Connecting People, Science and Regulation

REGULATORY REQUIREMENTS

PDA WORKSHOP
EXTRACTABLES – LEACHABLES

Brussels
13-14 March, 2014

Dr. Piet Christiaens

Introduction – Regulatory Aspects

What is Extractables /Leachables testing?

Determining the Interactions between Pharmaceutical Containers and Drug Products

Can have an impact on:

- Drug Product Efficacy
- Drug Product Safety
- Drug Product Compatibility

For Primary Packaging

For Materials in (Bio)Pharma Production

Introduction – Regulatory Aspects

Extractables:

Organic and inorganic chemical entities that can be released from a pharmaceutical packaging/delivery system, packaging component, or packaging material of construction under laboratory conditions including extraction solvent, technique, stoichiometry, temperature and duration.

Consistent with the specific purpose of the extraction study, these laboratory conditions might accelerate and/or exaggerate the normal conditions of storage and use for a packaged dosage form.

Extractables themselves, and/or substances derived from extractables, have the potential to leach into a drug product formulation under normal conditions of storage and use.

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

Introduction – Regulatory Aspects

Leachables:

Organic and inorganic chemical entities that migrate from a packaging/delivery system, packaging component, or packaging material of construction into an associated drug product formulation under normal conditions of storage and use or during accelerated drug product stability studies.
Leachables are typically a <u>subset of</u> extractables or <u>are derived from</u> extractables.

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

Introduction – Regulatory Aspects

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)

Introduction – Regulatory Aspects

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.

Introduction – Regulatory Aspects

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

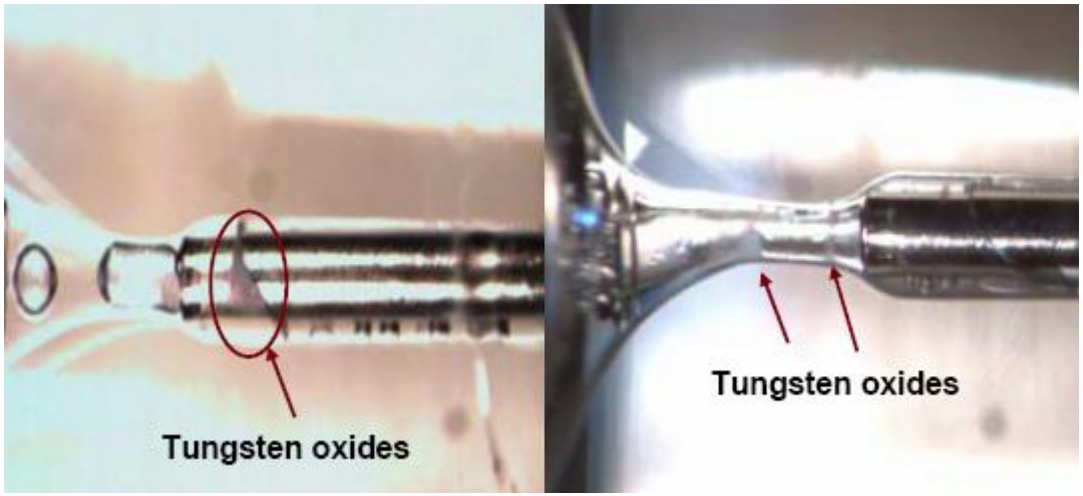
EPREX

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

- Apparently, the leachables (one or more) showed 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 solved the problem

Introduction – Regulatory Aspects

- **Tylanol** recall because of Nauseating “Moldy” Odor
- **Lipitor** recall due to “Musty” Odor emanating from the bottles
- **Glumetza** recall Blamed on treated wooden Pallets
- **Protein degradation** caused by Tungsten in Pre-Filled Syringes



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- **Release of (Halogenated) Rubber Oligomers,** causing interaction with the API
- **BPA (Endocrine Disruptor)** release from PC containers
- **PolyNuclear Aromatics (PNA's, carcinogenic)** released from rubbers (Carbon black)
- **N-Nitrosamines** leaching from rubbers
- **DEHP (Endocrine Disruptor) leaching** from PVC containers (I.V.)

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- **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
- **Protein aggregation/degradation** caused by Tungsten in Pre-Filled Syringes
- **Barium and Aluminum,** released from glass, to form particles
- ....

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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)

Introduction – Regulatory Aspects

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!

