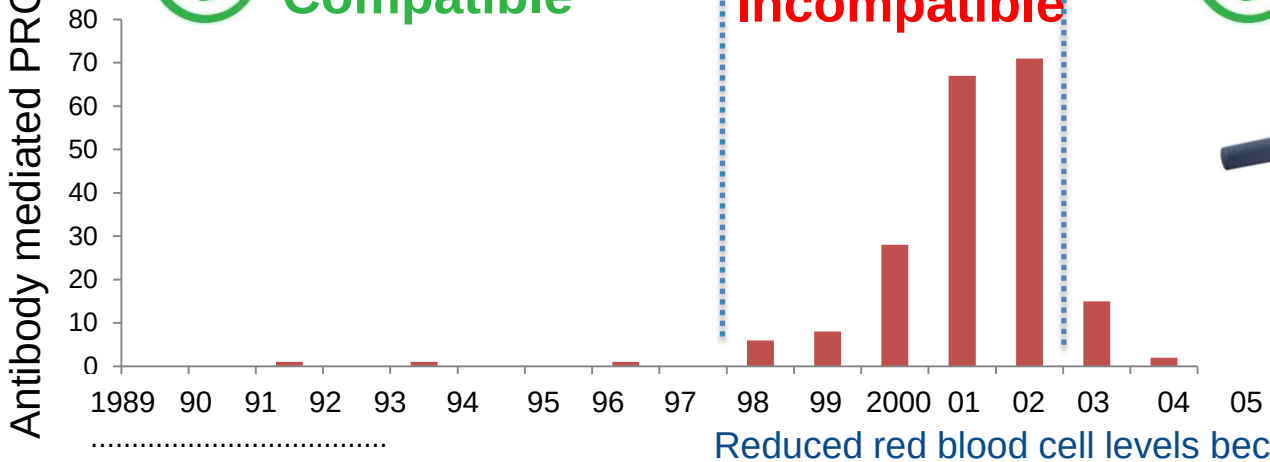
**Leachables are formulation dependent**

# Are interaction concerns for real?

**Eprex® case (1998) – serious adverse events**

**1998** **2003**

| Human serum albumin Non-coated plunger | Change in formulation | Polysorbate 80 Coated plunger |
|---|---|---|
| CCS Compatible | CCS Incompatible | CCS Compatible |



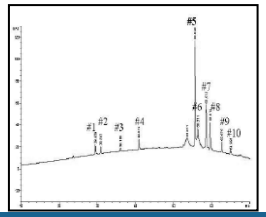

Reduced red blood cell levels because of an antibody mediated immune response*

*CCS=container/closure system*
*PRCA=Pure Red Cell Aplasia*

* 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

# Are interaction concerns for real?

**Eprex® case (1998) – serious adverse events**



**CCS Incompatible**

| 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

# Are interaction concerns for real?

**Tribromoanisole case – wood preservative**

Tertiary packaging affects quality of drug product due to lack of good barrier properties of primary packaging

## 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….*

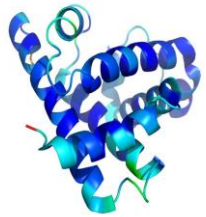
## Glumetza Recall: 52 Lots of Diabetes Drug May Have Chemical Contamination

*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.*

# Are interaction concerns for real?

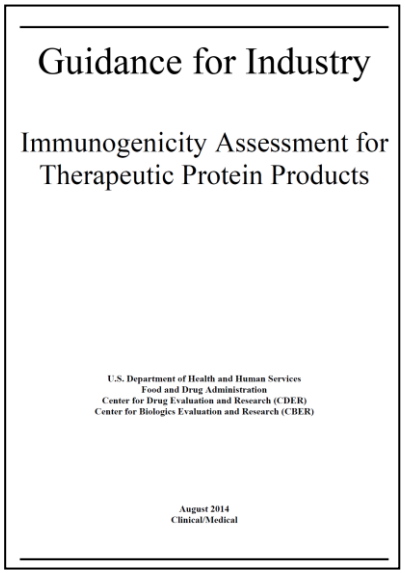
## Protein-based drug products require special care

- **Administration** by injection: highest concern
- High likelihood of **interaction** between CCS and injectable DP
- Biologics are **complex**
  - ✓ High 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)



# FDA Guidance for Industry (2014) Immunogenicity – Therapeutic Proteins

**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


**Reactive Leachables** may form **covalent bonds** with Biologics and may lead to **immuno responses**

# How does an E&L study look like?

*Analytical Chemistry and Toxicology in Tandem*

# The flow of an E&L study

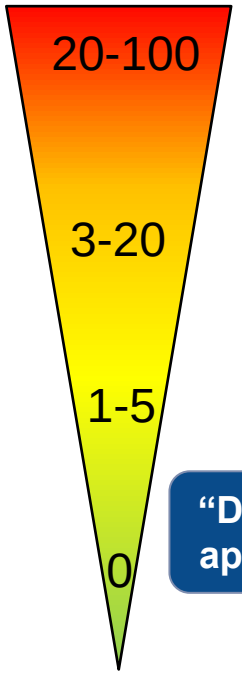
**EXT**
- What are the chemical **impurities of the packaging**?
  - Extractables study – focus on identification

**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




**"Derisking approach"**


**Extractables & Leachables studies**
- **Identification** and **quantification** of migrating compounds
- **Assessing the risk** of the packaging to the patient

# The flow of an E&L study

EXT TOX LEA TOX

GOAL

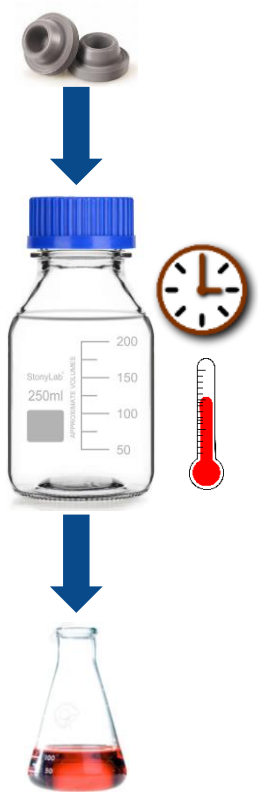
What **CAN** come out of a **material?**

