PDA Training Container Closure Systems

Development of Container Closure Systems

Content

- Set-up of target profile
- Packaging materials
- Modification of materials
- Extractables & Leachables (E&L) testing
- Permeability
- Light transmission
- Processability
- Functional testing
- Container closure integrity (CCI)
- Shipping assessment
- Combination products

Set-up of target profile

Formulation

- Solid, semi-solid, liquid
- Lyophilisate for reconstitution
- Patient related dosing (e.g. body weight or surface)
- Concentration of active ingredient
- Pharmacological activity of active ingredient
- Content of volatile components (e.g. alcohols)
- Preservatives and/or other critical excipients

Route of administration and application

- Oral, topical, parenteral (sc, im, iv – injection/infusion), others
- Use of application aids for product preparation (infusion sets, spikes, disposable syringes)
- Application with injectors (mechanical, automated)
  - Injection speed
  - Needle size
  - Resistance against mechanical stress (e.g. pressure resistance)

User profile

- Application by professionals (nurses, physician) or by patients
  - Fool proof system vs. complex equipment
  - Known system vs. need for intense training
- Age and/or impairment of patients
  - Size of systems
  - Ease of use, easy to understand
  - Safety, hygiene

Set-up of target profile

- Influence of humidity
  - Barrier films
  - Alu-pouch for plastic infusion bags
- Influence of light
  - Light resistant (colored) glass
  - Light protection via secondary container
- Influence of gases (O_2, NO_x, CO_2)
- Other environmental influences on product quality
  - Temperature controlled storage and shipment
  - -70°C storage

Marketing area

- USA, EU, Japan, others (consideration of climatic zones)
- Different pharmacopoeial requirements
- Cultural, political and social specifics
    - Japan: „We are a zero fault country”

Processability

- Aseptic processing
- Lyophilization
- Sterilization (e.g. for plastic packaging components)
- Processability on existing equipment
- Development of new process technology

Other Aspects

- Stability target (t and T)
- Child resistant packaging/ Senior friendly packaging
- Supply safety of basic materials, components or packaging solutions
- Anticounterfeiting
- ……

Packaging materials

Materials used for containers for Parenterals are

- Glass: type I and II, colorless and amber
- Plastics: PE, PP, COC, COP, PVC
- Rubber: Bromobutyl-, Chlorobutyl-, Butylrubber, synthetic Polyisoprene

Plastic/Rubber challenges

- Leachables from plastics are mostly organic components of the material
  - Monomers, oligomers of basic polymer
  - Curing system (for rubber components)
  - Additives: UV-stabilizer, plasticizer, antioxidants
  - Inorganic filler or colorants
- Plastic components are less heat resistant compared to glass
  - Depyrogenization by heating up to 300°C impossible
- Container size, fill volume and storage conditions are influencing the amount of leachables

Glass challenges

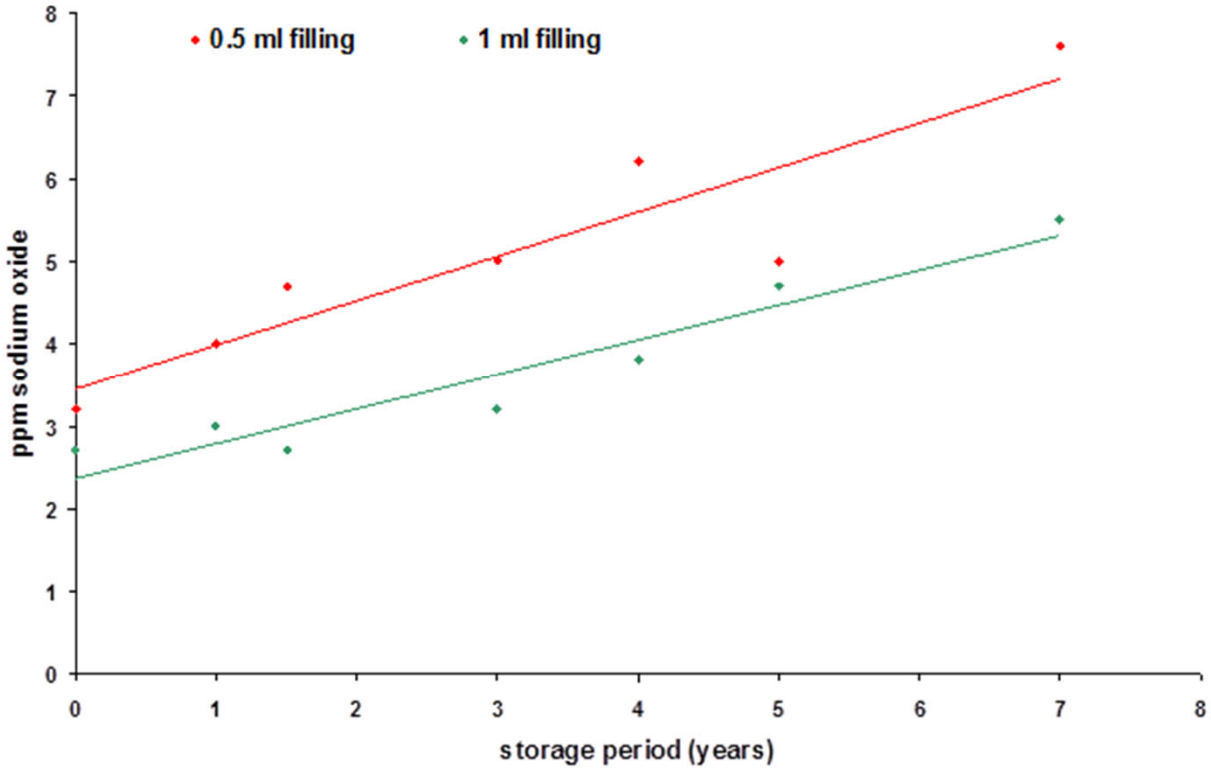
- Leachables from glass are inorganic components of the glass bulk material
  - major extractables: Si and Na
  - minor extractables: K, B, Ca, Al
  - trace extractables: Fe (in colored glass)
- The composition of the filling impacts the extent of extraction, especially:
  - pH, type of buffer system, surfactants, complexing agents
- Container size, fill volume and storage conditions are influencing the amount of leachables
- Manufacturing processes (e.g. sterilization time and temperature) impact the extent of leaching

Glass challenges: Influence of storage time on Alkali-release

1 ml ampoules filled with WFI

Ampoules were autoclaved for 20 minutes at 121° C

Na_2O was measured by flame photometry



source: Dr. J. Pfeifer, Schott-Rohrglas GmbH, DPhG Fachgruppentagung Analytik 2003

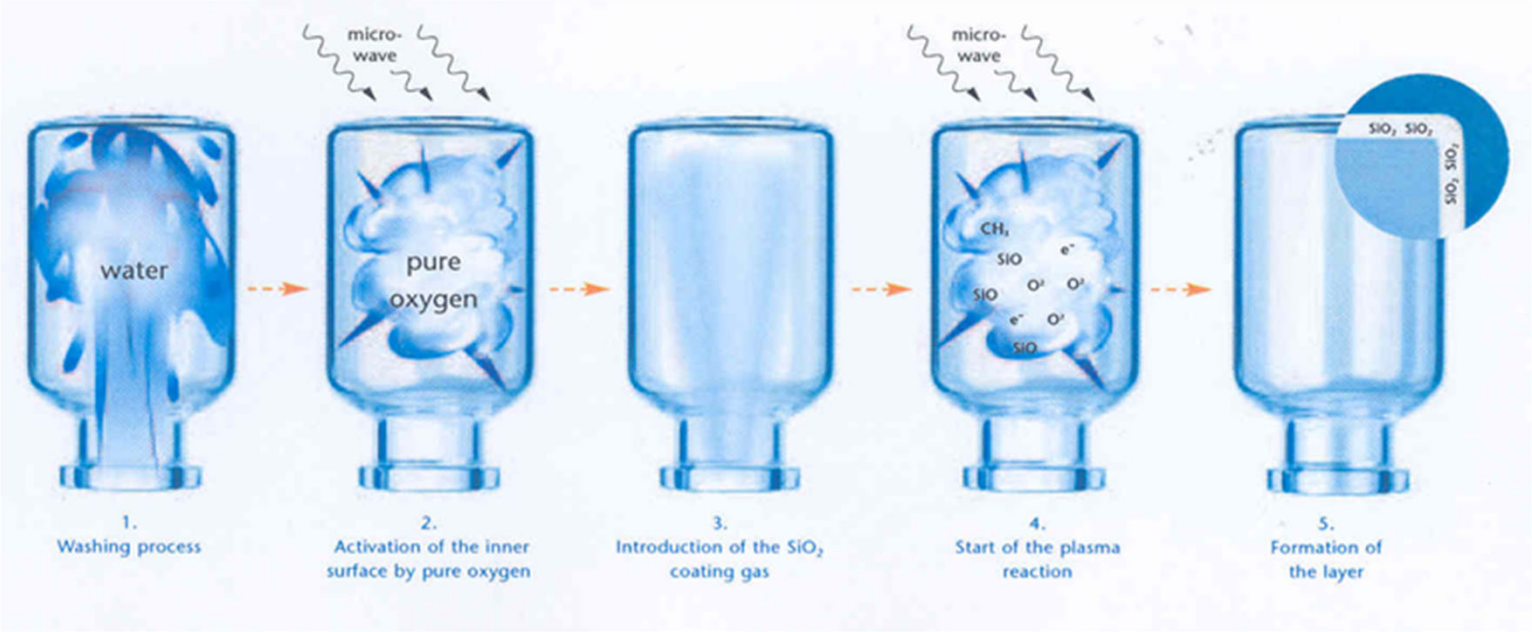
Requirements for packaging solutions for Biologics

