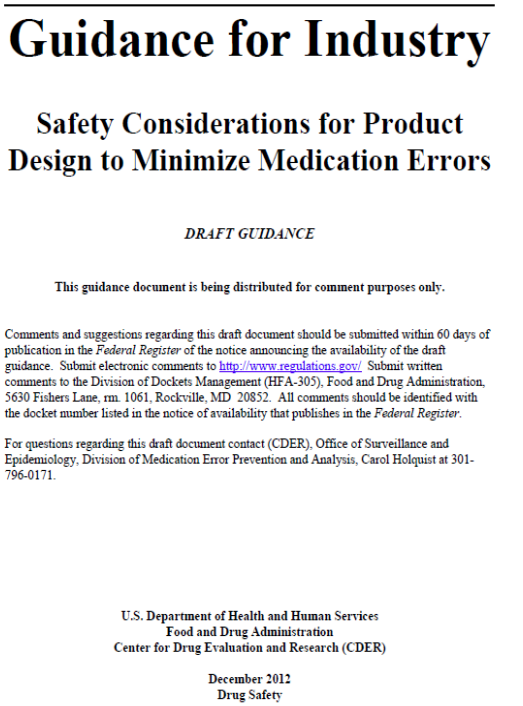
Recent Innovations in Blow-Fill-Seal

- Increased functions by inserted parts
- Adapters/closures for minimizing administration errors and increasing safety
- Cool-BFS for temperature sensitive formulations

Preventing Errors Associated with the Preparation and Administration of IV Admixtures.

ROMMELAG ENGINEERING

Medication errors in i.v. administration /1-3/



Guidance for Industry

Safety Considerations for Product Design to Minimize Medication Errors

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov/ Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER), Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis, Carol Holquist at 301-796-0171.

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

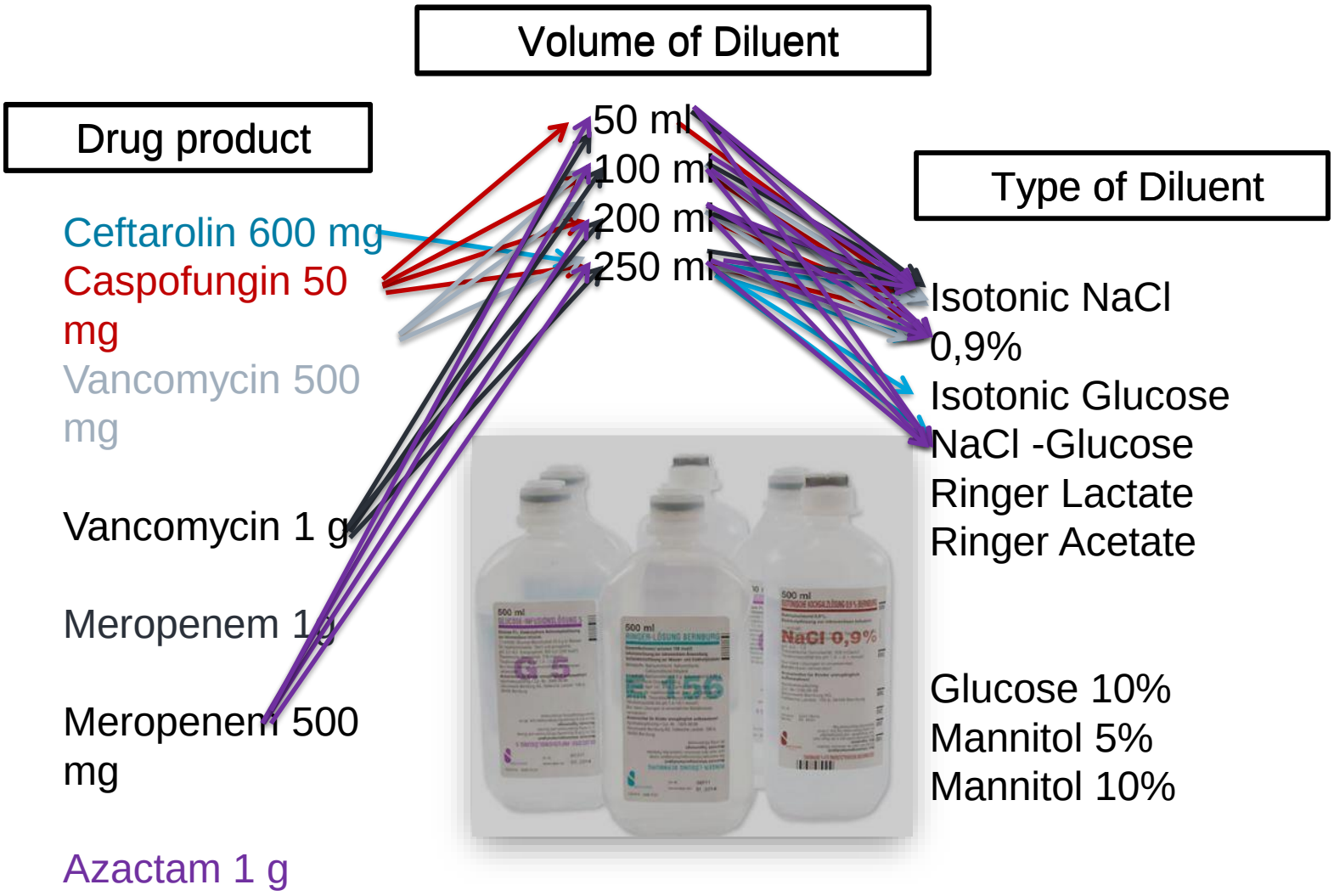
December 2012
Drug Safety

Key messages

- Prepared intravenous medicines were left for short periods of time unlabelled before being administered to patients. This is a previously unidentified risk that may cause the wrong drug or dose of a medicine to be administered in error to a patient.
- A frequent error involved using the wrong diluent to prepare an intravenous medicine. This may cause difficulties in dissolving drug powders, inactivation, and possible precipitation of the drug out of solution.
- Intravenous bolus medicines required to be administered by hand in a syringe were frequently administered too quickly and this practice is associated with phlebitis and loss of cannula patency.
- Aseptic procedures required for the safe preparation of intravenous doses were frequently violated by staff who were not always aware of the clinical consequences of not following these procedures.

