
Filling of heat sensitive products / biologicals with BFS equipment

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BFS International Operators Association

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- I. Introduction – Biological Products**
- II. Introduction – BFS process**
- III. Temperature Sensitivity**
- IV. Methods**
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- VII. Literature**

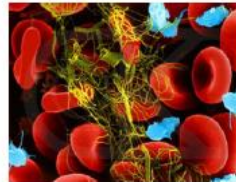
I. Introduction – Biological Products



Blood Derivatives

Whole Blood

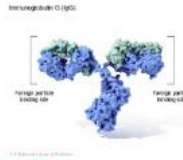
**Blood
Components**



Proteins



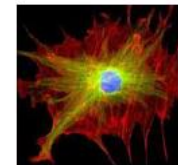
Human Tissues



**Vaccines (preventive
and therapeutic)**



**Allergenic
Extracts**

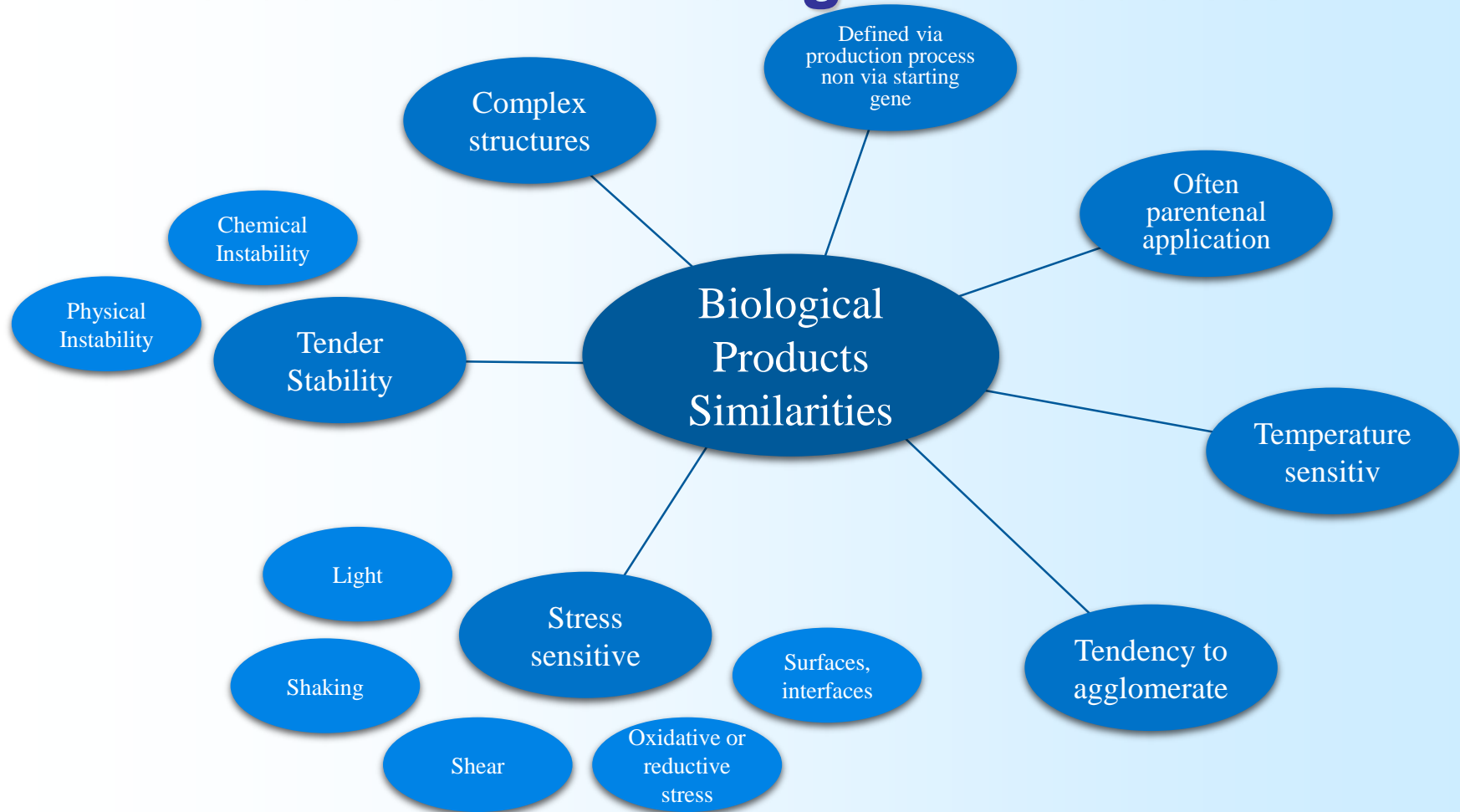


**Cellular &
Gene
Therapies**



**Xenotransplantation
Products**