- Containers or container components needs to be able to be handled in aseptic processes
  - Sterilized/ depyrogenized in the process (e.g. glass heating to > 300°C)
  - Manufactured to be used in aseptic processes without manipulation (e.g. RTF quality of components)
- Low leaching potential of the container materials
- Low adhesion/ absorption potential of the container materials
- Mechanical stability for storage and shipment, e.g. below freezing point

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

Coating of glass surfaces



source: Schott - Product brochure type I plus

Coating of glass surfaces

Evaluation: autoclaving at 121° C for 6h, AAS-analysis:

	type I	type I plus®
Na^{+}	3.5 ppm	< 0.01 ppm
Ca^{2+}	1.1 ppm	< 0.05 ppm
B^{3+}	3.5 ppm	< 0.1 ppm
Si^{4+}	5.0 ppm	< 0.3 ppm
Al^{3+}	2.3 ppm	< 0.05 ppm

source: Schott - Product brochure type I plus

Coating of rubber surfaces – The Eprex® case

- August 2003: Johnson & Johnson recalled certain batches of prefilled syringes of the anemia drug, Eprex, due to a significant increase of the incidence of a severe adverse event (pure red cell aplasia = PRCA)
- The root cause was a leachable from the rubber closure, which was found in the drug after a drug reformulation
- The issue could be solved by coating of the rubber surface with a teflon film. The leachable was no longer detectable in the drug, the incidence of PRCA decreased significantly

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

Leachables testing

Leachables study

- Selection of analytical targets after extractables study and toxicological assessment
- Analytical methods
  - GC + detection with FID, ECD or MS
  - HPLC + detection with UV/DAD or MS
  - ICP-OES for inorganic leachables
- Development and validation of quantitative analytical methods
- Conduct leachables analysis as part of formal stability studies

↳ 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

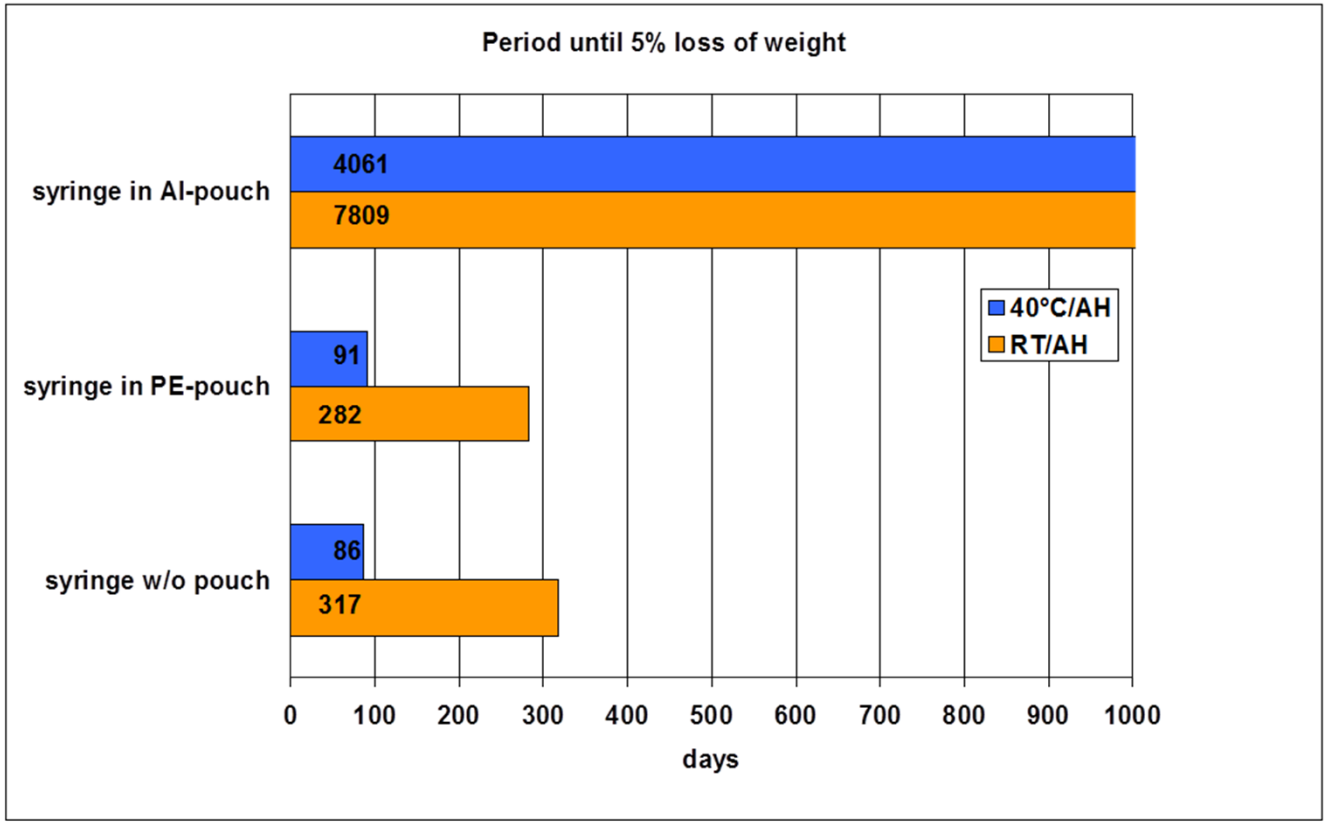
Regulatory requirements (for semi-permeable containers)

- 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.

Tight secondary container for high permeable packaging

Method:

gravimetric measurement + subsequent calculation

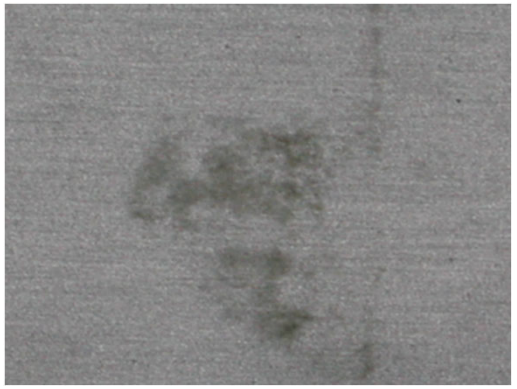


Tight secondary container for high permeable packaging

The risk:

Mold formation due to humid climate in tight pouches

Mold on label



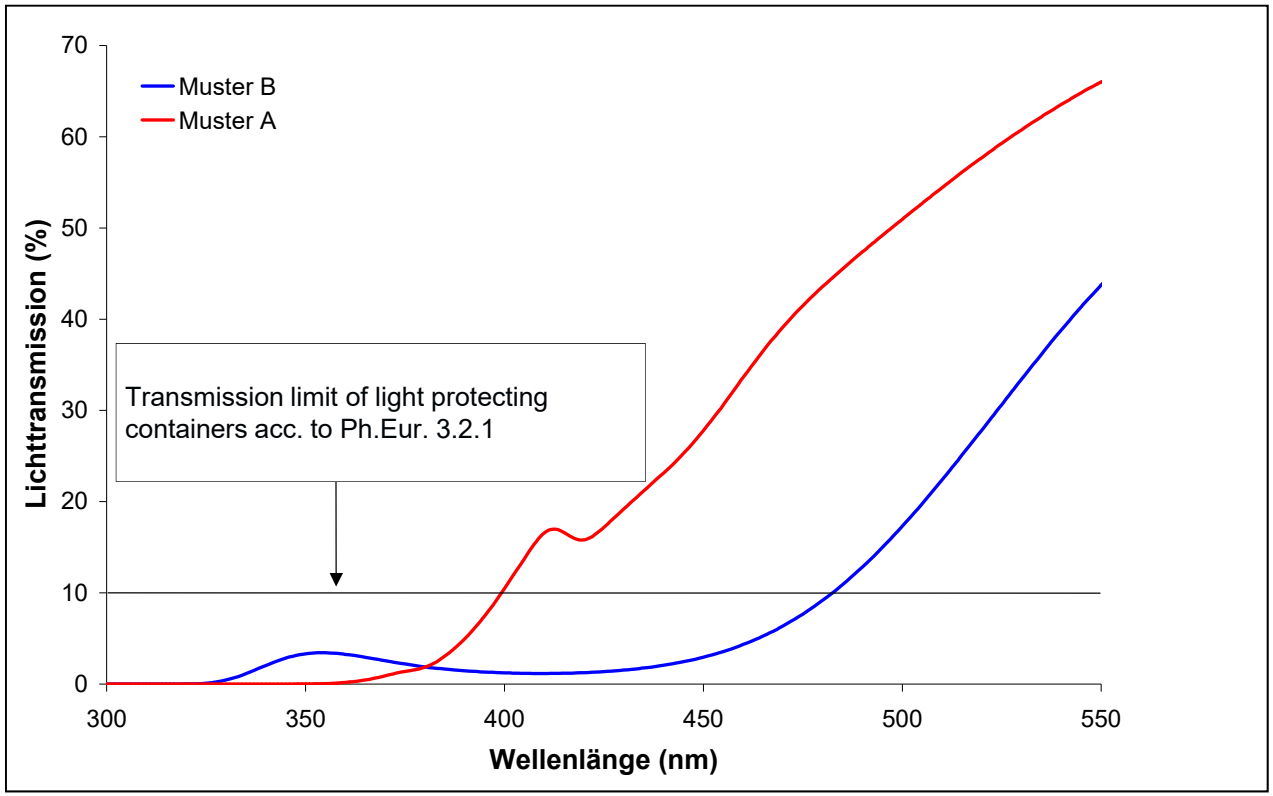
Mold on Al-foil

Method description

glass fragment is prepared from container

fragment is scaned in a UV photometer between 290 and 550 nm

light transmission is calculated from the scan



Case study: Infusion bag X-ray contrast agent

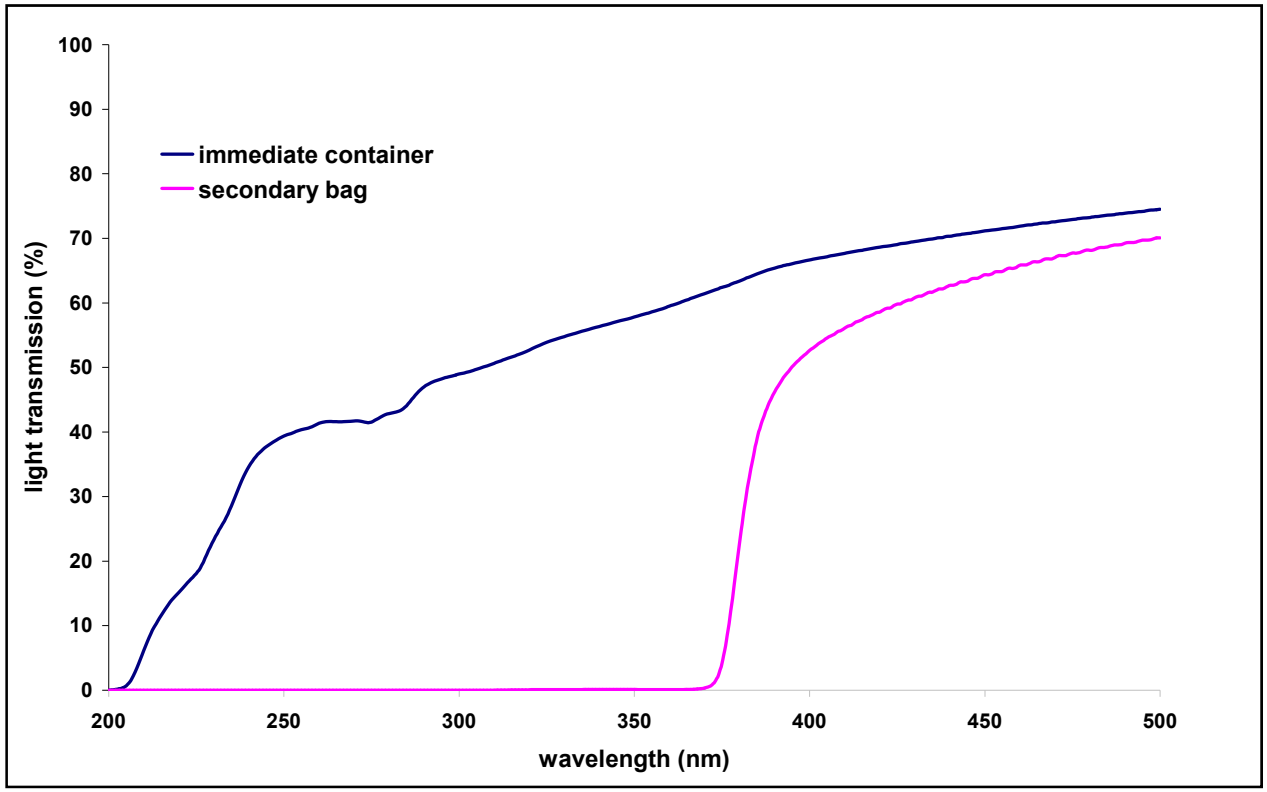
⇨ Is there any light protection by the immediate or secondary container?