**What are the chemical impurities of the packaging?**

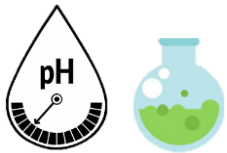
*Extractables study = analytical study of the packaging/packaging components*

## 1 Generating the extract

- Test item = packaging or packaging components
- 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)
- DP vehicle




- Temperature
- Time

- Extraction stoichiometry

**Exaggerated conditions!**

Separate Chapter

# The flow of an E&L study

EXT → TOX → LEA → TOX

**GOAL**

What **CAN** come out of a **material?**
**IDENTIFICATION** of migrating compounds**!**

**What are the chemical impurities of the packaging?**

*Extractables study = analytical study of the packaging/packaging components*

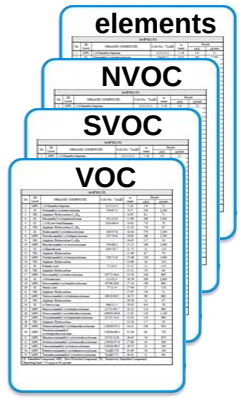
## 2 Analyzing the extract

- Detection of **as many compounds as possible**
- Complementary techniques: **screening** & **targeted**
- Semi-quantitative results

*orthogonal*


*screening*

Chemical ‘fingerprint’




Separate Chapter

# The flow of an E&L study

EXT → TOX → LEA → TOX

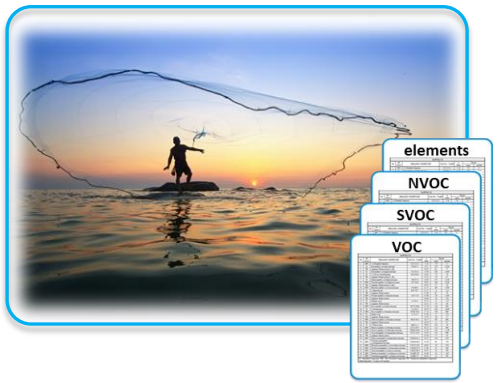
GOAL

What **are the compounds of concern?**

## 3 *In silico* evaluation of extractables data

Classification and comparison of concentrations with thresholds

*Extractables data*




(Q)SAR software

General toxicity
*Highest treshold*

Sensitizers, irritants

Carcinogens, mutagens
*Lowest threshold*

$Conc_{compounds}$ > class specific threshold → **target compounds** for leachable study!

*(Q)SAR: (Quantitative) structure-activity relationship*

# The flow of an E&L study

EXT → TOX → LEA → TOX

**Which compounds are migrating into the drug product?**
**QUANTITATION** of migrating compounds!

4 ***Analysis of the drug product***

**Normal conditions!**

*Leachables study = analytical study of the drug product*

*Targeted approach*

**Target 'known' compounds**
- Quantitative
- Compound-specific thresholds
- Complex drug products

*Screening approach*

*Blank Sample*

**Unexpected leachables**
- Chemical 'fingerprint'
- Semi-quantitative
- Safety Concern Threshold/ Qualification Threshold
- Not compatbile with complex drug products

# The flow of an E&L study

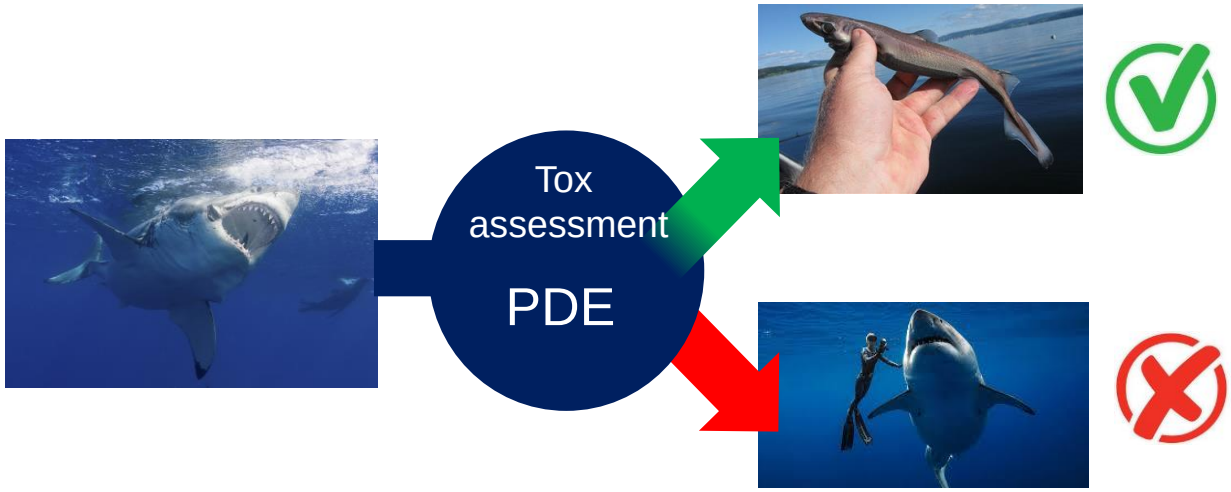
EXT → TOX → LEA → TOX

GOAL

What is the risk to the patient?