I. Introduction – Biological Products



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II. Introduction – BFS Process

BFS

- -
- -
- -
- Newly created container
- Transport and storage only for resin material
- Immediately filled
- No cleaning necessary
- No sterilization necessary
- Very few particles
- Single automated equipment

Glass

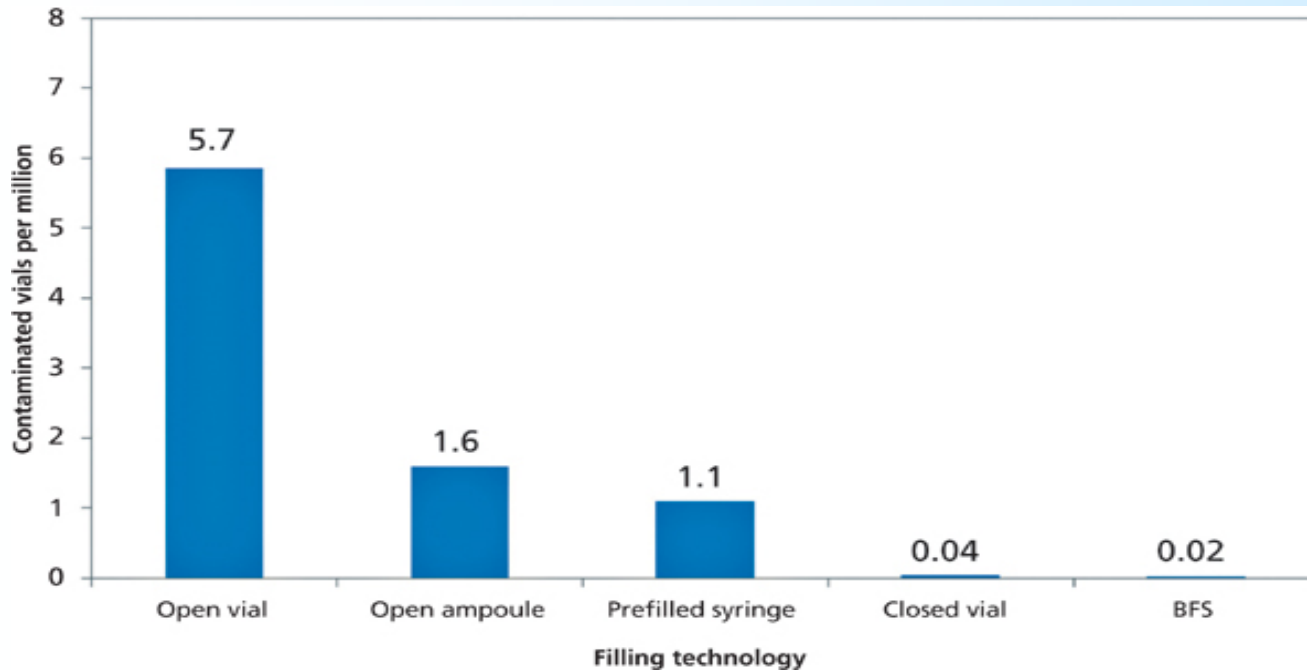
- Can break
- Risk of cuts and glass splinters
- Use of silicone
- Performed container, rubber stopper, cap
- Transport and storage of all parts (glass, stopper, caps)
- Storage month / year
- Critical contamination possible (from manufacturing, open longer etc.)
- Multiple integrated systems

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The BFS process minimizes the risk of contamination by reducing particles, process steps & human interaction