/1/ D. H. Cousins et al. Medication errors in intravenous drug preparation and administration… Qual safe Health care 2005; **14**: 190-195
/2/ J.I. Westbrook et al. Errors in the administration of intravenous medications in hospital… BMJ Qual Saf 2011; 20; 1027-1034
/3/ ASHP reports Proceedings of a summit on preventing patient harm and death from i.v. medication errors Am J Health-Syst Pharm Vol 65, Dec 15, 200, 2367-2379

i.v. Administration must consider drug type and strength in combination with volume of diluent & diluent type.



Uwe Frank, Evelina Tacconelli
Physical Incompatibility of Antibiotics and Antimycotics in Infusion Solutions in The Daschner Guide to In-Hospital Antibiotic Therapy; Springer 2012; pp 292-29

Nipro's-half kit is well established in the Japanese market; standard vials can be used.

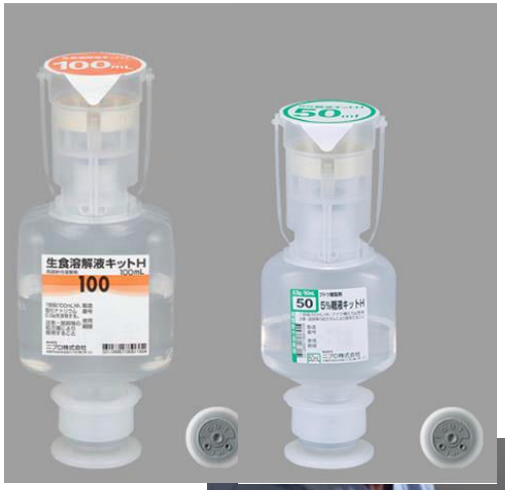
Example Nipro-half kit

Complete terminal sterilization

Nipro-half kit

http://med.nipro.co.jp/list_basic?free_word=キットH

Nipro's-half kit gave good results in an European usability study (n=8).



"…Intuitive handling…"

"…I it like standing on cap…."

"…easy mixing…"

Margarete Sandelowski; Focus on Qualitative Methods - Sample Size in Qualitative; Research in Nursing & Health, 1995, 18, 179-1 83
Ko de Ruyter; Norbert Scholl, (1998),"Positioning qualitative market research: reflections from theory and practice", Qualitative Market Research: An International Journal, Vol. 1 Issue 1 pp. 7 – 14

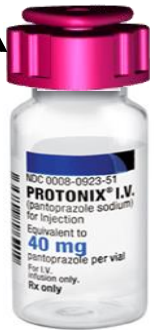
Our coded adaptor system CASY prevents administration errors with infusions.

From established systems to CASY

Standard vials with rubber crimp seal

Replace flip-off by key overcap

Key

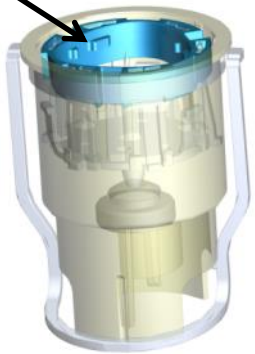


Key states DP needs:
all types of diluents allowed and min volume required

Container (Nipro half kit);
established in Japan over decades

Add lock

Lock ring



Lock ring states bottle content (type & volume of diluent)

If key and lock fit mixing is possible

Michael W. Spallek et al Preventing Errors Associated with the Preparation and Administration of IV AdmixturesPDA Parenteral Packaging Conference Venice April 13th, 2016

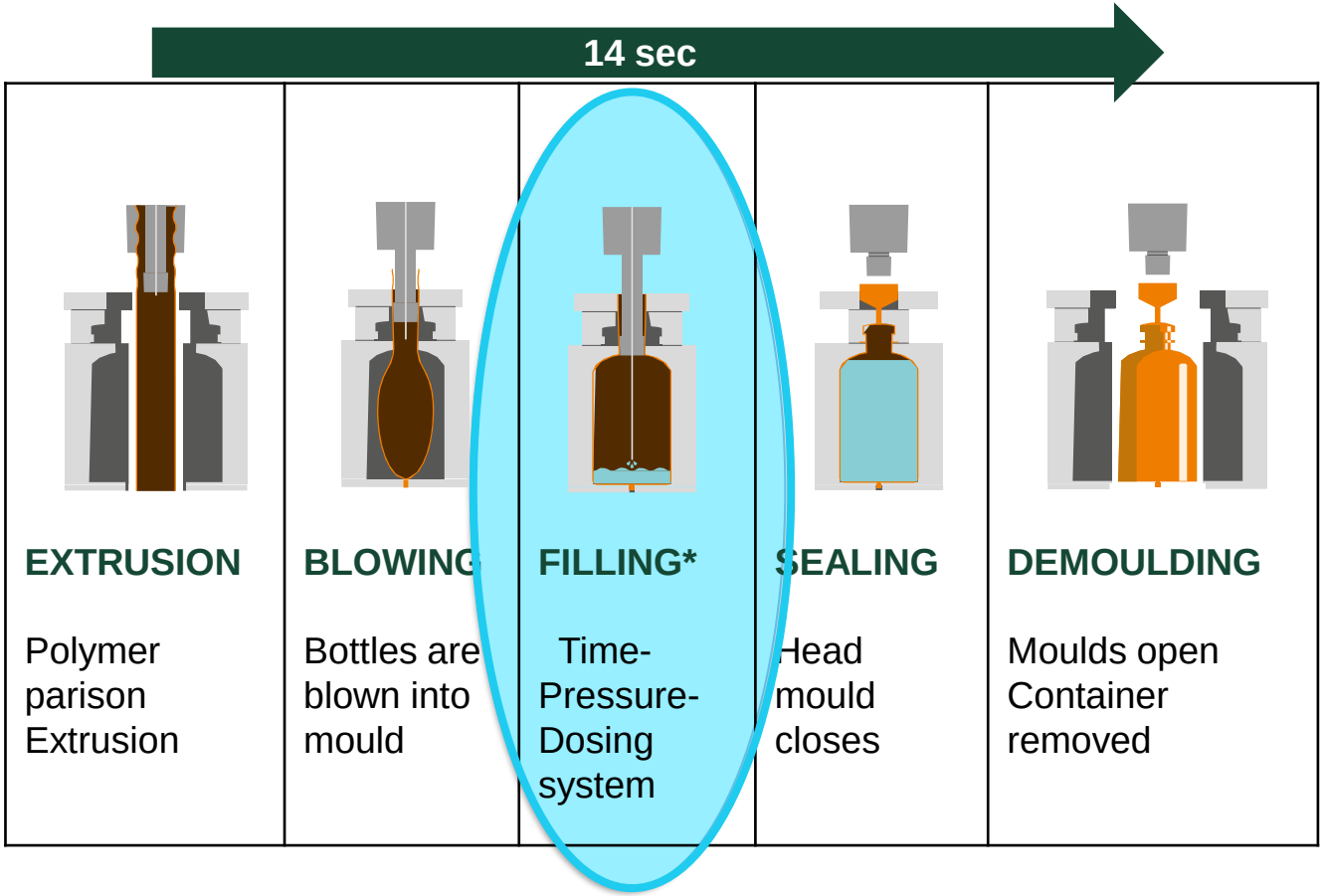
CASY´s motion sequence is well defined.