Introduction – Regulatory Aspects

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

2006: "PQRI Safety Thresholds and Best Practices for E/L in OINDP's"

- *First technical recommendations for E/L-studies!*
- *Threshold concept!!*

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- *Classification, based on likelihood of interaction and route of administration*

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- *"Decision Tree" what information to provide for different dosage forms*

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

- *Classification, based on **likelihood of interaction** and **route of administration***

Table 1
Examples of Packaging Concerns for Common Classes of Drug Products

Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	**Medium**	**Low**
Highest	Inhalation Aerosols and Solutions; Injections and Injectable Suspensions[a]	Sterile Powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules

“CONTAINER/CLOSURE SYSTEMS FOR PACKAGING HUMAN DRUGS AND BIOLOGICS” (FDA-Guidance for Industry)

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

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High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules

LIKELIHOOD OF INTERACTION = LOW

Packaging Component - Dosage Form

DEGREE OF CONCERN

FOR **ROUTE OF ADMINISTRATION = LOW**

THEN: CERTIFICATE OF ANALYSIS

- COMPENDIAL testing
- ROUTINE QC testing

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

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

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LIKELIHOOD OF INTERACTION = HIGH

Packaging Component - Dosage Form

DEGREE OF CONCERN

FOR **ROUTE OF ADMINISTRATION = HIGH**

THEN: 1. CERTIFICATE OF ANALYSIS

- COMPENDIAL testing
- ROUTINE QC testing

2. ADDITIONAL EXTRACTABLES/LEACHABLES DATA

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

TYPICAL COMPENDIAL TESTING: USP 37

<381> Elastomeric Closures for Injections

<661> Containers (under revision!!)

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

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

REVISION OF THE USP <661> - in progress

<661.1> Plastic Material of Construction

<661.2> Plastic Packaging Systems for Pharmaceutical Use

<661.3> Manufacturing Systems

<661.4> Devices

As these Chapters are still under development, no further comments will be given – in this Workshop - on their content

REVISION OF THE USP <661> - in progress

<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

USP Monographs higher than USP <1000>: More Consultancy, Not Binding

Introduction – Regulatory Aspects

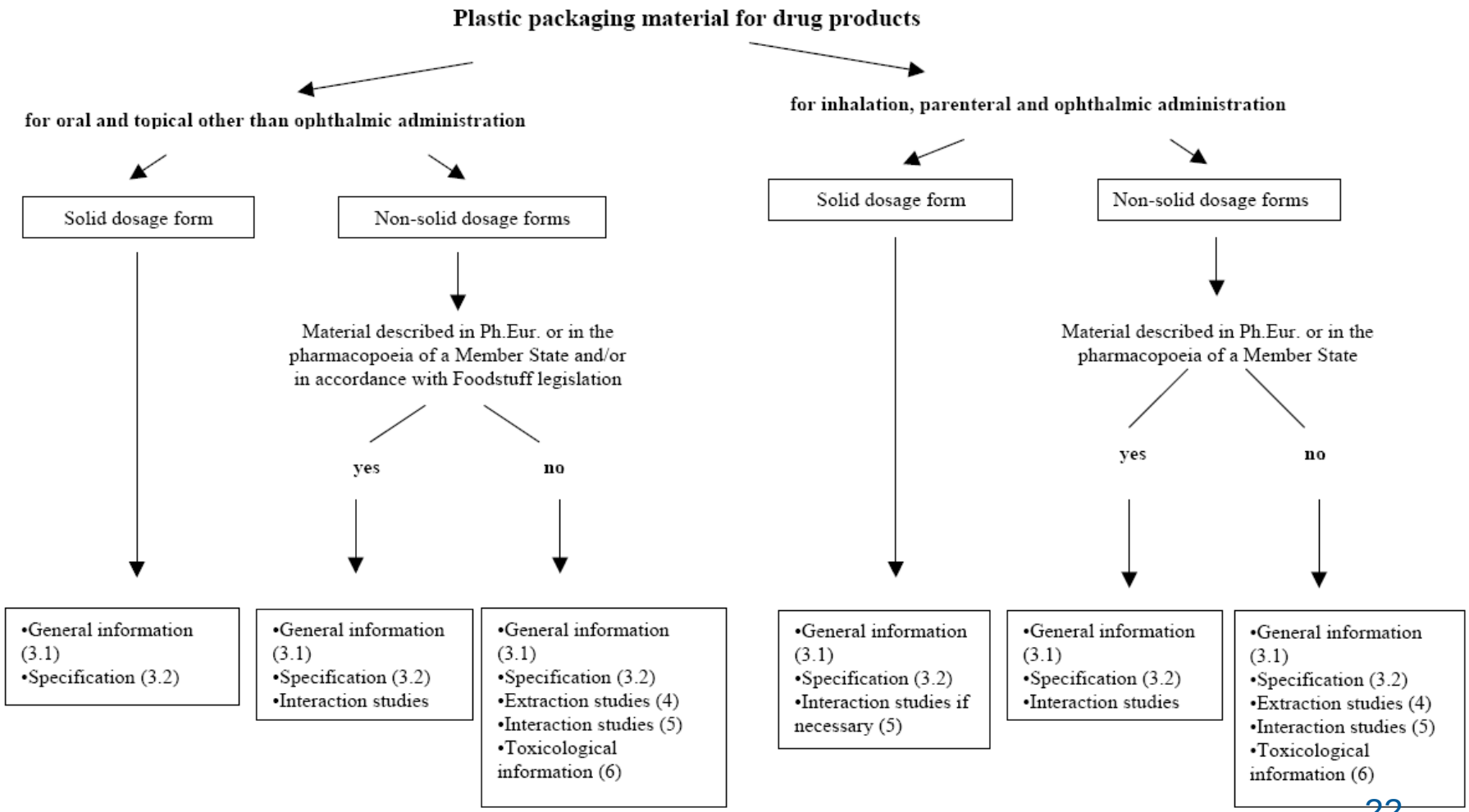
REMARK:

THE REQUIREMENTS FOR DOCUMENTATION, SPECIFIED IN THE *1999 CONTAINER/CLOSURE GUIDANCE* DOCUMENT **DO NOT REFLECT THE ACTUAL POSITION OF THE FDA** WITH REGARD TO THE TESTING AND DOCUMENTATION NEEDED FOR THE CCS

MARKOVIC (FDA):
FOCUS ON LEACHABLE TESTING!

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

- *"**Decision Tree**" what information to provide for different dosage forms*



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

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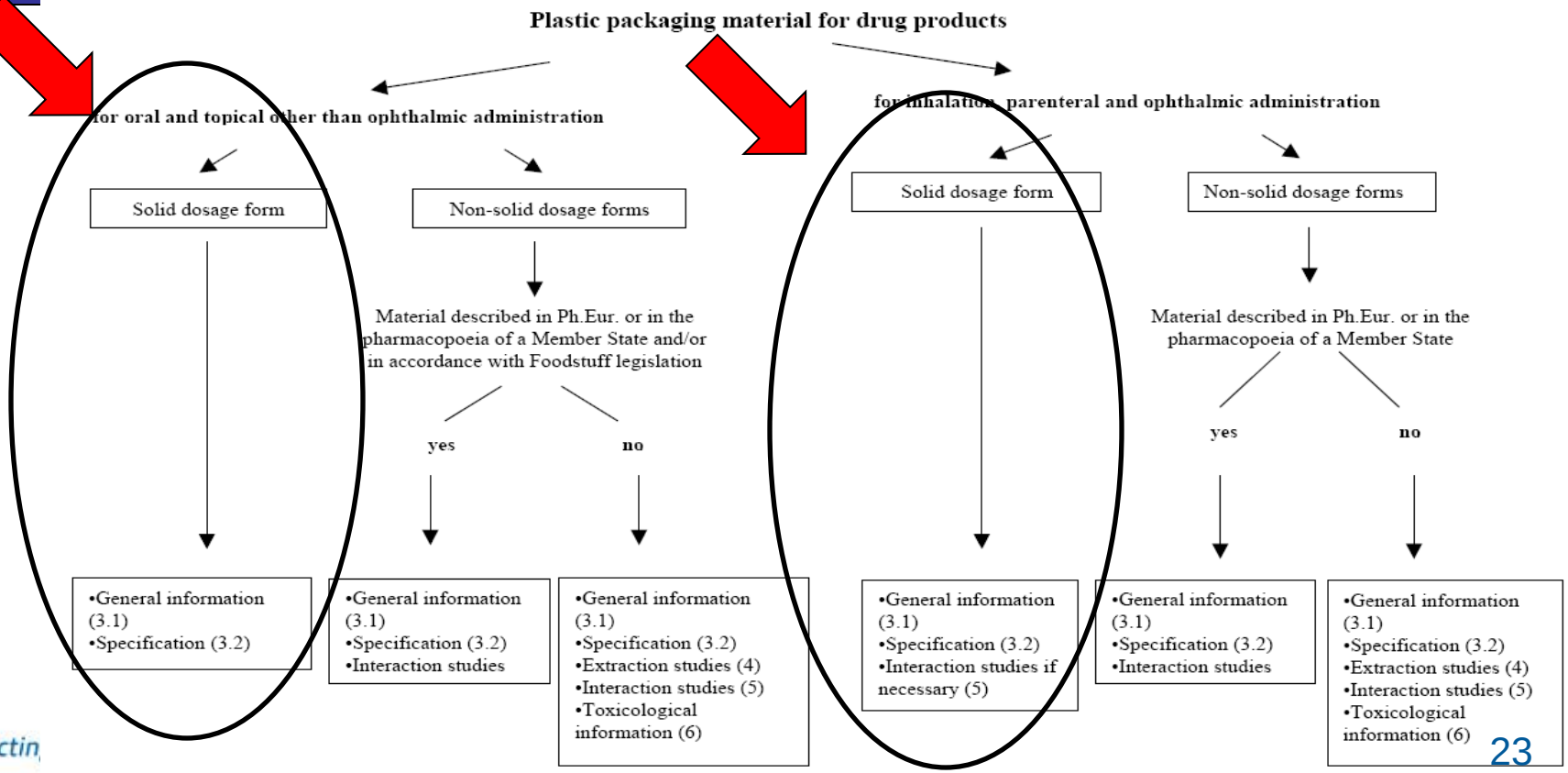
2005: "GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS" (EMEA Guideline)