Case study: Infusion bag X-ray contrast agent

Test description

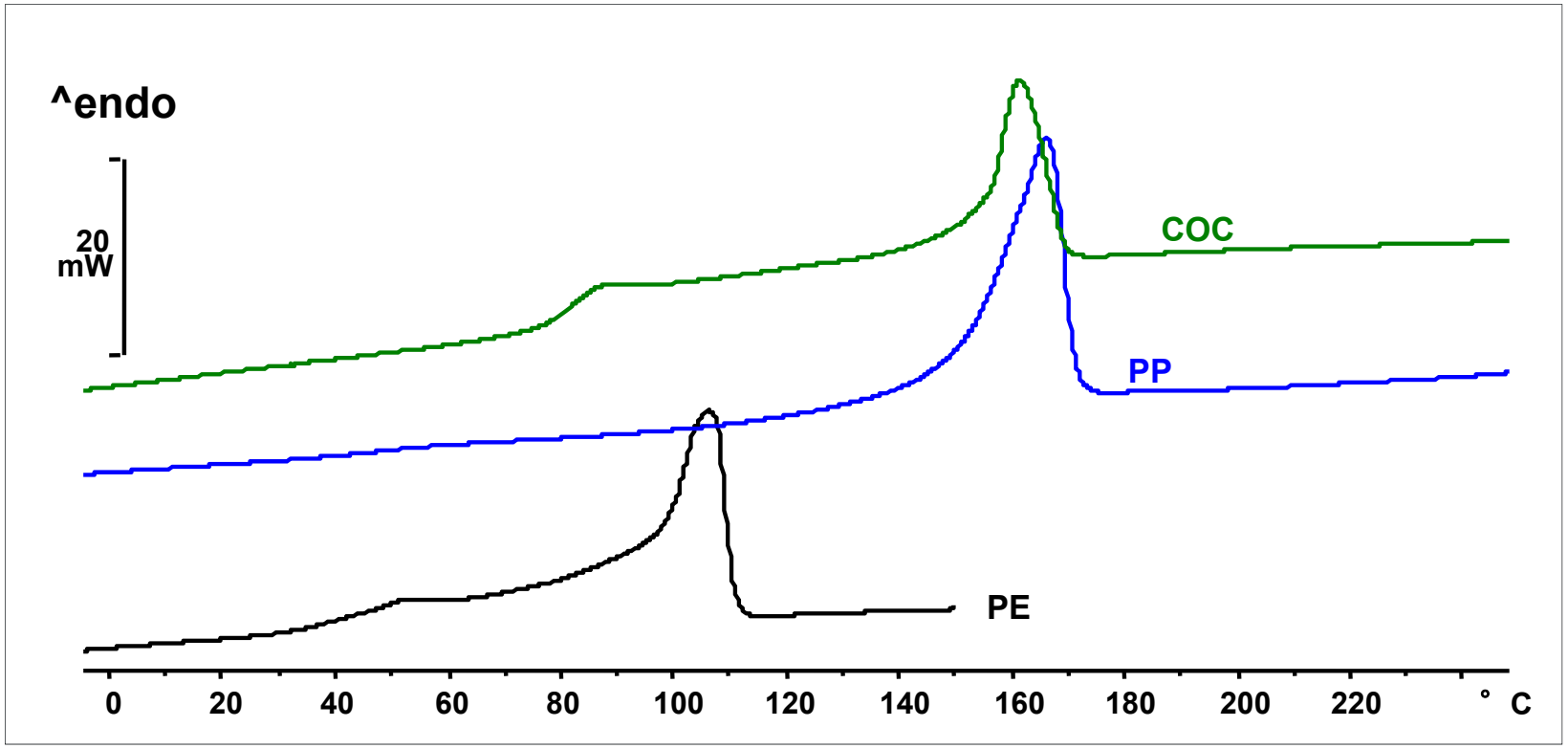
Place film in UV-photometer

Scan from 800 to 200 nm

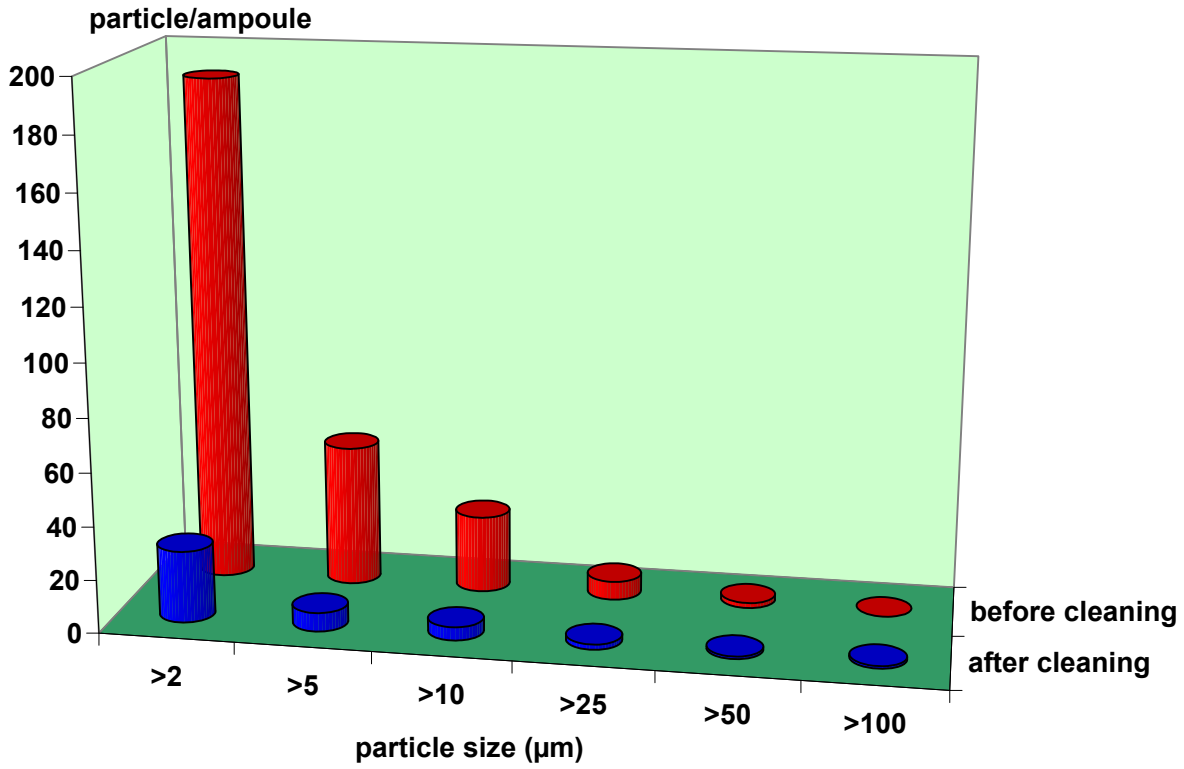


⇨ light protection is integrated into secondary container

Sterilization conditions - Melting characteristics of polymers evaluated bei DSC



Cleaning of parenteral containers (glass ampoules)



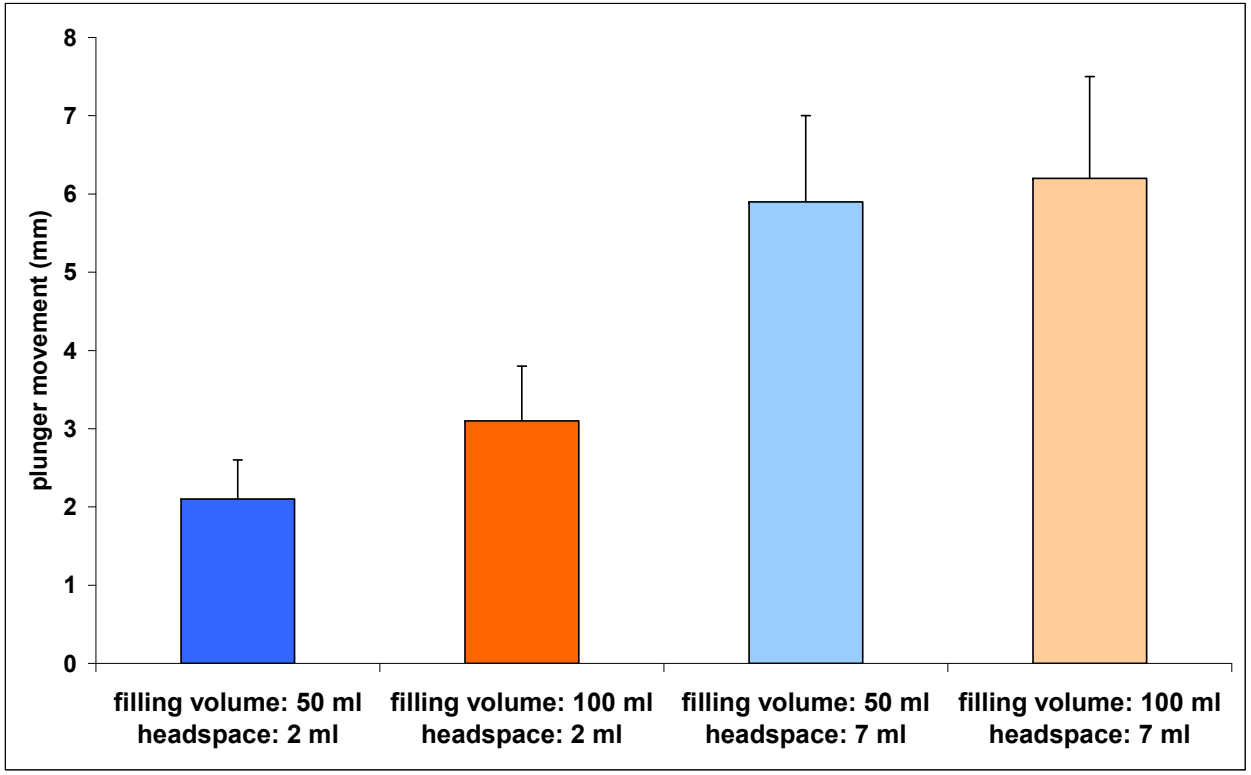
Plunger movement of prefilled syringes during autoclaving

Conditions:

150 ml PP-syringe

121°C/ 20 min

3.5 bar counter pressure



Manufacturing process – Lubrication process

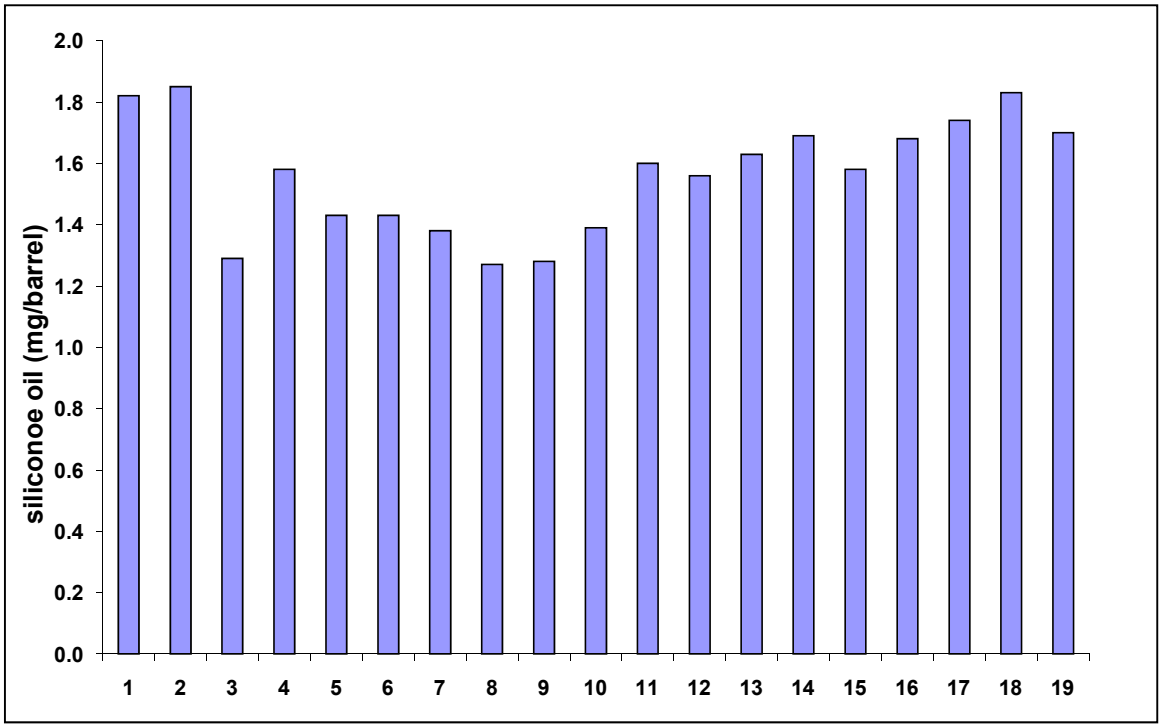
- Annealing of silicone oil
  - Spray-on of silicone-oil emulsion with low viscosity (350 – 1000 cSt)
  - Heat annealing, e.g. 10 min. at 300°C

- Direct application of silicone oil on barrel surface
  - Spray-on of silicone oil with high viscosity (≥ 1000 cSt)

- For glass barrels both processes are possible,
  for plastic barrels only direct application is possible