Video

Michael Spallek, Johannes Geser & Christoph Kaschta
Preventing Errors Associated with the Preparation and Administration of IV Admixtures PDA Parenteral Packaging, Venice April 13, 2016

What about temperature effects on the formulation ?

Blow-Fill-Seal (BFS)-Process

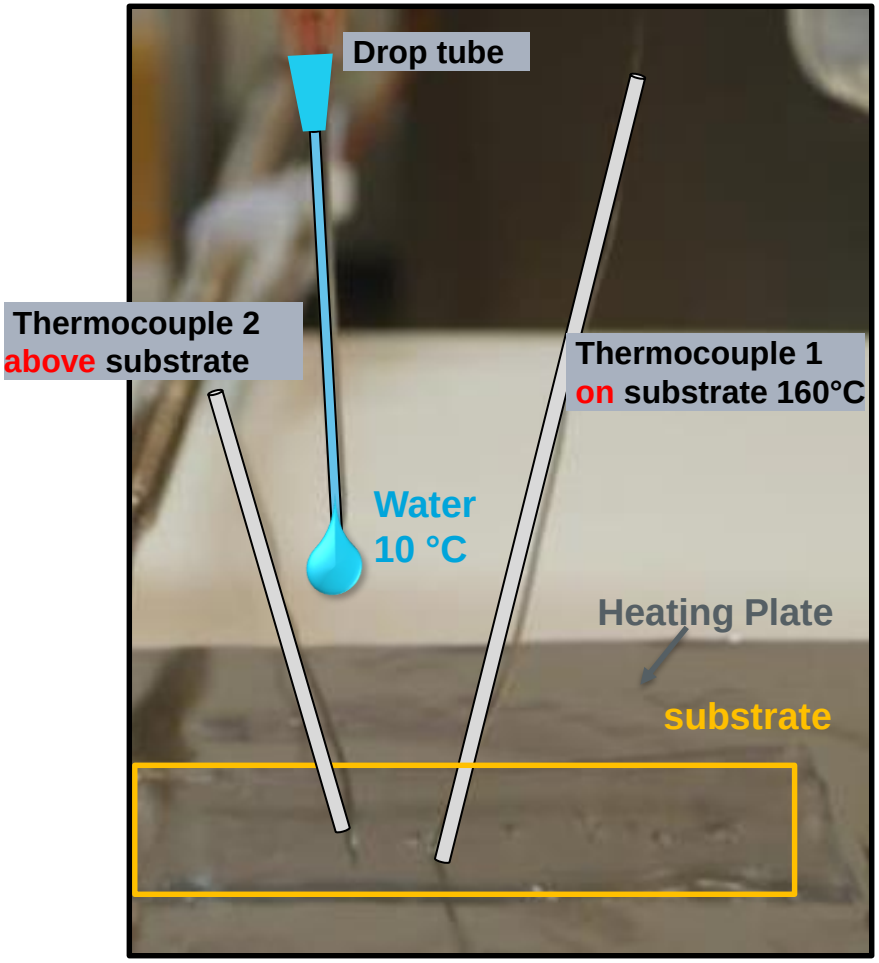


/1/ R. Oschmann, and O.E. Schubert, Eds, *Blow-Fill-Seal Technology*, (CRC Press, Stuttgart, 1999).
/2/ The manufacture of sterile Pharmaceutical Products Using Blow-Fill-Seal-Technology Parenteral Drug Association technical report No 77, 2017

* Michael Spallek et al. Heat effects on sensitive formulations during blow-fill-seal processing PDA Parenteral Packaging, Brussels, 3-2014

A dedicated experimental set up has been developed to assess the first drop.

Experimental set up & Parameters



- Heating plate: 120°C to 160°C
- Substrate: LDPE 0,55 mm thick
- Thermocouples Type T (0.5 mm diameter)
- Water Temperature: 10°C and 30°C
- Drop size: 15-20 µl

A dedicated experimental lab-set up has been developed to assess the first drop.

