Practical considerations during development/ selection of packaging system

Guidance documents

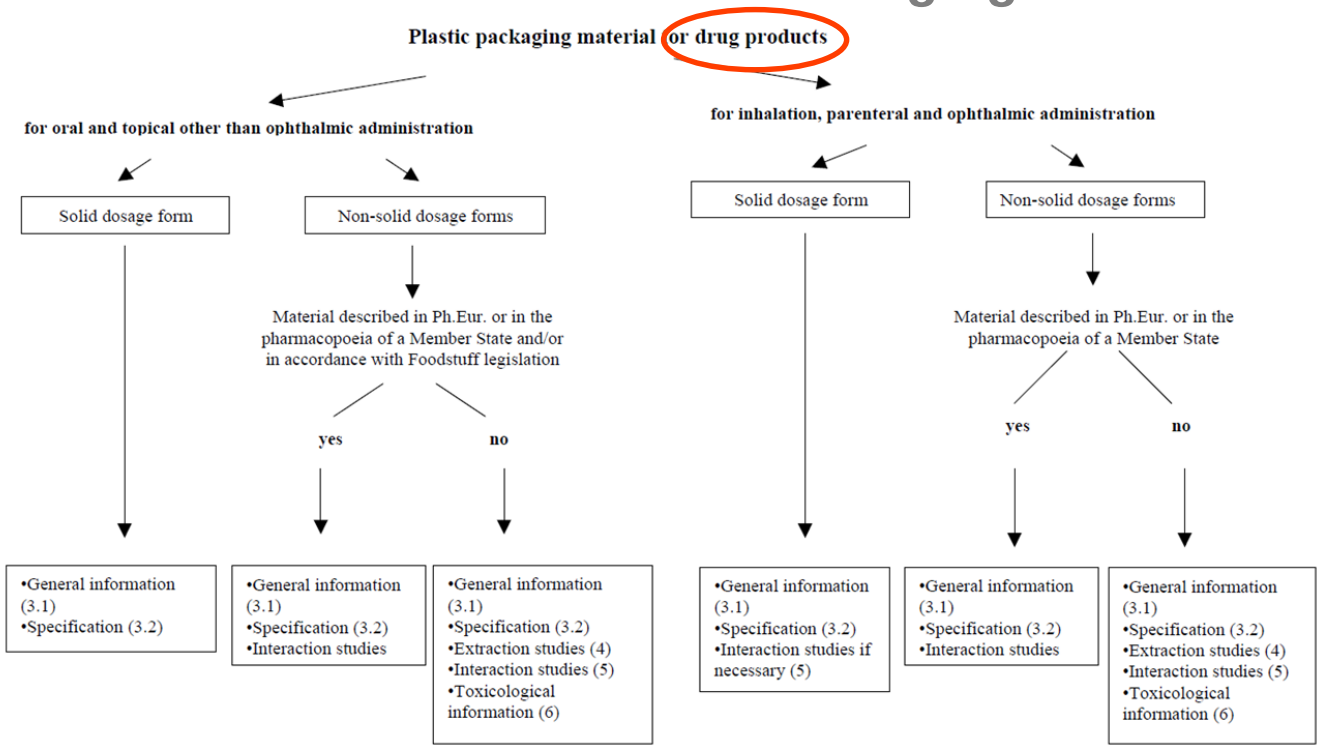
Guidance documents

FDA Guideline Container Closure Systems for Packaging Human Drugs and Biologics

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 Suspension	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

Guidance documents

EU Guideline on Plastic Immediate Packaging Materials



Guidance documents

EU Guideline on Plastic Immediate Packaging Materials

3 Data to be submitted

3.1 General information:

- For all plastic materials that are used as immediate packaging material for active substances or medicinal products
  - the chemical name of the material;
  - the chemical name(s) of any monomer used;
  - have to be indicated.
  - …..