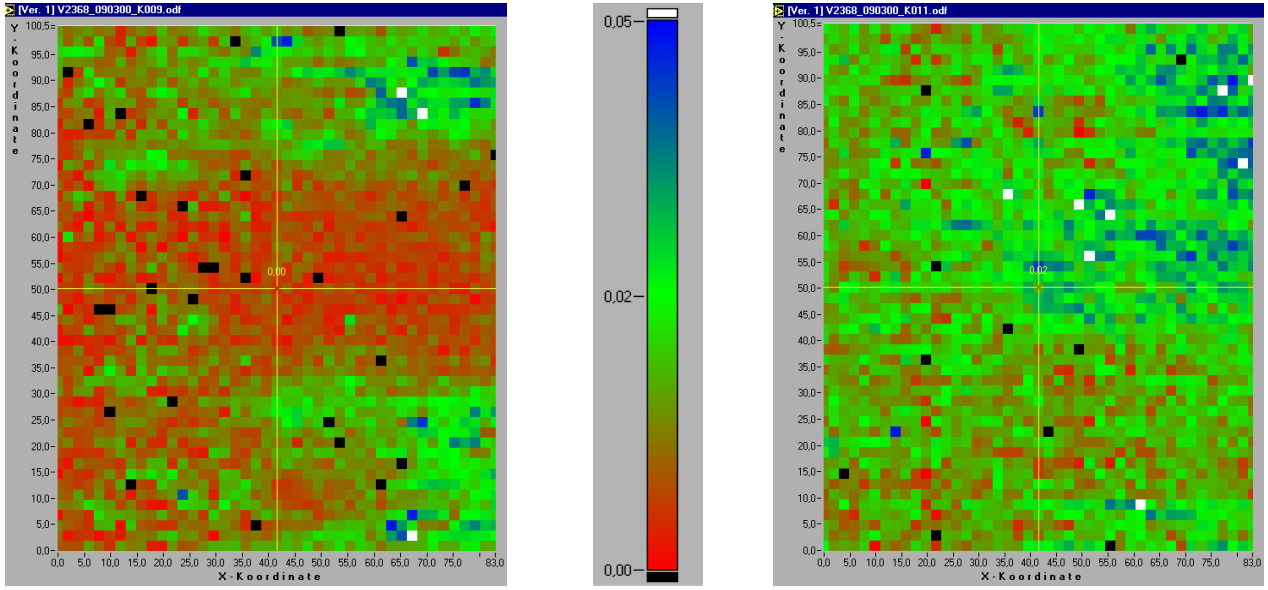
Manufacturing process – Lubrication glass barrel

- Silicone oil amount (mg/barrel)



Manufacturing process – Lubrication glass barrels

- Silicone oil distribution



uneven distribution

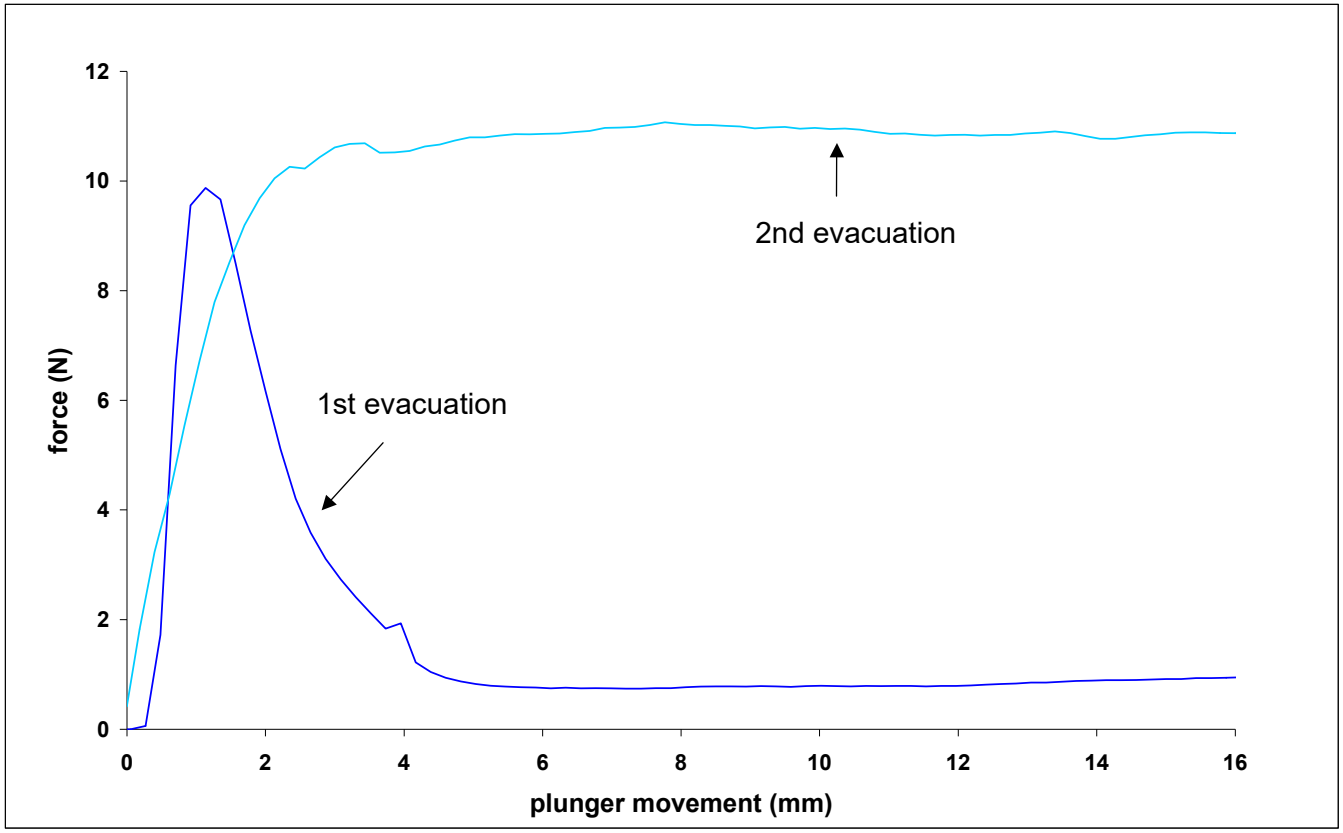
improved distribution

Use test – Case study

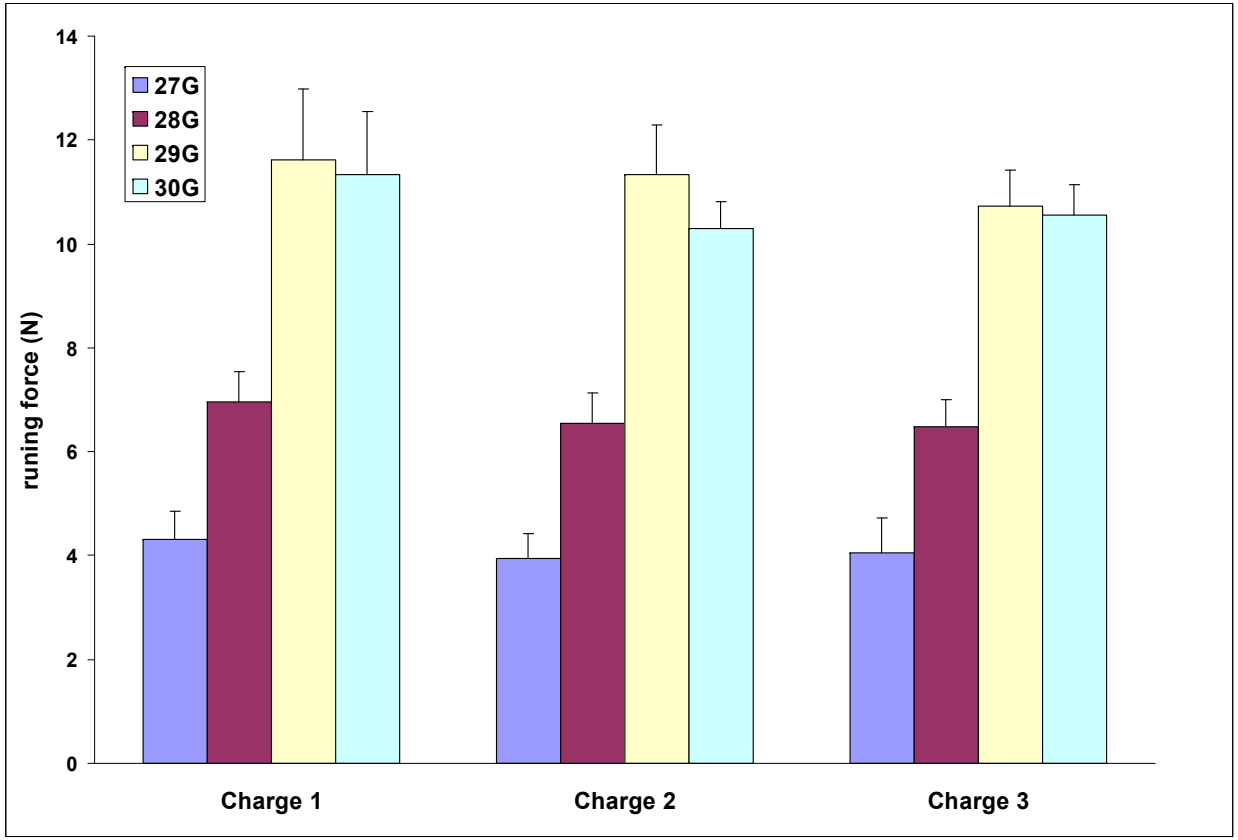
Description:

1st evacuation diluent (saline) without needle

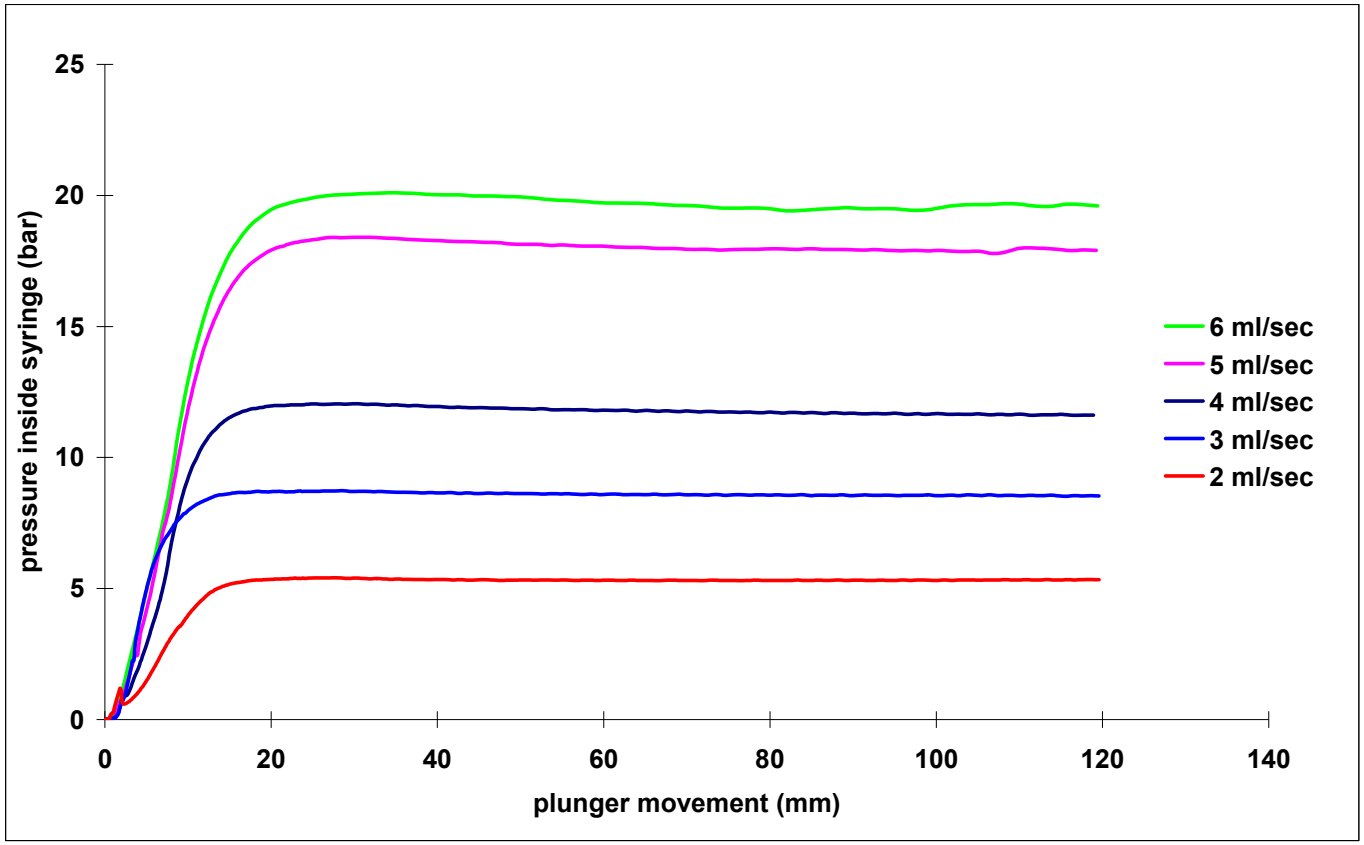
2nd evacuation reconstituted lyophilisate with 27G-needle



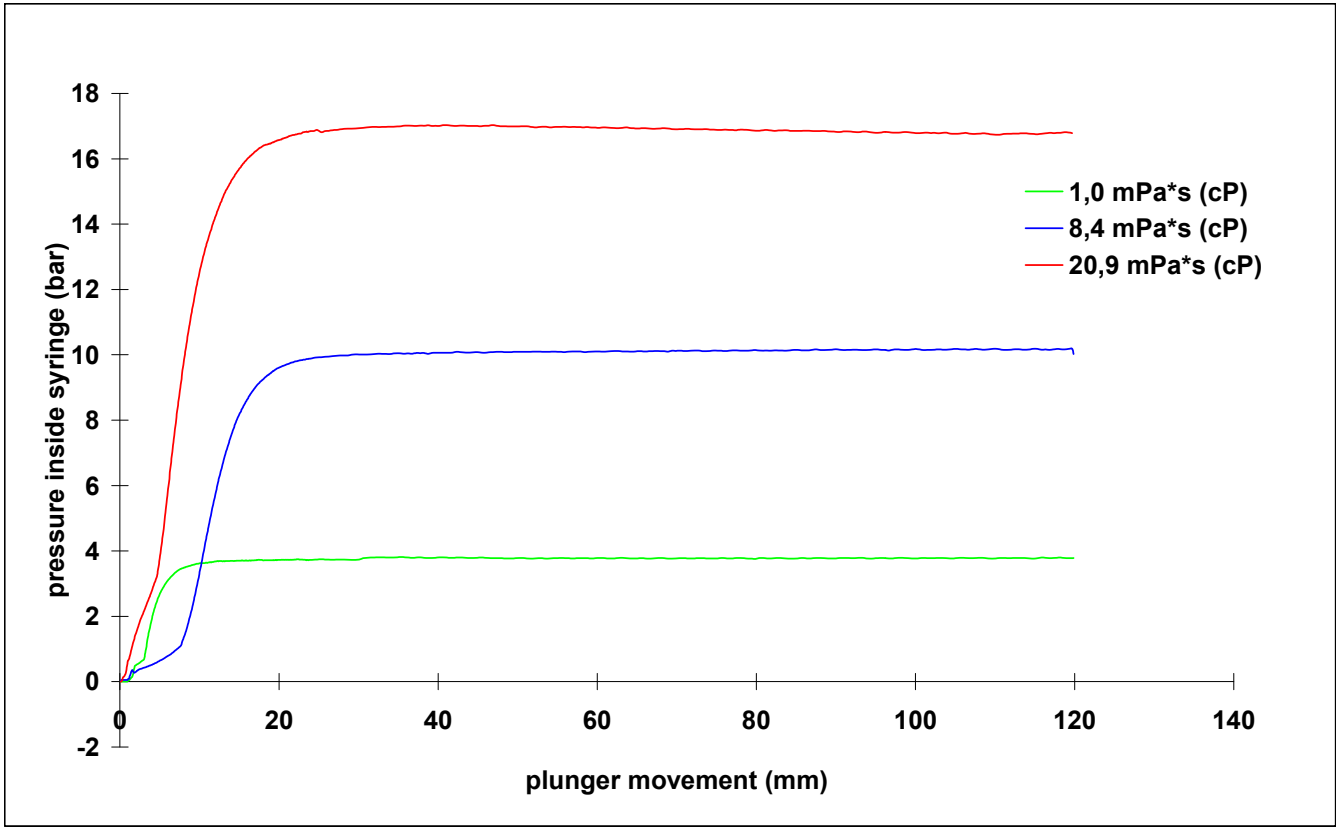
Use test – Influence of attached canula



Use test – Influence of flow rate



Use test – Influence of viscosity of filling



Definition - Container Closure Integrity (CCI)

- 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.
  ("Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" (December 3, 1993, 58 FR 63996), section V. A., page 16)
- 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.
  (USP <1207>)

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

When to test CCI?

- Development of container closure system (CCS)
- Manufacturing process (e.g. sterilisation parameters)
- Preparation of packaging components (e.g. lubrication, cleaning, surface treatment)
- Variability of composition and dimensions of packaging components and/or materials as well as defects
- Variability of manufacturing processes (e.g. torque adjustment or sealing parameters)

The ideal CCI test

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

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

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)

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

Regulatory Background - USP

⟨1207.1⟩ Package Integrity Testing in the Product Life Cycle - Test Method Selection and Validation

- Leak test selection criteria
  - Package content
  - Package design and materials of construction
  - Product package maximum allowable leakage limit
  - Deterministic vs. probabilistic methods
  - Method limit of detection (LOD)
  - Method largest leak detection capability
  - Method outcome
  - Quantitative vs. qualitative
  - Nondestructive vs. destructive
  - On-line vs. off-line

Regulatory Background - USP

⟨1207.2⟩ Package Integrity Leak Test Technologies

- Technologies categorization review

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**

Regulatory Background - USP

⟨1207.2⟩ Package Integrity Leak Test Technologies

- 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	

☝The methods are examples and are not binding!