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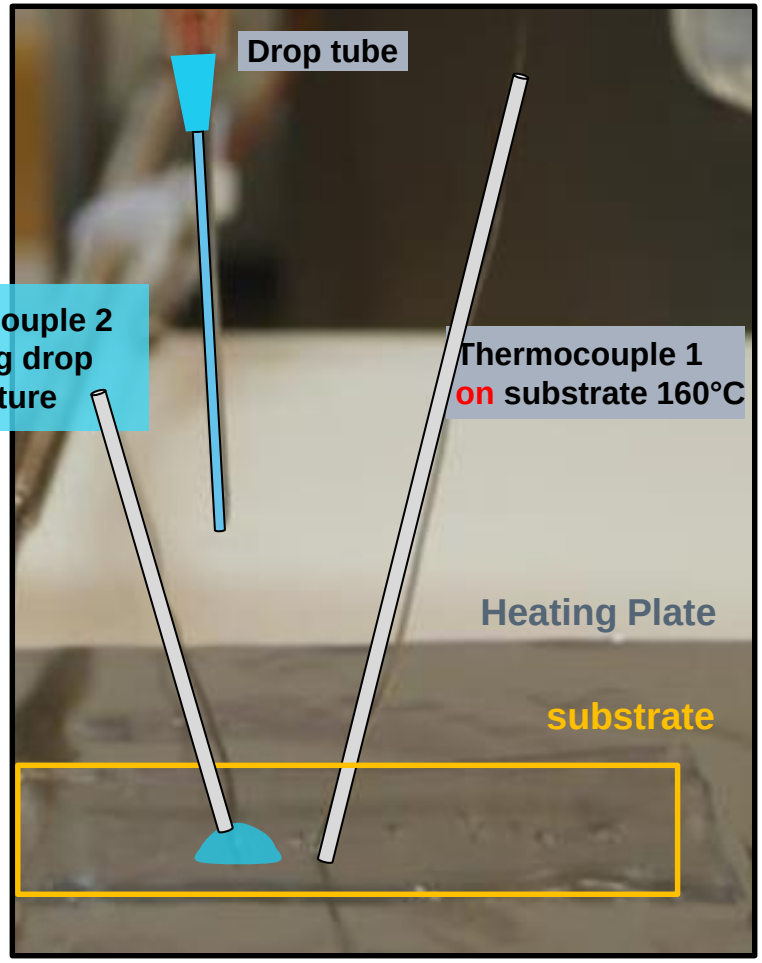
Experimental set up & Parameters



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- Water Temperature: 10°C and 30°C
- Drop size: 15-20 µl

A dedicated experimental lab-set up has been developed to assess the first drop.

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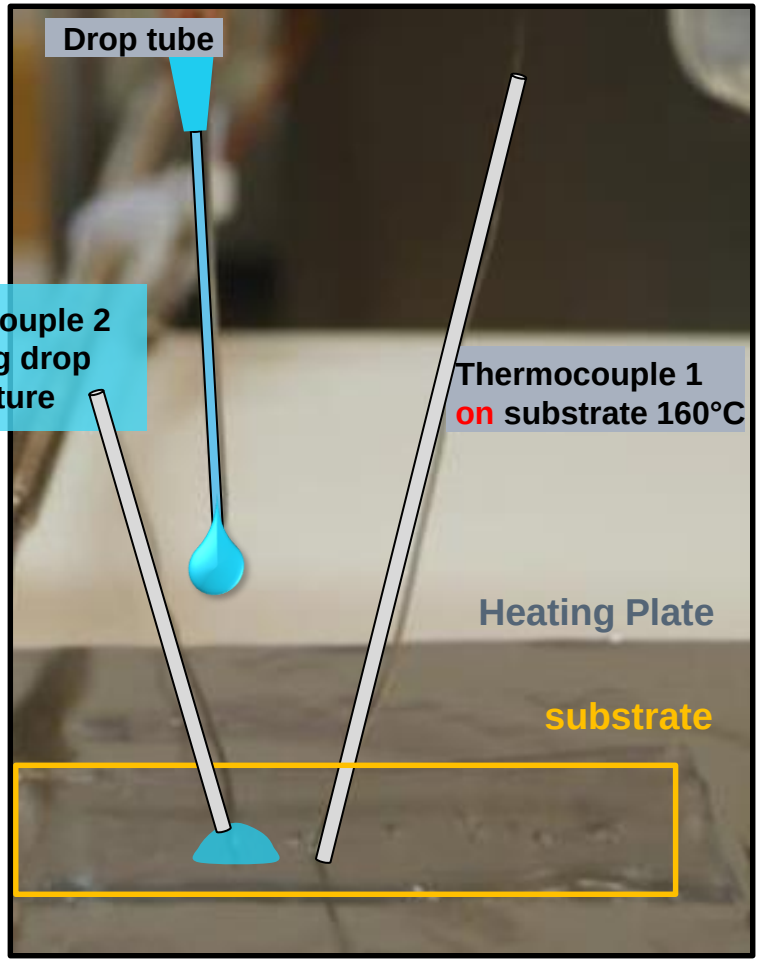
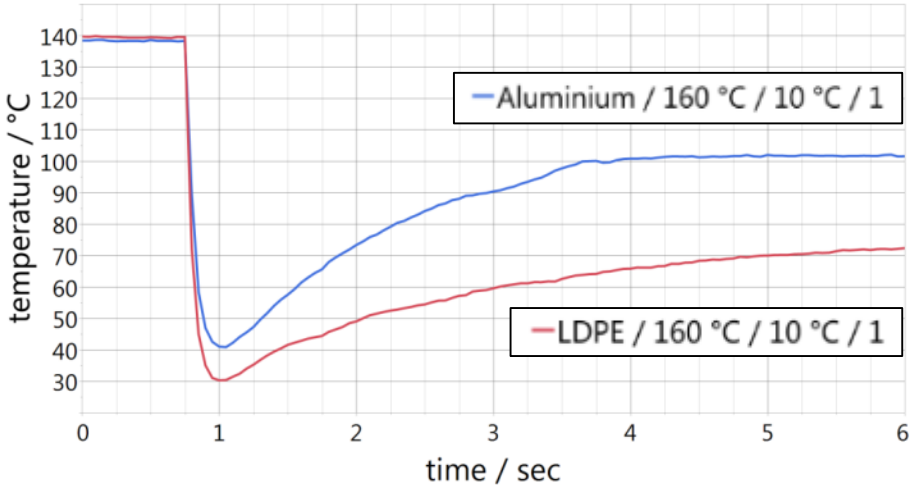
Results 1st drop





1.2 sec: typical fill-time for 1.3 ml (approx. 65 drops)

A dedicated experimental lab-set up has been developed to assess the first drop.