## 5 *Toxicological evaluation of leachables*

Leachables concentration > conservative treshold ➔ toxicological assessment

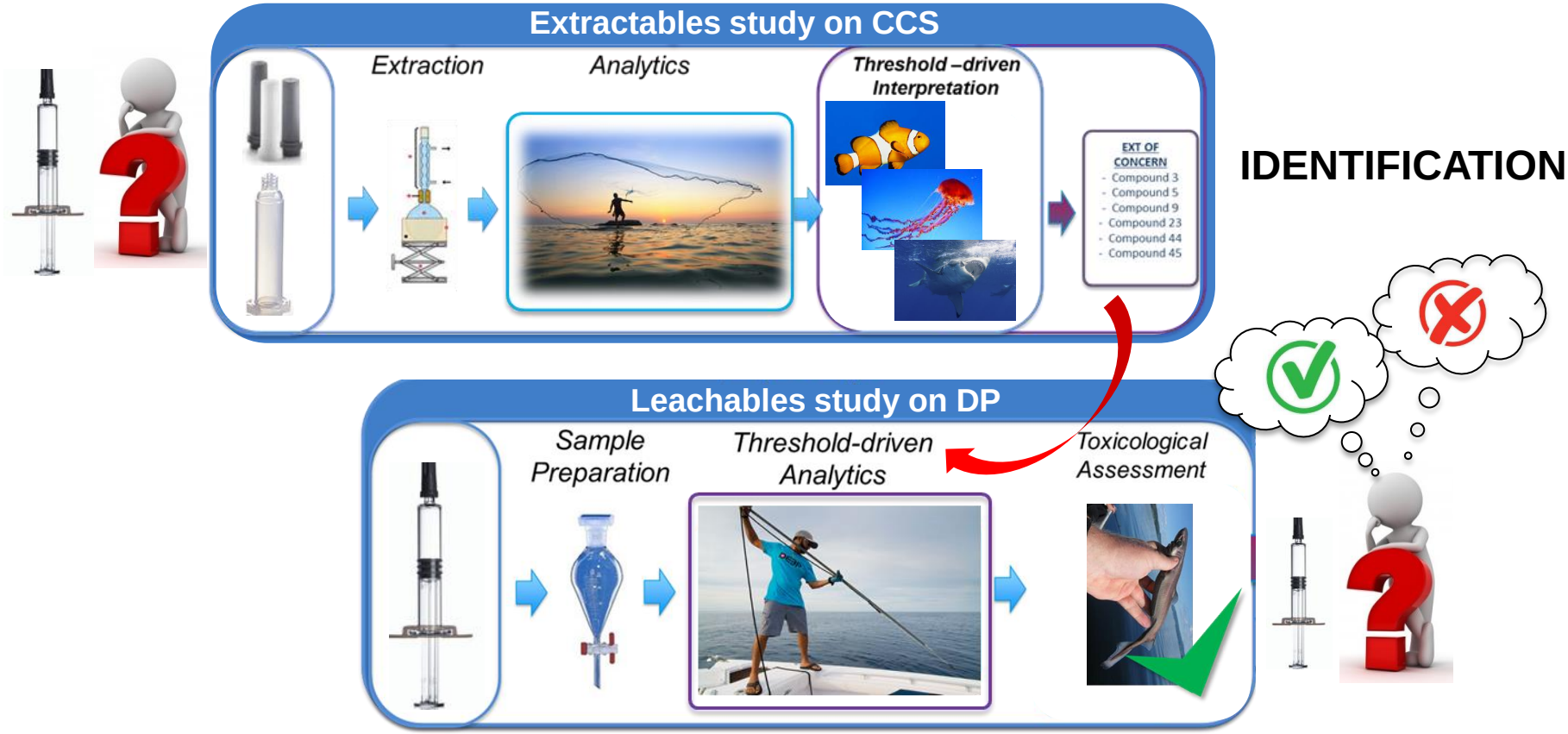



Comparison of worst-case patient exposure with Permitted Daily Exposure (PDE)
(In most cases: conservative threshold < PDE)

# The flow of an E&L study

## Analytical chemistry and toxicology in tandem

*Let's recap!*



# Regulatory Requirements

*Browsing through the Regulatory Landscape*

# Regulatory Requirements


WHAT?

**<u>What</u> kind of information should be provided?**

- US Guidances
- EU Guidelines
- Code of Federal Regulations (CFR)
- ICH

**<u>How</u> can the testing be performed?**

- Pharmacopoeias (USP, JP, EP, ...)
- Standards Organizations (ISO)
- Recommendations of Workgroups (PQRI)
- Consortia

HOW?