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 — ASTM F3004
    - Cap application/ removal torque — ASTM D2063, D3198, etc.
    - Package burst test — ASTM F1140, F2084
    - Package seal strength (peel) test — ASTM F88
    - Residual seal force

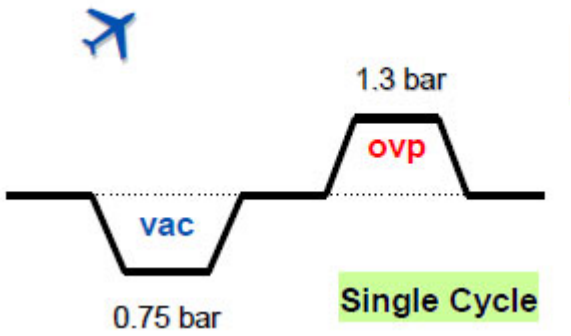
Introduction

- 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

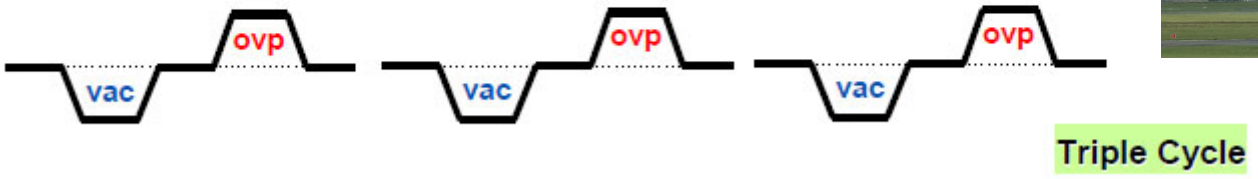
Shipping Conditions - Temperature conditions

- Freezing of liquid products may lead to breakage of the container
- Freezing/ thawing of liquids may lead to changes of functionality, e.g. friction forces of prefilled syringes
- Freezing/ thawing of liquids may impact integrity due to plunger movement in prefilled syringes
- Materials are not suitable for shipping conditions – e.g. -70°C shipping
- Pharmaceutical standard rubber materials have glass transition temperature around -55 to 60 °C and are thus brittle at shipping temperature
- To solve the issue innovative approaches are required – one commercially available component is a „hybrid“ injection stopper:
  - The rubber material in contact to the drug is a standard pharmaceutical rubber
  - The rubber material sealing the vial has a glass transition temperature below -80°C and is thus elastic under shipping conditions

Shipping Conditions - Pressure conditions



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

Case Study - Product shipment on dry ice (Lighthouse)

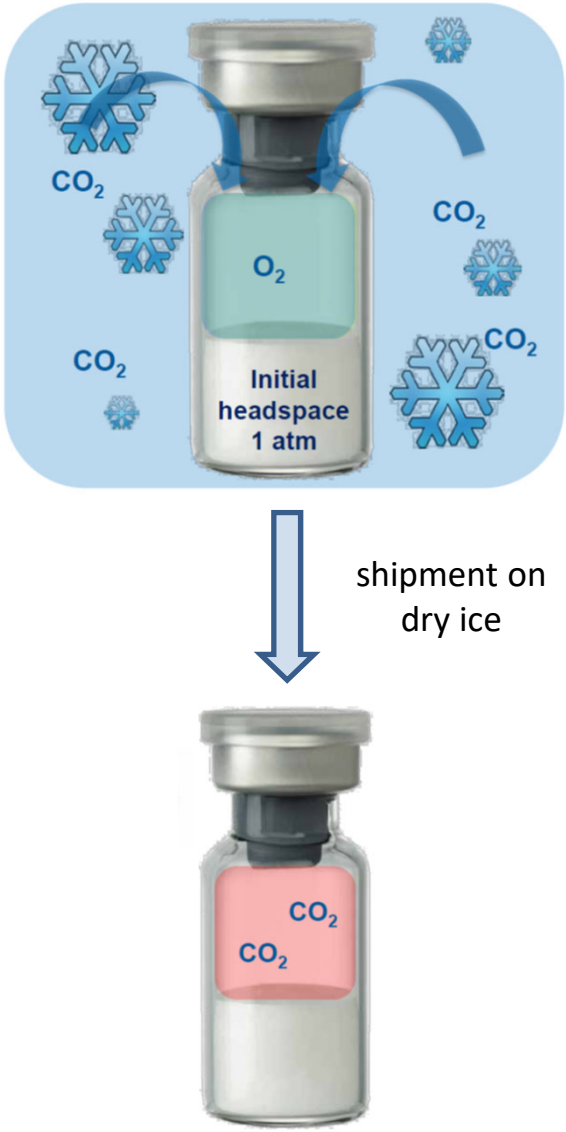
Source:

D. Duncan: Container Closure Integrity of Sterile Vials During Deep Cold Storage – Presentation on PDA Europe Parenteral Packaging Conference, Prague 2013

Case Study - Product shipment on dry ice (Lighthouse)

The issue:

- Air filled vial at 1 atm at room temperature
- On dry ice (-78 °C) the initial headspace condenses and creates underpressure
- The stopper can lose its elastic properties and closure can be lost
- Cold dense CO_2 from environment fills headspace
- Warming container to room temperature regains stopper elasticity and reseals closure



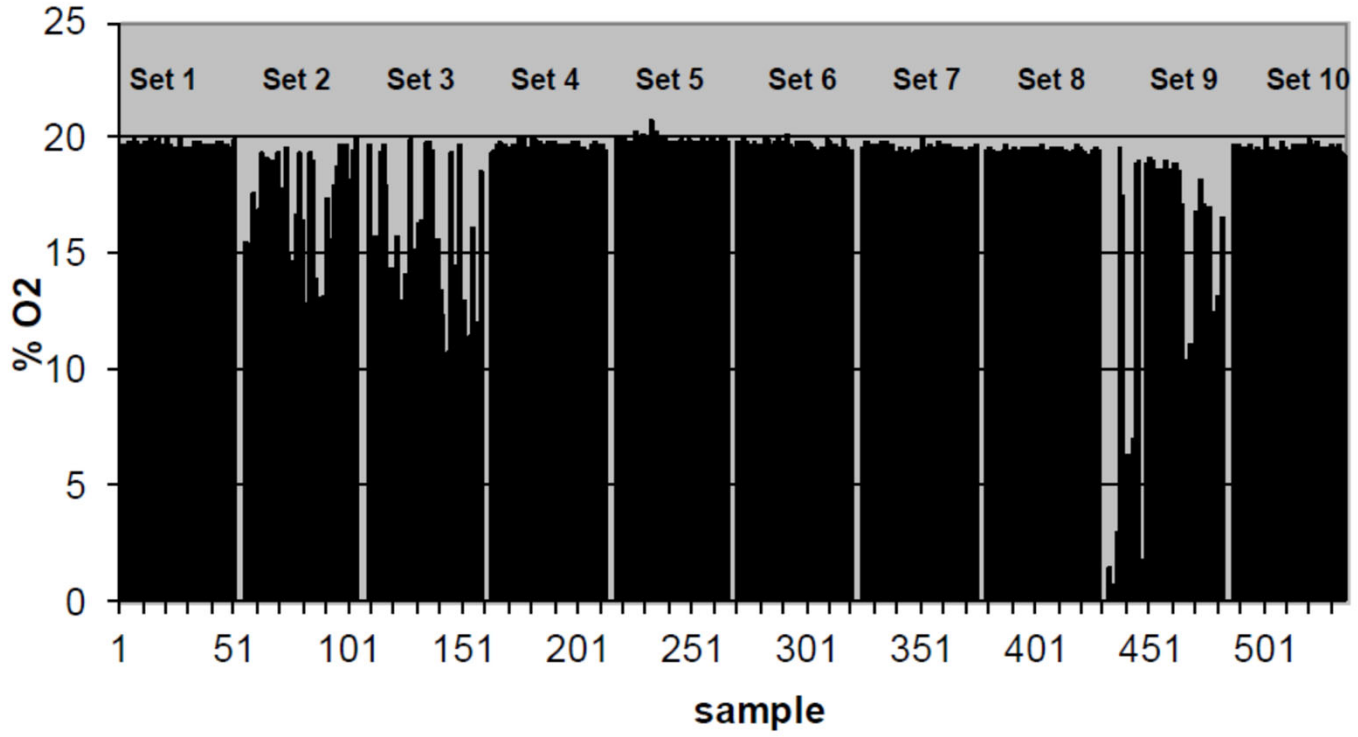
Case Study - Product shipment on dry ice (Lighthouse)

Test method/study set-up:

- Ten sets of vials/stopper combinations (different materials, different sealing conditions) were manufactured at 1 atm at room conditions
- The samples were stored on dry ice and analyzed after warming up to room conditions
- Quantifying of the physical headspace conditions was performed with Laser-based Headspace Analysis

Case Study - Product shipment on dry ice (Lighthouse)

Results: Vials with O_2 < 17%



Set 1:	4
Set 2:	27
Set 3:	39
Set 4:	0
Set 5:	0
Set 6:	0
Set 7:	0
Set 8:	0
Set 9:	31
Set 10:	0