SOLID DOSAGE FORMS:

LIKELIHOOD OF INTERACTION IS LOW: LOW requirements



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

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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**

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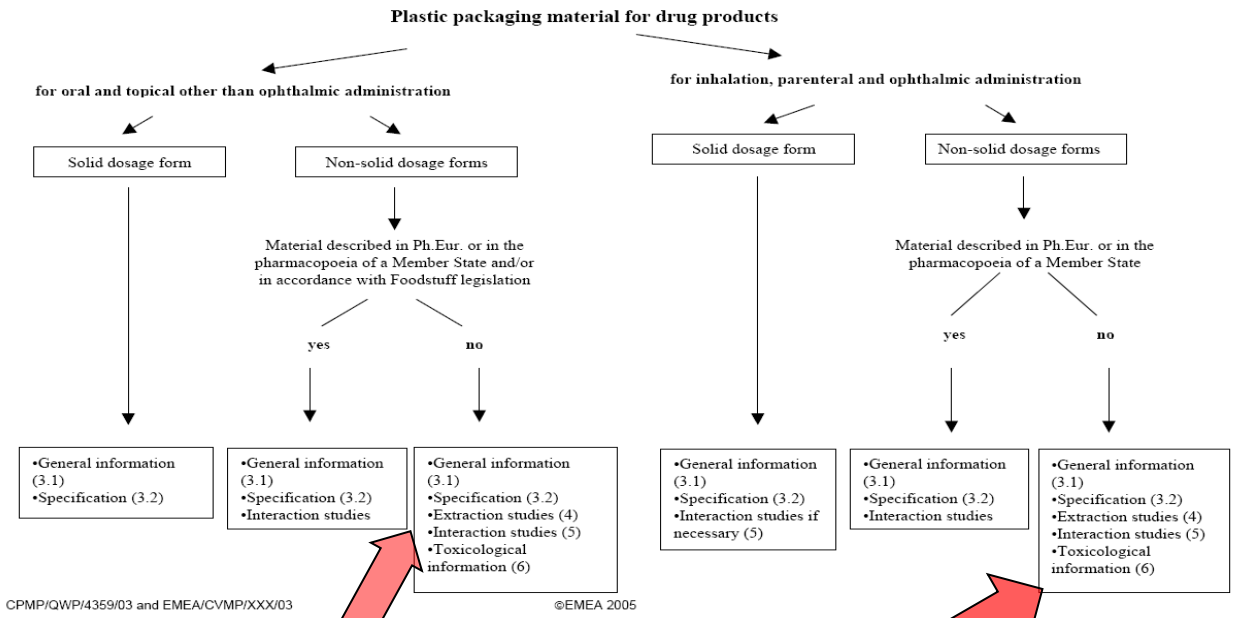
European Pharmacopoeia : 3.2 *Containers*

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

"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

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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)

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APPLICABLE ICH Guidances:

- **ICH Q6B**: test proceudres 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**: Pahrmaceutical Development (2006)
- **ICH Q9**: Quality Riks Management (2006)
- **ICH Q10**: Pharmaceutical Quality Systems (2008)

NON-APPLICABLE ICH Guidances:

- **ICH Q3A**: Chemical Impurities in New Drug Substances
- **ICH Q3B**: Impurities in New Drug Products
- **ICH Q3C**: Impurities: Residual Solvents

Thank you!