Guidance documents

EU Guideline on Plastic Immediate Packaging Materials

3 Data to be submitted

3.1 General information:

- For plastic materials used in packaging of non-solid medicinal products:
  - the name of material supplier, if the medicinal product is intended for inhalation, parenteral or ophthalmic administration

Guidance documents

EU Guideline on Plastic Immediate Packaging Materials

3 Data to be submitted

3.1 General information:

- For plastic materials used in packaging of non-solid medicinal products:
  - the **complete qualitative composition of the plastic material** as listed above, if the medicinal product is intended for inhalation, parenteral or ophthalmic administration, and the material is neither decribed in the European Pharmacopoeia, nor in the pharmacopoeia of a Member State or, additionally, in cases where the monograph authorises the use of several additives from which the manufacturer may choose one or several in defined limits…….

Practical considerations during development/ selection of packaging system

Development aspects

Development aspects

Compatibility assessment

- Testing methods
  - Stress testing, e.g. multiple autoclaving cycles in contact with rubber component material; evaluation of product properties, that indicate incompatibility (e.g. pH-value, content of stabilizers, degradation products)
  - Product storage at elevated temperatures (up to 60 oder 70 °C); evaluation of product properties, that indicate incompatibilities over time

Development aspects

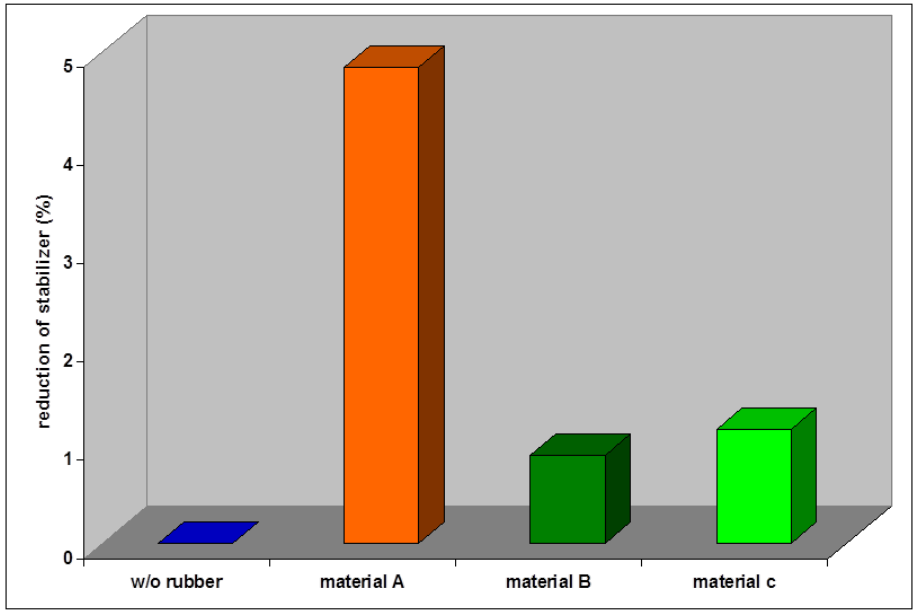
Compatibility assessment

- Rubber material example

Test set-up:

60 minutes autoclaving at 121° C

Measurement of stabilizer



Development aspects

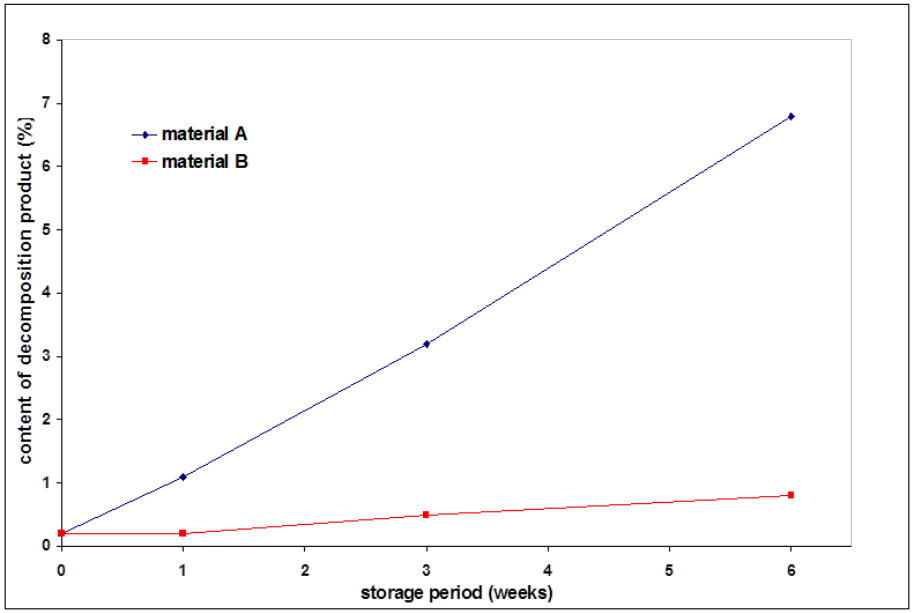
Compatibility assessment

- Rubber material example

Test set-up:

Storage at 40 ° C

Quantification of degradation product



Development aspects

Extractables & Leachables

- Extractables
  - … are compounds that can be extracted from elastomeric, plastic components or coatings of the container closure system when in the presence of an appropriate solvent (FDA-Guidance for Industry: MDI and DPI Drug Products)

Development aspects

Extractables & Leachables

- Extractables testing
  - Identification of potential leachables
    - Toxicological assessment of extractables considering the use of the product (route of administration, frequency of use, patient population, etc.)
    - Select analytical targets for establishment of quantitative and specific methods for leachables testing
    - Specify the analytical threshold for relevant targets
  - Definition/ set-up of leachables study

Development aspects

Extractables & Leachables

- Leachables
  - … are compounds that can leach from elastomeric, plastic components or coatings of the container closure system as a result of direct contact with the formulation .... (FDA-Guidance for Industry: MDI and DPI Drug Products)

Development aspects

Extractables & Leachables

- Leachables testing
  - Selection of analytical targets after extractables study and toxicological assessment
  - Understand the quantities of leachables over product shelf-life to enable toxicological assessment of the drug product - leachables can be regarded as a special type of impurities

Development aspects

Light transmission

- Product example (X-Ray contrast medium)

The product is light-sensitive - is there any light-protection integrated into the container closure system?

Development aspects

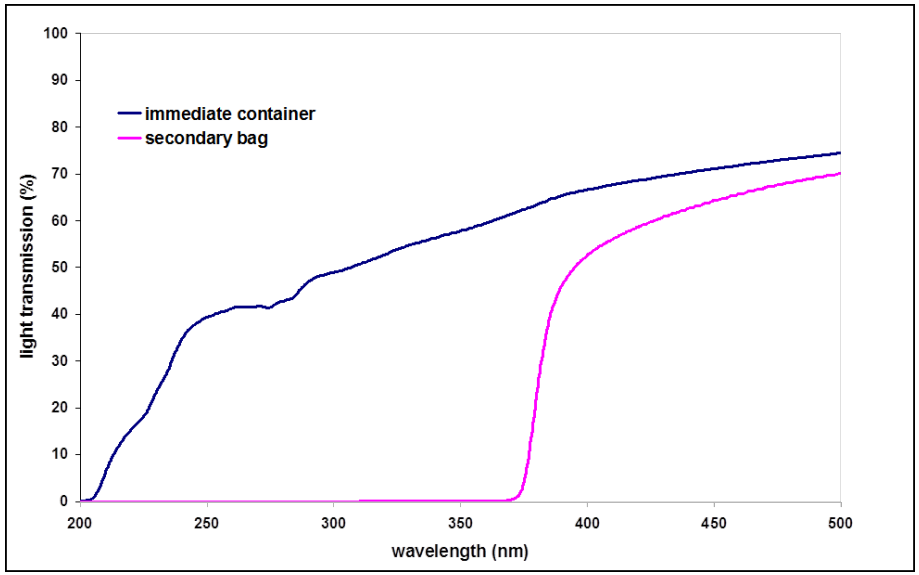
Light transmission

- Product example (X-Ray contrast medium)

Test set-up:

Place film in UV-photometer

Scan from 800 to 200 nm



↳ light protection is integrated into secondary container

Development aspects

Permeability

- Regulatory requirements (for semi-permeable containers)
  - For semi-permeable containers ICH-guideline Q1A (Stability Testing of New Drug Substances and Products) requires specific storage conditions for stability testing.
  - The conditions for accelerated testing are 40 □ 2°C at not more than (NMT) 25%RH.
  - 6 months data from these conditions are required for submission.