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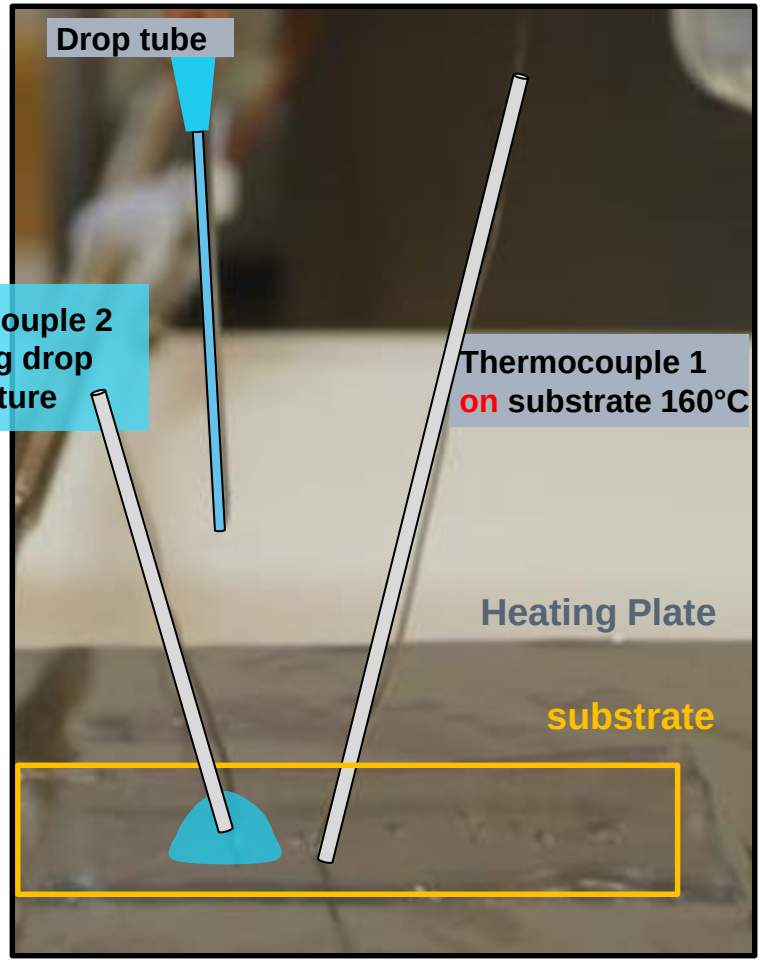
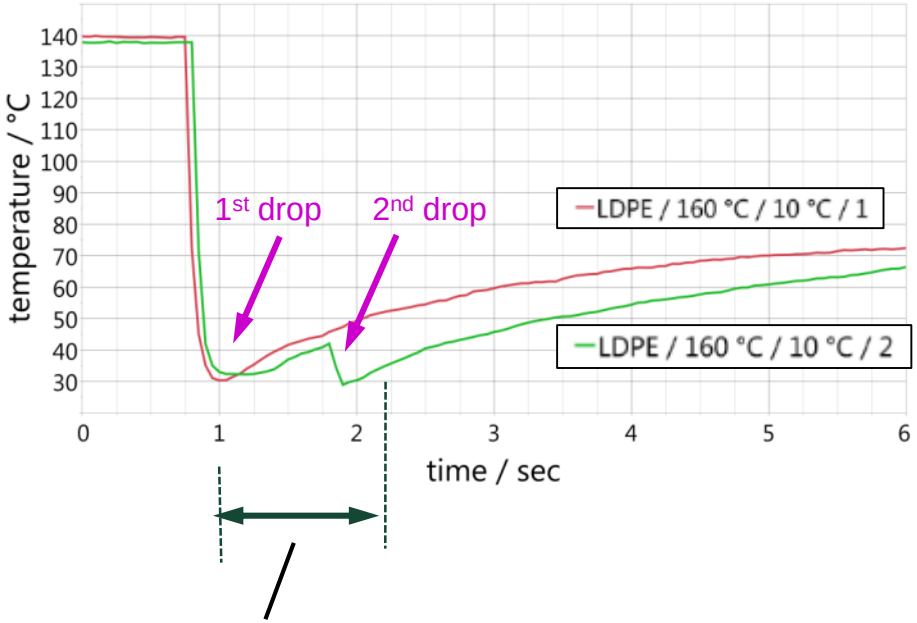
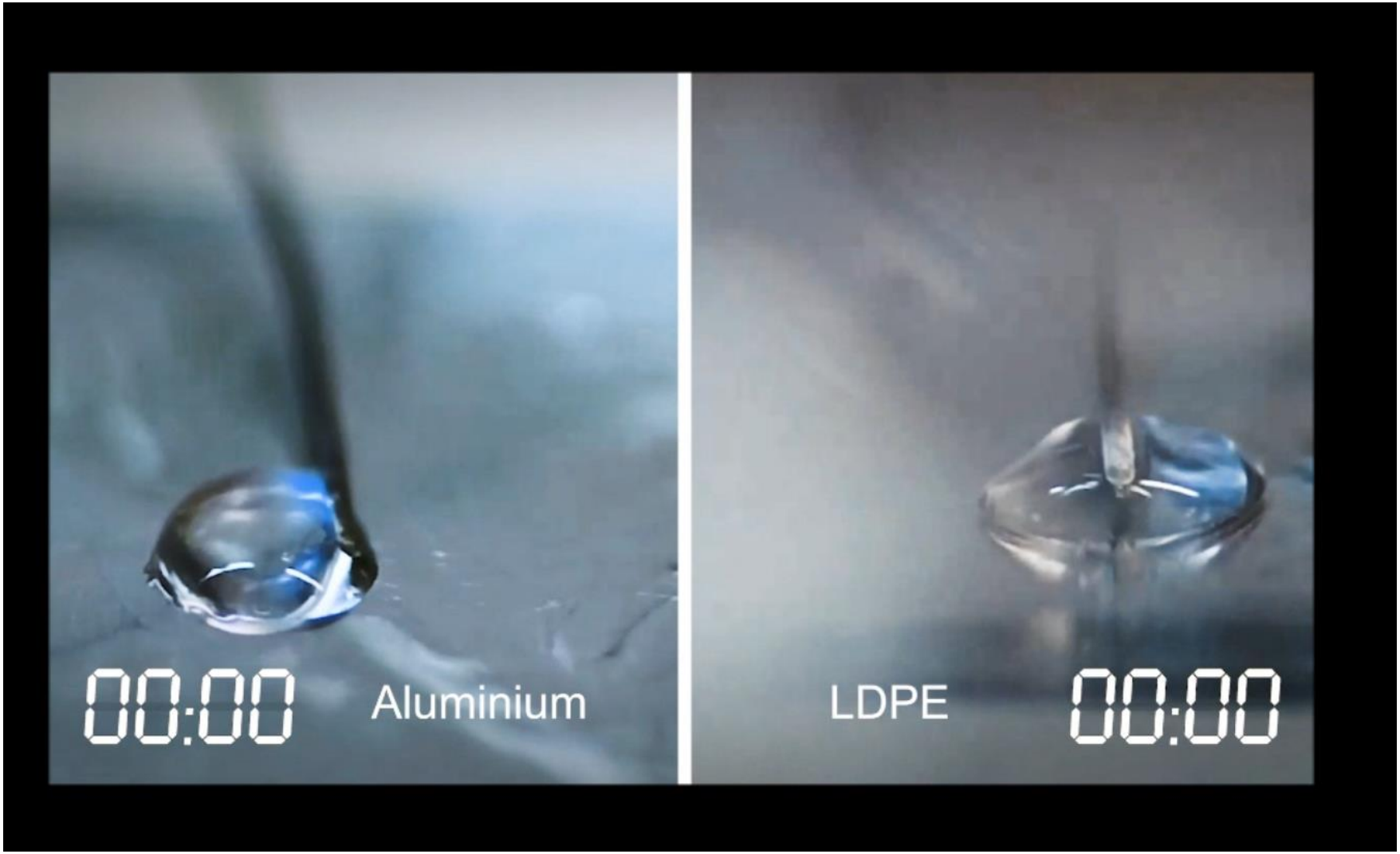
Results 2nd drop