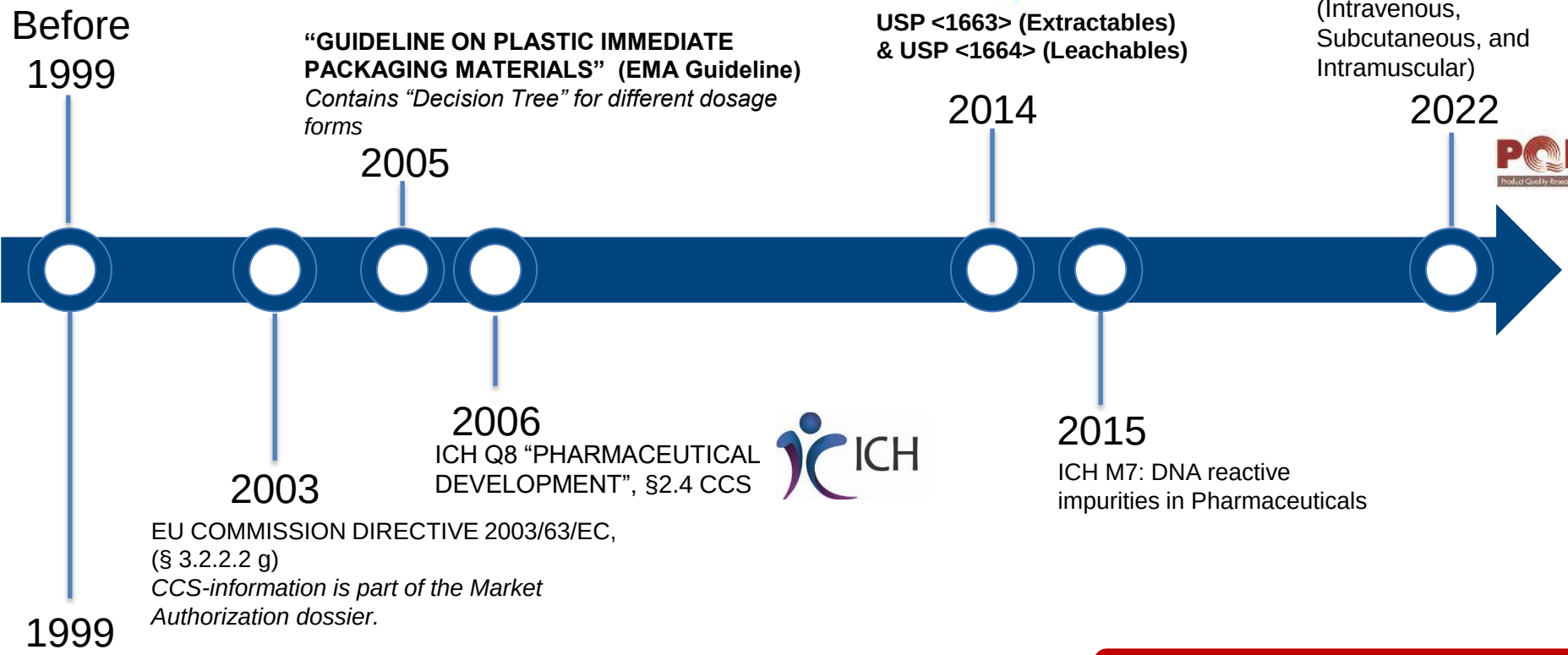
# Regulatory Requirements

WHAT **kind of information should be provided?**


**PRIMARY PACKAGING**

# Regulatory Requirements

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




**"CONTAINER/CLOSURE SYSTEMS FOR PACKAGING HUMAN DRUGS AND BIOLOGICS" (FDA Guidance for Industry)**
*Classification, based on likelihood of interaction and route of administration*

FDA

**PRIMARY PACKAGING**

*Parenterals – Non-limitative list*



*ICH=International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; PQRI=Product Quality Research Institute*

# Regulatory Requirements

**PRIMARY PACKAGING**

## Likelihood of Packaging Components – Dosage Form Interactions

**Degree of Concern Associated with the Route of Administration**

| | High | Medium | Low |
|---|---|---|---|
| **Highest** | Inhalation Aerosols and Sprays | - Injections and Injectable Suspensions<br>- Inhalation Solutions | - Sterile Powders and Powders for Injection<br>- Inhalation Powders |
| **High** | Transdermal Ointments and Patches | - Ophthalmic Solutions and Suspensions<br>- Nasal Aerosols and Sprays | - |
| **Low** | - Topical Solutions and Suspensions<br>- Topical and Lingual Aerosols<br>- Oral Suspensions and Solutions | - | - Oral Tablets and Oral (Hard and Soft Gelatin) Capsules<br>- Topical Powders<br>- Oral Powders |

Adapted from USP <1664>, items in red show revisions from original table from **FDA 1999 packaging guideline**

# Regulatory Requirements

**PRIMARY PACKAGING**

- **Likelihood of packaging components – dosage form interaction**
  **= LOW**

- **Degree of concern for route of administration**
  **= LOW**

e.g. Oral Tablets/Capsules/Powders…

**Certificate of analysis may be sufficient**

- Compendial testing
- Routine QC testing

**Likelihood of Packaging Components – Dosage Form Interactions**

**Degree of Concern Associated with the Route of Administration**

| | High | Medium | Low |
|---|---|---|---|
| Highest | Inhalation Aerosols and Sprays | - Injections and Injectable Suspensions<br>- Inhalation Solutions | - Sterile Powders and Powders for Injection<br>- Inhalation Powders |
| High | Transdermal Ointments and Patches | - Ophthalmic Solutions and Suspensions<br>- Nasal Aerosols and Sprays | - |
| Low | - Topical Solutions and Suspensions<br>- Topical and Lingual Aerosols<br>- Oral Suspensions and Solutions | - | - Oral Tablets and Oral (Hard and Soft Gelatin) Capsules<br>- Topical Powders<br>- Oral Powders |

Oral solutions/suspensions

# Regulatory Requirements

**PRIMARY PACKAGING**

- **Likelihood of packaging components – dosage form interaction**
  **= HIGH/MEDIUM**

- **Degree of concern for route of administration**
  **= HIGH**

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

**Likelihood of Packaging Components – Dosage Form Interactions**

| Degree of Concern Associated with the Route of Administration | High | Medium | Low |
|---|---|---|---|
| Highest | Inhalation Aerosols and Sprays | - Injections and Injectable Suspensions<br>- Inhalation Solutions | - Sterile Powders and Powders for Injection<br>- Inhalation Powders |
| High | Transdermal Ointments and Patches | - Ophthalmic Solutions and Suspensions<br>- Nasal Aerosols and Sprays | - |
| Low | - Topical Solutions and Suspensions<br>- Topical and Lingual Aerosols<br>- Oral Suspensions and Solutions | - | - Oral Tablets and Oral (Hard and Soft Gelatin) Capsules<br>- Topical Powders<br>- Oral Powders |

**EXTRACTABLES and/or LEACHABLES testing required**

# Regulatory Requirements

**PRIMARY PACKAGING**

- **Likelihood of packaging components – dosage form interaction**
  **= LOW**

- **Degree of concern for route of administration**
  **= HIGH**

e.g. Powders for injection or inhalation

**EXTRACTABLES and/or LEACHABLES testing required**

**Likelihood of Packaging Components – Dosage Form Interactions**

**Degree of Concern Associated with the Route of Administration**

| | High | Medium | Low |
|---|---|---|---|
| Highest | Inhalation Aerosols and Sprays | - Injections and Injectable Suspensions<br>- Inhalation Solutions | - Sterile Powders and Powders for Injection<br>- Inhalation Powders |
| High | Transdermal Ointments and Patches | - Ophthalmic Solutions and Suspensions<br>- Nasal Aerosols and Sprays | - |
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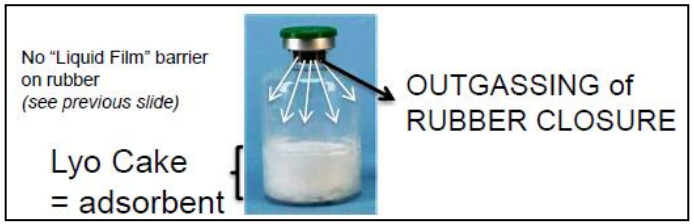
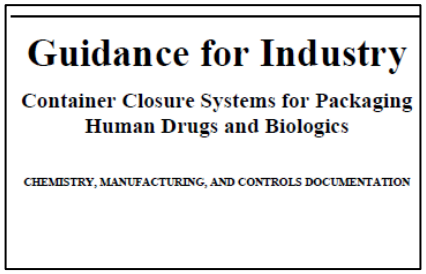
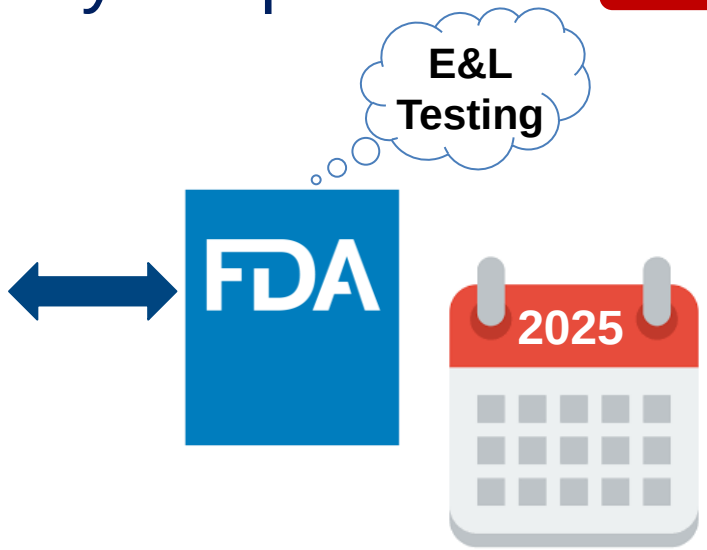