Development aspects

Permeability

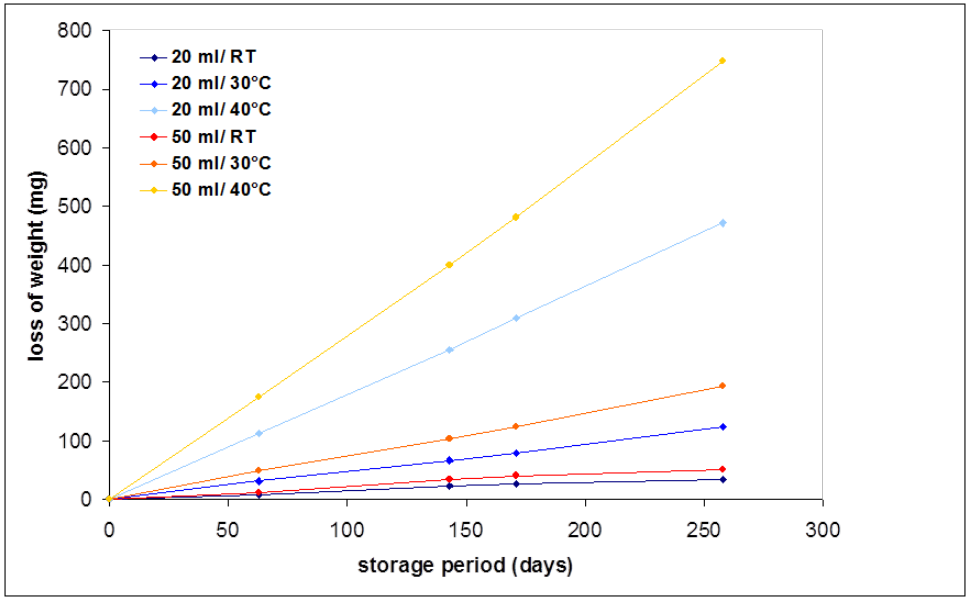
- Vapor loss study

Test set-up:

HDPE bottles

Ambient humidity

Weight control



Development aspects

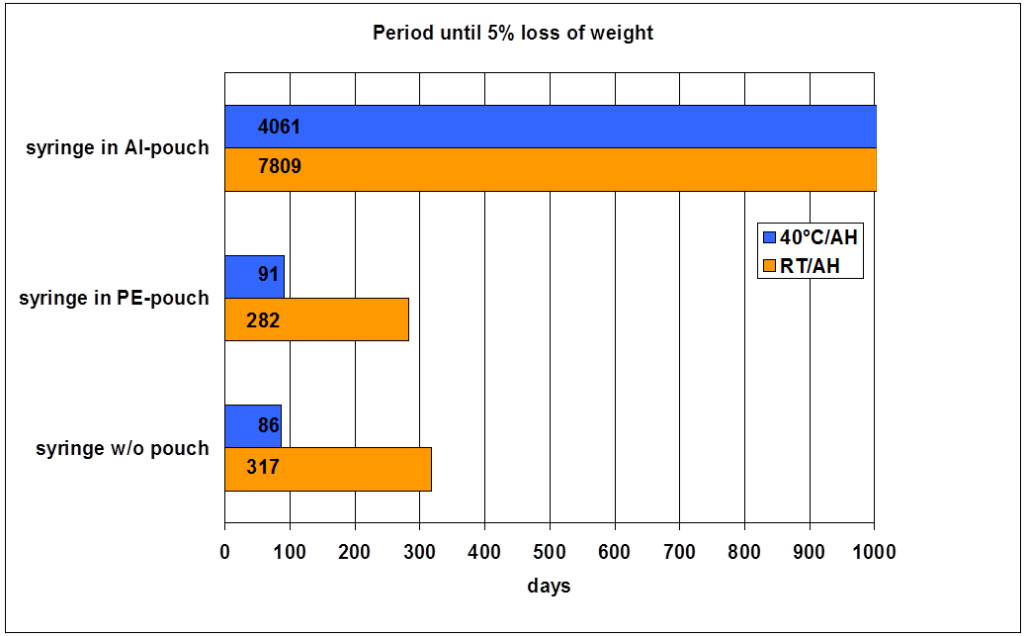
Permeability

- Case study – plastic syringe in aluminum pouch

Test set-up:

Ambient humidity

Weight control



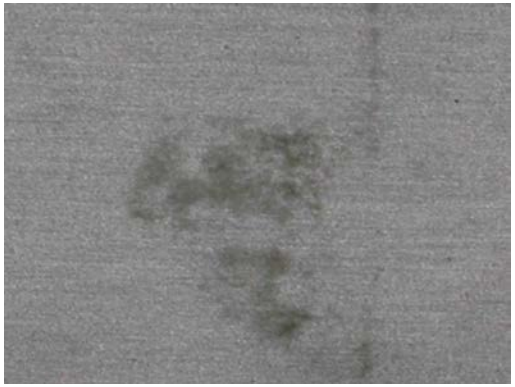
Development aspects

Permeability

- Case study – plastic syringe in aluminum pouch

The issue:

Mold on label, mold on aluminum foil



Development aspects

Modification of materials

- Surface coatings on packaging component are used to reduce the amount of leachables by “sealing” the packaging material.
- Coatings are feasible for glass, rubber and plastics.
- Examples for coatings are:
  - Silicone oil on glass and plastics
  - SiOx on glass
  - Teflon on rubber

Development aspects

Container closure integrity testing (CCIT)

- Definition - Container Closure Integrity
  - Historcial definition (as of 1993): The ability of the container-closure system to maintain the integrity of its microbial barrier, and, hence, the sterility of a drug product throughout its shelf life.
  - Current defnition (USP <1207>): Container Closure Integrity (CCI) is proven, when a package meets the maximum allowable leakage limit required to ensure product quality attributes of sterility and physicochemical stability through expiry.

Development aspects

Container closure integrity testing (CCIT)

- Why is leakage critical?
  - Risks microbial ingress
    - ↳sterility loss
  - Loss of critical headspace gases/ intrusion of normal atmosphere
    - ↳instability
  - Loss of headspace vacuum
    - ↳instability
    - ↳product access difficulty

Development aspects

Container closure integrity testing (CCIT)

- The ideal CCI test
  - Non-destructive
  - Reliable (covering all potential defects)
  - 100% inspection in-line
  - Feasible for stability testing

Development aspects

Container closure integrity testing (CCIT)

- Regulatory Background - USP
  - ⟨1207⟩ Package Integrity Evaluation - Sterile Products
    - ⟨1207.1⟩ Package Integrity Testing in the Product Life Cycle - Test Method Selection and Validation
    - ⟨1207.2⟩ Package Integrity Leak Test Technologies
    - ⟨1207.3⟩ Package Seal Quality Test Technologies

Development aspects

Container closure integrity testing (CCIT)

- Regulatory Background - USP
  - ⟨1207⟩ Package Integrity Evaluation - Sterile Products
    - Definitions
      - Package Integrity = Container Closure Integrity (CCI): the absence of package leakage greater than the product package **maximum allowable leakage limit (MALL)**
    - Integral package
    - Leak Tests (CCIT)
    - Seal Quality Tests (SQT)

Development aspects

Container closure integrity testing (CCIT)

- Regulatory Background - USP
  - ⟨1207.1⟩ Package Integrity Testing in the Product Life Cycle - Test Method Selection and Validation
    - Product life cycle testing
      - Product package development and validation
      - Routine manufacturing
      - Marketed product stability