1.2 sec: typical fill-time for 1.3 ml (approx. 65 drops)

Video



Three methods have been used for temperature mapping during BFS-processing.

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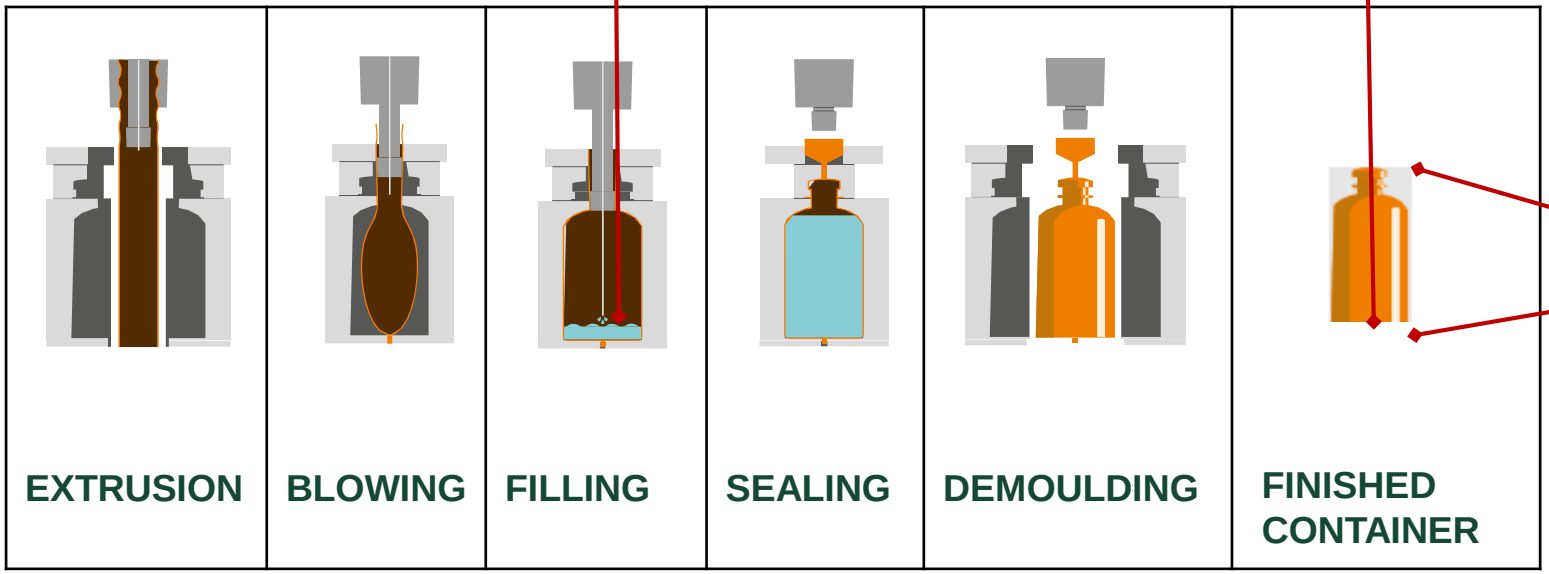
Overview

Method 1:
Thermocouple in liquid during filling

Method 2:
Thermocouple in liquid

Method 3:
IR Camera for complete container



Optris PI200

14 sec

300 sec

Three additional methods have been used for temperature mapping from first drop to full container.

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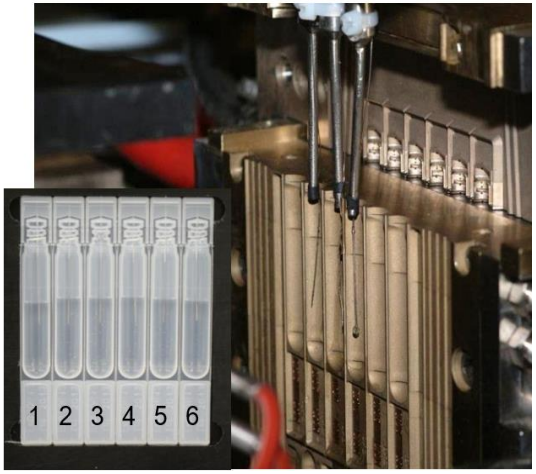
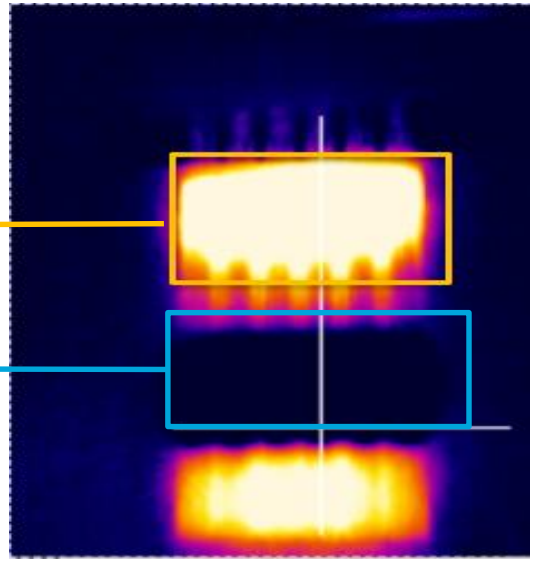
Some details