# Regulatory Requirements

**PRIMARY PACKAGING**

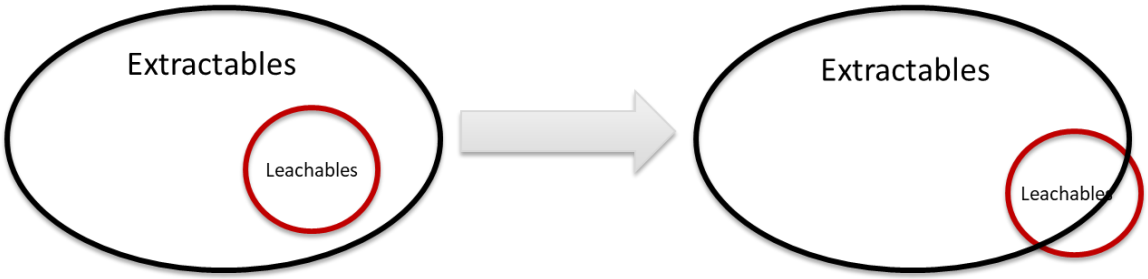
**Remarks**



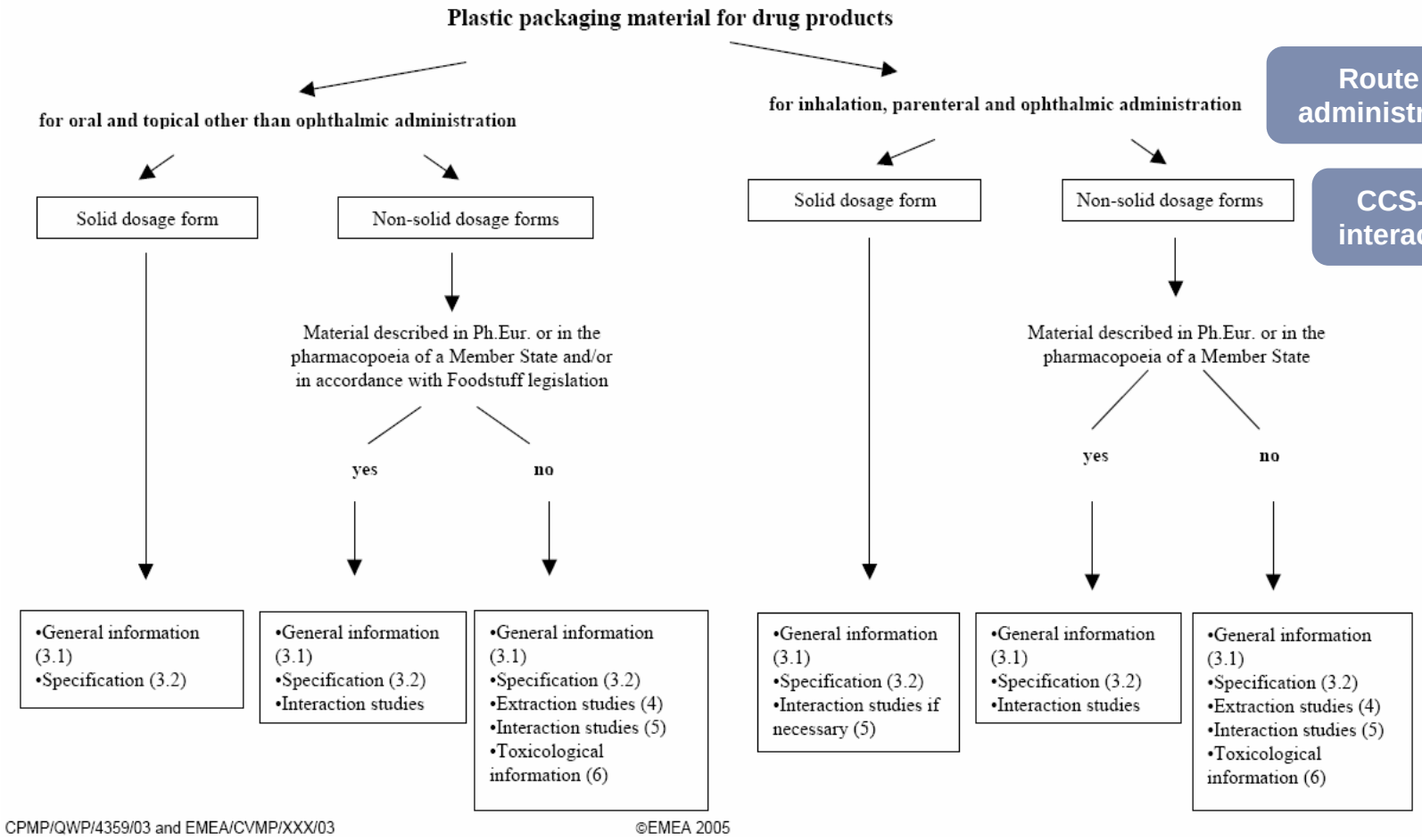

The requirements in the FDA Guidance Document "*Container Closure Systems for Packaging Human Drugs and Biologics*" of 1999 **do NOT reflect the current FDA/USP requirements for E&L testing and documentation**.