Development aspects

Container closure integrity testing (CCIT)

- Regulatory Background - USP
  - ⟨1207.1⟩ Package Integrity Testing in the Product Life Cycle - Test Method Selection and Validation
    - Leak test selection criteria
      - Package content, design, and materials of construction
      - Product package maximum allowable leakage limit
      - Deterministic vs. probabilistic methods
      - Limit of detection (LOD) and largest leak detection capability
      - Method outcome
      - Quantitative vs. qualitative / Nondestructive vs. destructive

Development aspects

Container closure integrity testing (CCIT)

- Regulatory Background - USP
  - ⟨1207.2⟩ Package Integrity Leak Test Technologies

Deterministic methods	Probabilistic methods
Reproducible	Not reproducible
Sensitive	Insensitive
Highly instrumental	Little or no instrumentation used
Quantitative test result outcome	Qualitative, interpretive results
Minimal test sample preparation or manipulation	Considerable test sample preparation and/or manipulation
Risk of error - LOW	**Risk of error - HIGH**

Development aspects

Container closure integrity testing (CCIT)

- Regulatory Background - USP
  - ⟨1207.2⟩ Package Integrity Leak Test Technologies

Deterministic methods	Probabilistic methods
Electrical conductivity and capacitance test (HVLD)	Microbial challenge by immersion
Laser based headspace analysis	Tracer liquid tests (e.g. dye)
Mass extraction	Bubble tests
Pressure decay	Tracer gas (sniffer mode)
Tracer gas (vacuum mode)	
Vacuum decay	

Development aspects

Container closure integrity testing (CCIT)

- Regulatory Background - USP
  - ⟨1207.3⟩ Package Seal Quality Test Technologies
    - Seal quality test methods
      - properly characterize and monitor seal quality
      - ensure consistency of package assembly
      - methods (not binding!)
        - » Airborne ultrasound
        - » Cap application/ removal torque
        - » Package burst test
        - » Package seal strength (peel) test
        - » Residual seal force

Development aspects

Shipping assessment

- Pharmaceutical products are more and more manufactured at one site and distributed globally, esp. complex products like biologicals or prefilled syringes
- Shipping of pharmaceutical products is done with standard equipment already established for global cargo shipment
- The relevant regulations are not pharma specific but specific with regard to shipping safety (e.g. IATA air shipment regulations)
- Critical aspects for pharma products are temperature, air pressure and mechanical stress

Development aspects

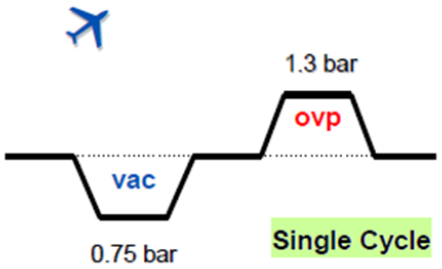
Shipping assessment

- Shipping conditions - temperature
  - Freezing of liquid products may lead to increased brittlenes and thus breakage of the container
  - Freezing/ thawing of liquids may impact integrity due to plunger movement in prefilled syringes
  - Materials are not generally suitable for shipping conditions – e.g. pharmaceutical standard rubber materials have glass transition temperature around -55 to 60 °C and are thus brittle at some shipping temperature

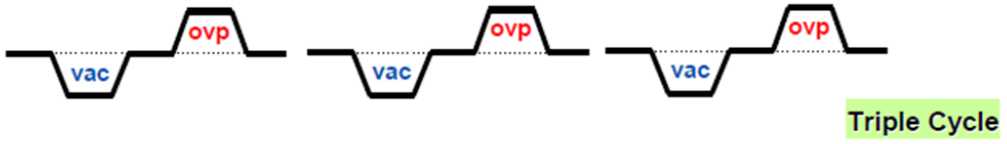
Development aspects

Shipping assessment

- Shipping conditions - pressure



Pressurization during air shipment: Reduction of cabin pressure down to approx. 800 mbar – even in the cargo cabin



Source: Post, E., Container Closure Integrity Test (CCIT), PDA Europe Conference, 07/2013