Method 1: Thermocouple in liquid during filling

Method 2: Thermocouple in liquid of closed container

Method 3: IR Camera for complete container





The results allow temperature mapping from first drop to full container.

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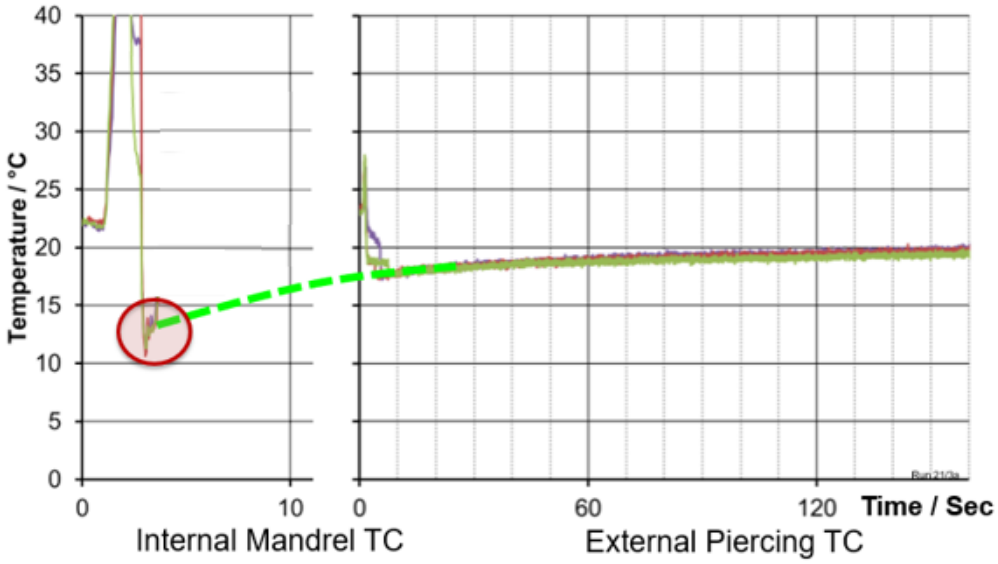
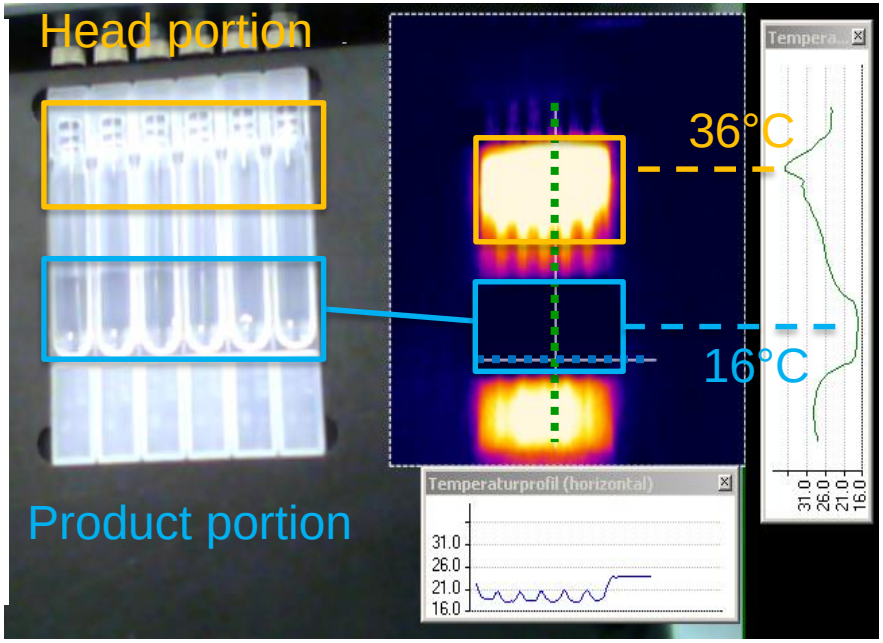
Results