**NOT ONLY EXTRACTABLES** evaluation ➔ Consider **LEACHABLES STUDIES**



# Regulatory Requirements

**PRIMARY PACKAGING**




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

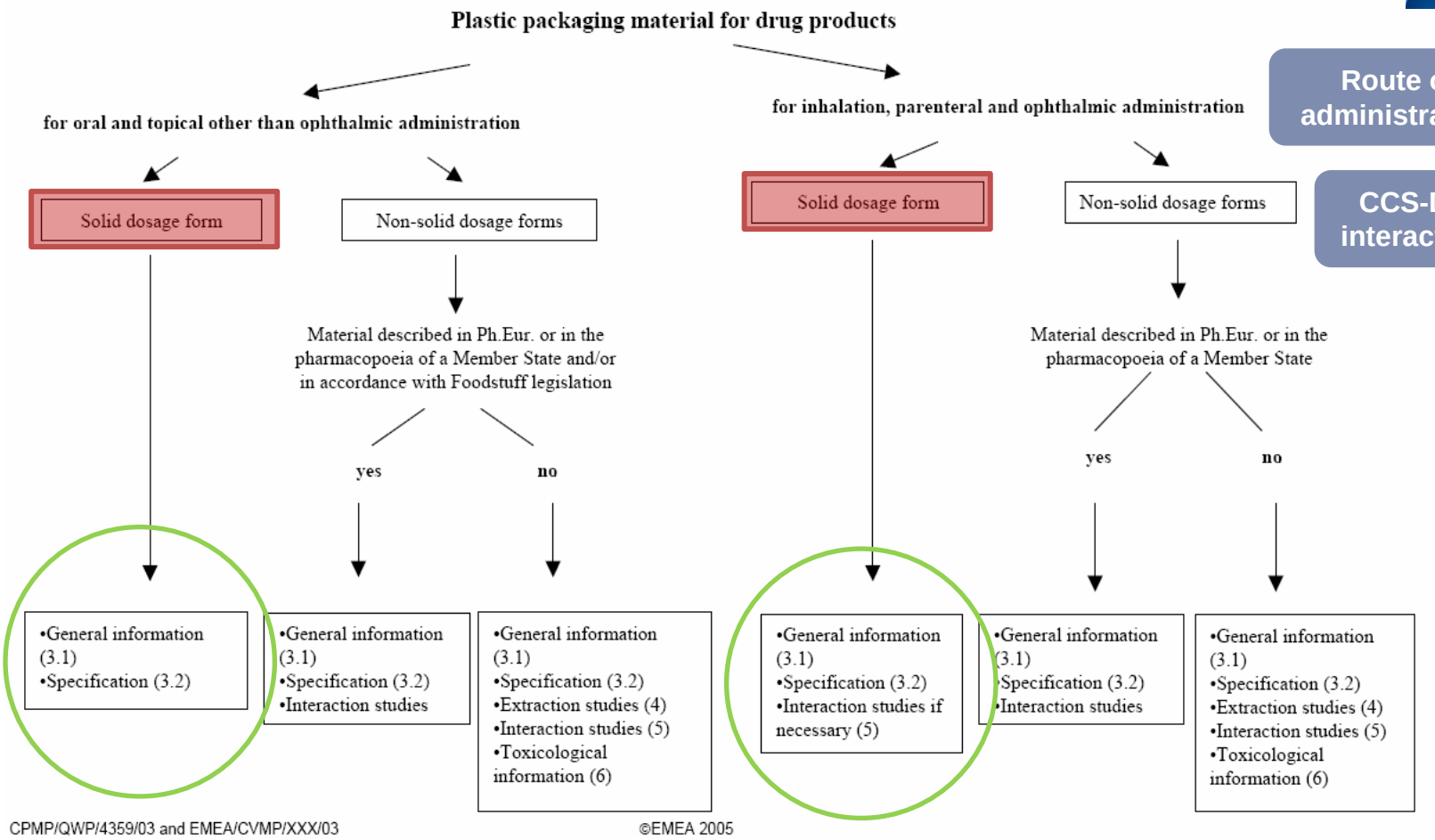
WHAT?