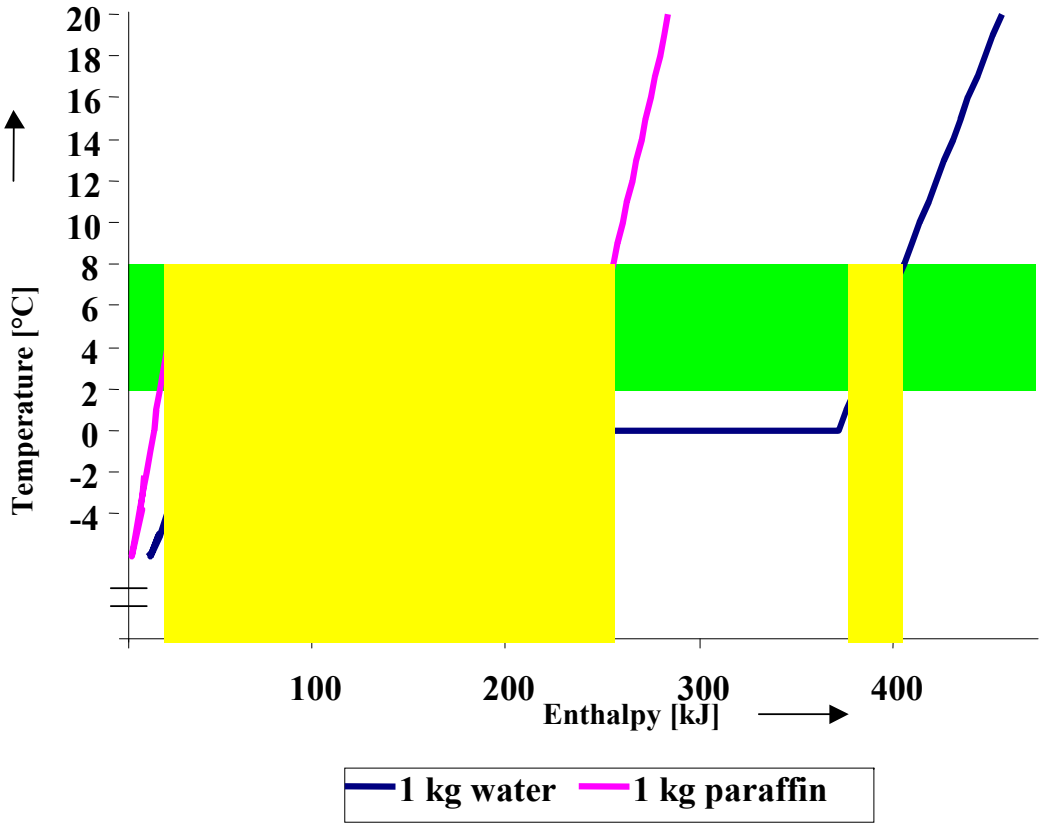
Temperature controlled shipment

- More and more products need to be shipped under controlled temperature conditions (e.g. Biologicals)
- Depending on the timely length of the shipment and the product specific temperature conditions, specific systems need to be developed.
- The system comprises a container, cooling elements as well as the exact temperature to which the elements need to be temperatured
- For temperature controlled shipment two principles are feasible
  - Active systems, which require power source (cable, battery)
  - Passive systems, based on cooling elements and a suitable packaging system
- For the evaluation of Cold Chain Supply solution the length of the shipment and the respective environmental conditions (winter, summer) need to be considered
- For validation of Cold Chain shipments test cycles were agreed by standardization groups (ISTA, DIN)

Phase change materials (PCM) – Scientific background

Phase Change Materials (PCM) provide the best temperature buffer in the temperature range of their melting point.

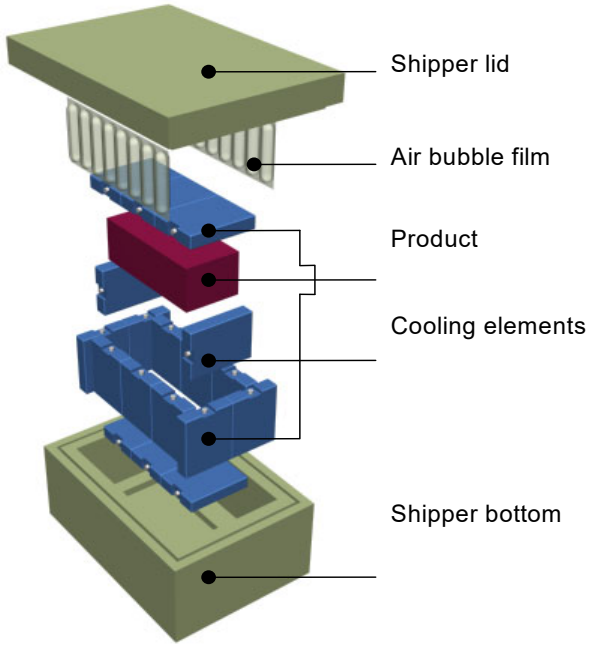
The graph compares a water and a paraffin filled PCM element regarding their cooling/heating properties



Phase change materials (PCM) – Description

0 % PCM aktiv → **100 % PCM aktiv**

Complete packaging solution



Packaging scheme

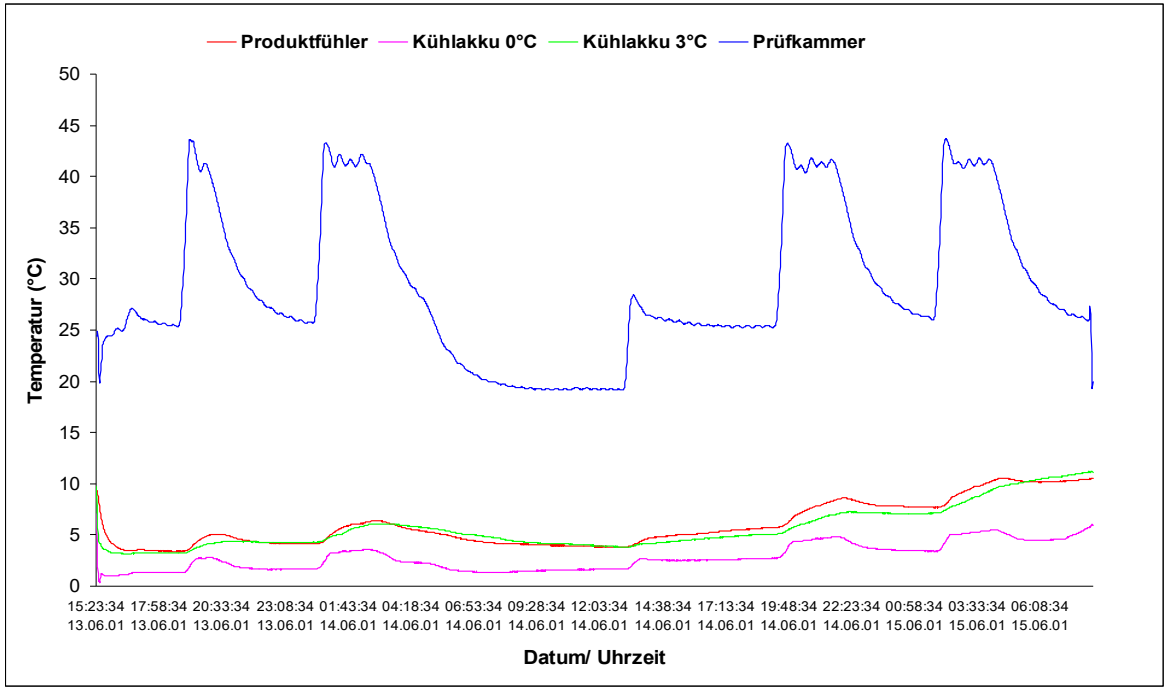
Real box

Evaluation of a Cold Chain package (2 to 8 °C shipment)

Thermosensors are located at different positions of the intire box

The box is stored at conditions simulating a shipment in the summer

The curves show the temperature at different points of the box



Definition

- Term “Combination Product” not defined in EU
- Drug-delivery product = Drug/Device
- Medical Device incorporating medicinal substance or an ancillary human blood derivative = Medical Device/Drug
- Pre-condition: fix combined (integral) and not only co-packed

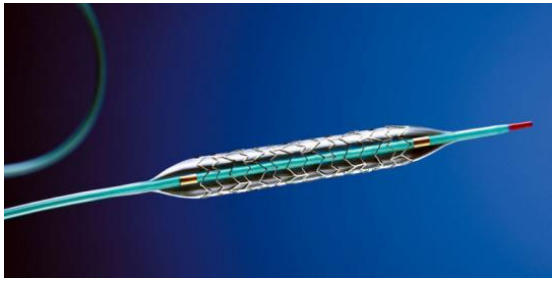
- Drug/Device: Directive 2001/83
- Medical Device/Drug: MDD 93/42/EEC or AIMDD 90/385/EEC

Definition

Examples

- Drug-delivery product (Drug/Device):
  - Pre-filled syringe

- Medical Device incorporating medicinal substance or an ancillary human blood derivative (Medical Device/Drug)
  - Drug-eluting stent



Definition

- 21 CFR Part 4 (Docket No. FDA–2009–N–0435) - Current Good Manufacturing Practice Requirements for Combination Products - Final rule, January 22nd, 2013

  This rule is effective as of July 22nd, 2013

- FDA Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (January 2017)

Definition

- Drug/device
- Biologic/device
- Drug/biologic
- Drug/device/biologic

- Single entitity (e.g. pre-filled syringe, drug-eluting stent)
- Co-packed product (e.g. surgical or first aid kit)
- Cross-labeled products (e.g. a light-emitting device and a light-activated drug)

Thank you very much for your attention!!