Method 1: Thermocouple in formulation during filling

Method 2: Thermocouple in formulation after piercing

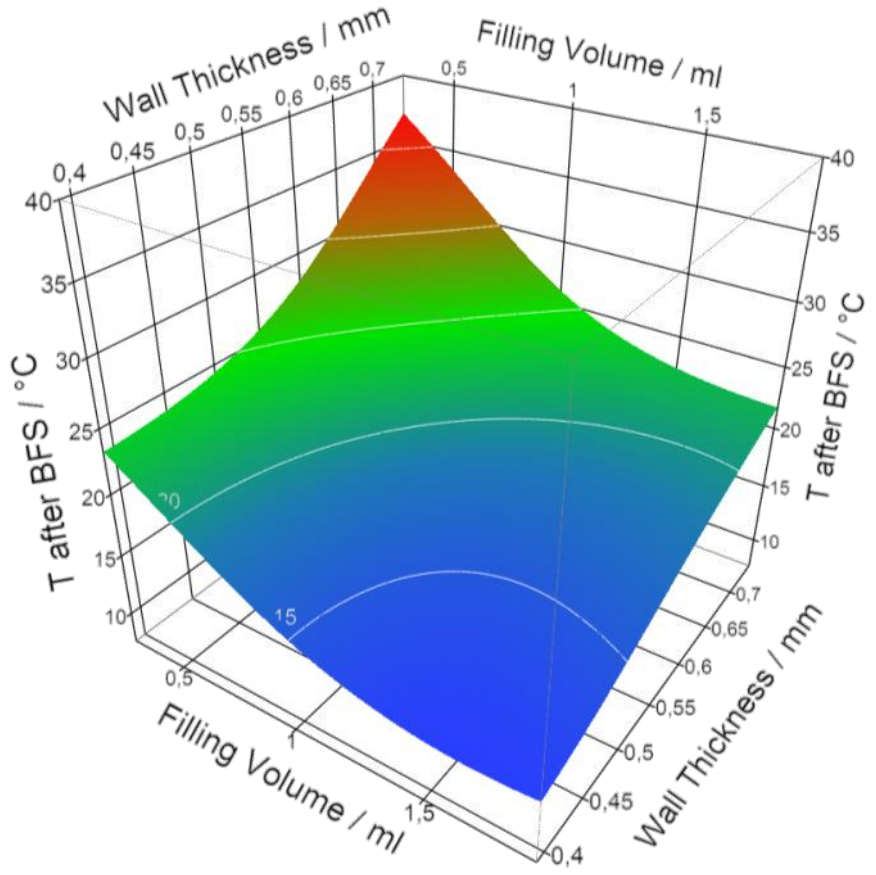


Method 3: IR Camera for complete container



CoolBFS®: Parameters affecting the product temperature are understood and can be minimized.

DoE response curve (Example)



Formulation Temperature	8°C
Filling Volume	0.34 ml…1.67 ml
Wall Thickness	0.4 mm…0,7 mm
Mould & Formulation Cooling	on

M. Spallek et al. Heat effects on sensitive formulations during blow-fill-seal processing PDA Parenteral Packaging, Brussels, 3-2014

Selected transparent materials are suited for BFS.

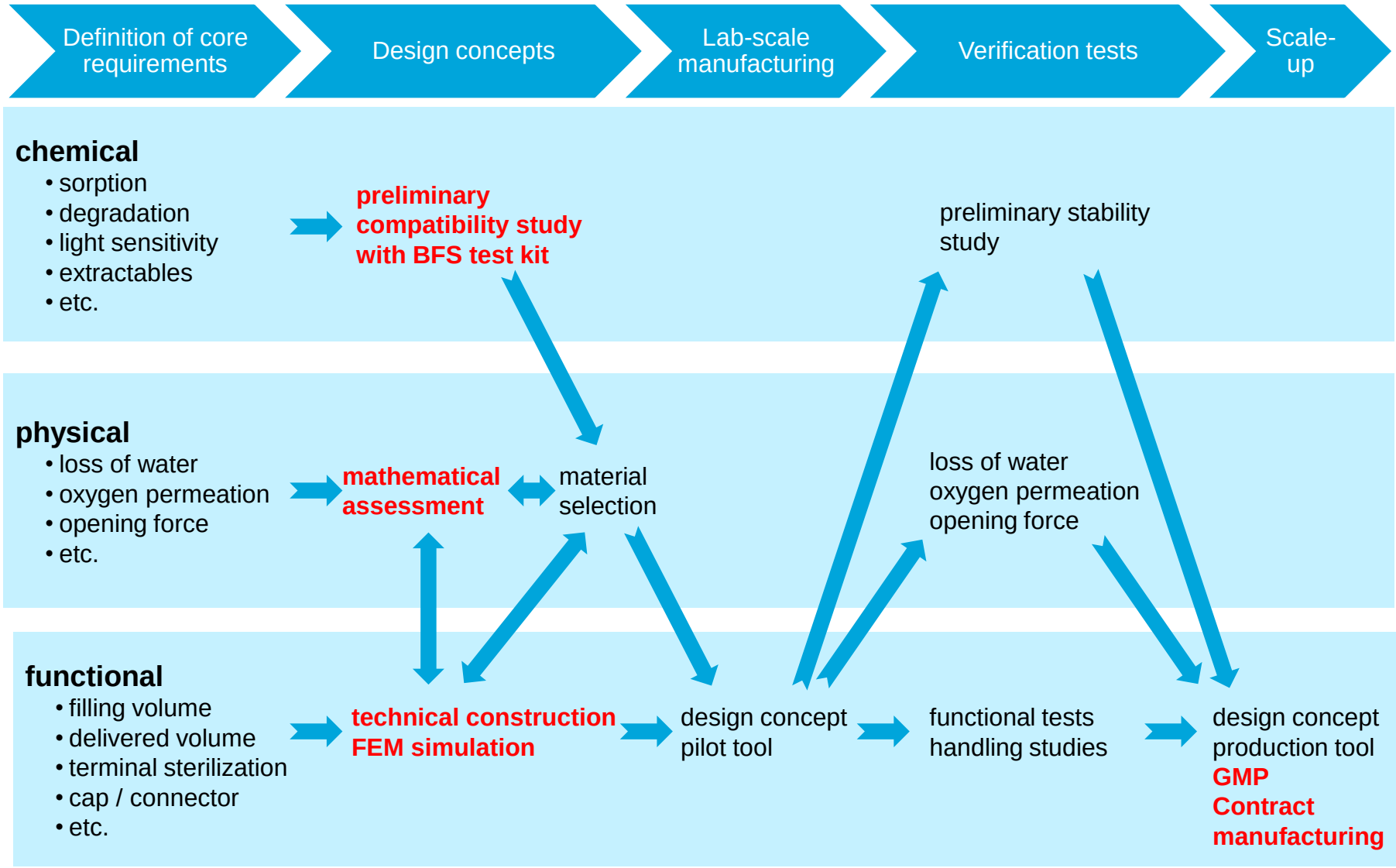
PET / PETG

- low oxygen permeation

COC / COP

- supplier: e.g. TOPAS/Polyplastics or ZEON
- low sorption, good water barrier
- elastomeric grades available

Modern simulation tools, extractables data & test kits support fast Drug Product development.



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/2/ The manufacture of sterile Pharmaceutical Products Using Blow-Fill-Seal-Technology Parenteral Drug Association technical report No 77, 2017

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/13/ ASHP reports Proceedings of a summit on preventing patient harm and death from i.v. medication errors Am J Health-Syst Pharm 65, Dec 15, 2000, 2367-2379

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