# Regulatory Requirements

**PRIMARY PACKAGING**

**Route of administration**

**CCS-DP interaction**




**Low risk – limited testing**

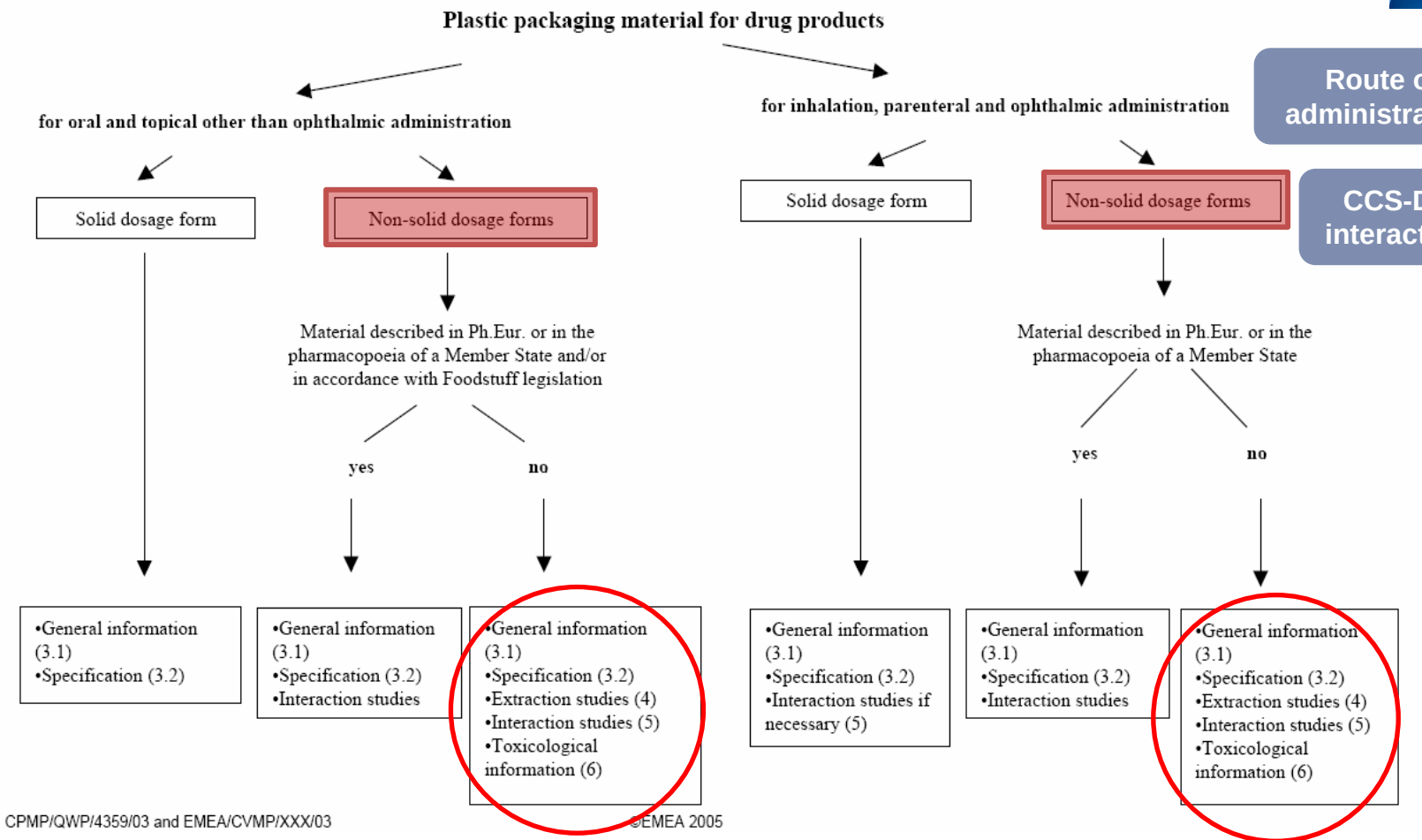
WHAT?

# Regulatory Requirements

**PRIMARY PACKAGING**

**Route of administration**

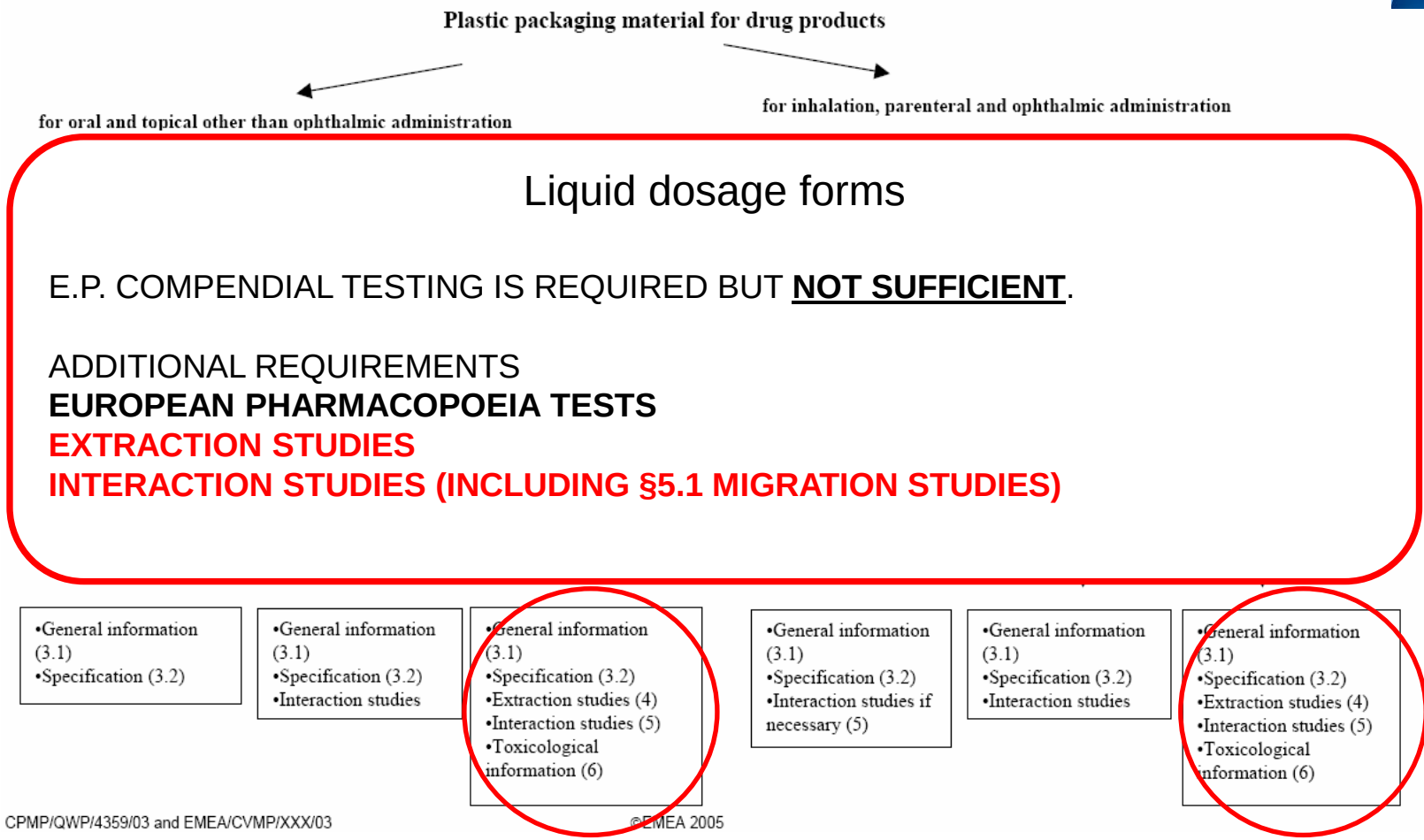
**CCS-DP interaction**




**High risk – E&L testing**

# Regulatory Requirements

**PRIMARY PACKAGING**



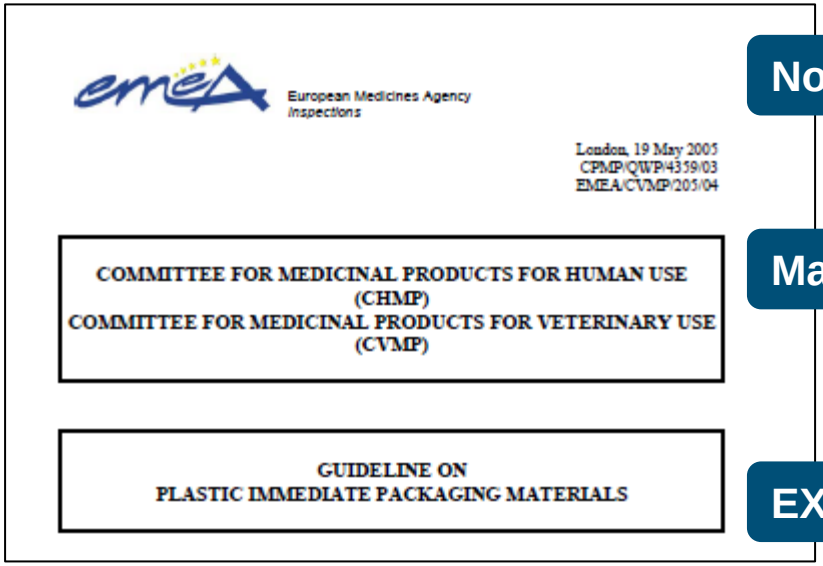

**High risk – E&L testing**

WHAT?

# Regulatory Requirements

**PRIMARY PACKAGING**

## Remarks



European Medicines Agency
Inspections

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

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

GUIDELINE ON
PLASTIC IMMEDIATE PACKAGING MATERIALS

**Not for elastomers (?)**

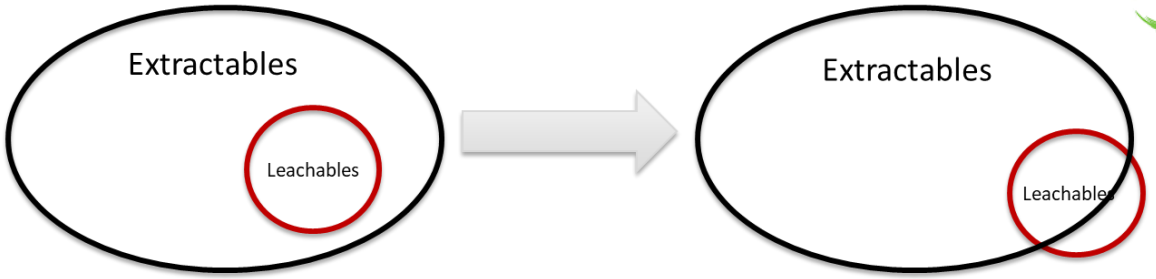
**Also for rubbers!**

**Material compliant with specifications in EP**

**Extractables testing?!** YES

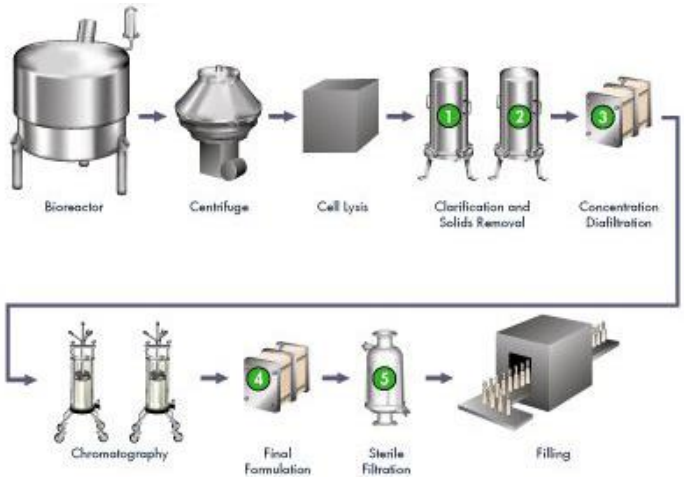
**EXT: compounds of low risk and low concentration**

**Leachables testing?!** YES



# Regulatory Requirements

WHAT **kind of information should be provided?**





**MANUFACTURING EQUIPMENT**

# Regulatory Requirements

**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. Parts of production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product ant thus present any hazard"*

**Know your process/SUS!**

- More than only impact on safety: quality, purity, strength (e.g. adsorptive behavior), reactive and additive behavior
- Prove that you have made an assessment
- Contribution of SUS to potential immuno-responses



*SUS=single-use systems*

HOW? **should the test be performed?**


# Regulatory 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

**US Pharmacopoeia (USP)**

**USP monographs** (<1000) → **MANDATORY TESTS**

<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> replaced by <665> Manufacturing Systems (targeted official date: 01 May 2026)

<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

**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)**

**Well Defined Analytical Approach**:

- Sample Preparation (Extraction Method, Time, Temperatures...)
- Analyses
  - **“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!!

HOW?

# Regulatory Requirements

**Compendial testing (USP and EP)**

**STRENGHTS**


Provide **basic information** on the **quality** of Materials

Can be used to **monitor the quality in production**

*(e.g. In combination with physical tests)*

Clear **PASS / FAIL** Criteria

Can be used in the **development** of a new material formulation

Assists in the **initial safety assessment** of a material


*(e.g. Additives may define which compounds may be encountered as leachables)*

HOW?

# Regulatory Requirements

**Compendial testing (USP and EP)**

**Sample preparation**: not always relevant!

*Relevance of WFI is as extraction vehicle?!*

*(e.g. Rinsing procedure: loss of potential impurities/ extractables)*

**LIMITATIONS**

**No detailed information** on:

- Process impurities
- Polymer and additive degradation compounds
- Oligomers
- Solvent residues
- ...

*(e.g. E.P.: Polymer additives, extractable total ...als)*

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**



**Compendial testing is not a substitute for Extractables testing**

# Regulatory Requirements

## US Pharmacopoeia (USP)

HOW?

**USP 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> Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products (targeted official date: 01 May 2026)

Separate Chapter

# Regulatory Requirements

**Applicable ICH guidelines**

- **ICH Q3D(R2)**: Elemental Impurities (2022)
- **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)

# Pitfalls in E&L submissions

Dr. Dan Mellon – FDA - YouTube

# Questions?