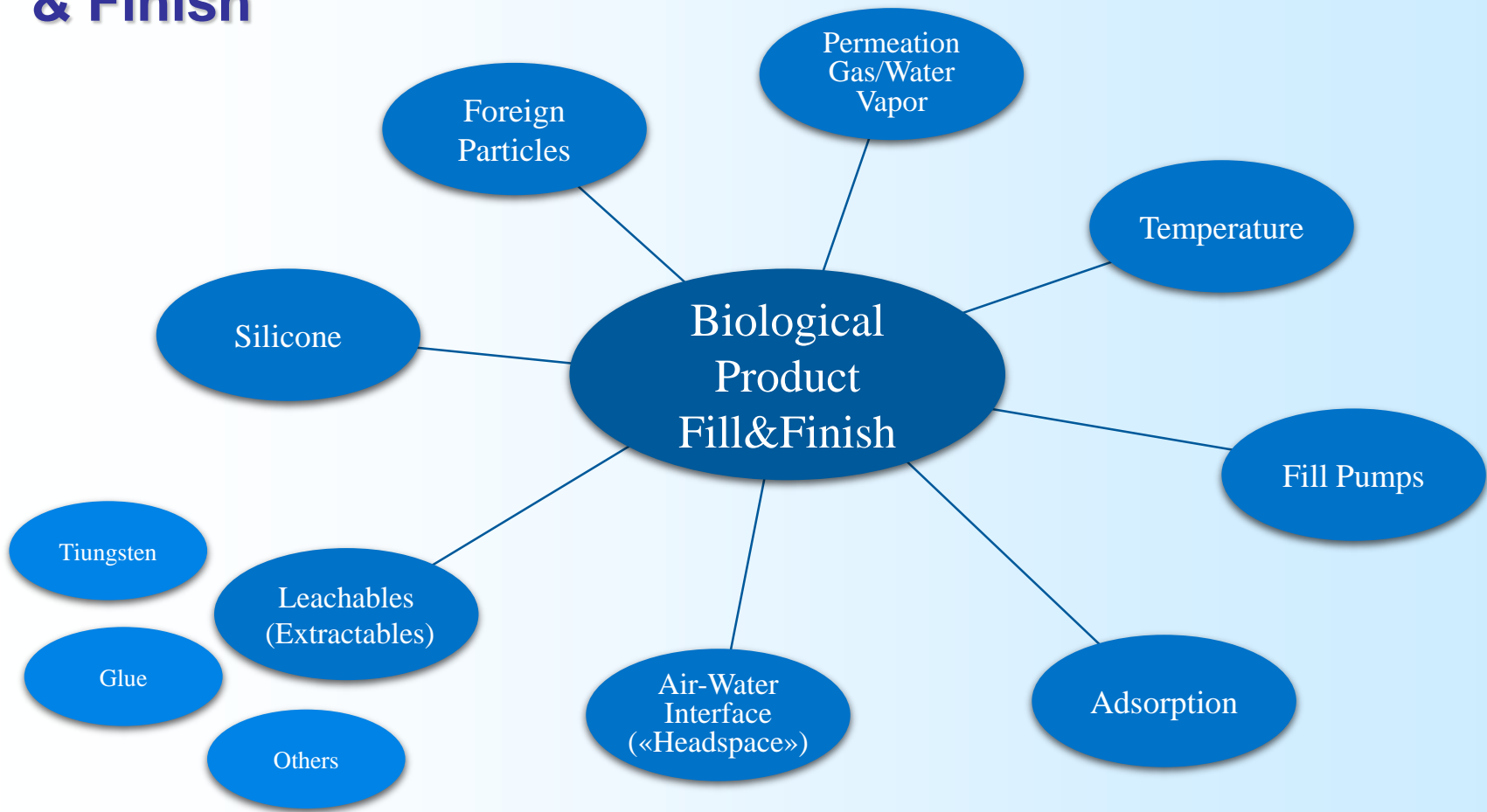
¹¹ Reference: Verjans, B. Reed, C. (2012). "Assessing Filling Technologies for Contamination Risk." *Biopharm International*. 25(3), pp. 46-58.

Potential risk of contamination by filling technology based on air quality and exposure time

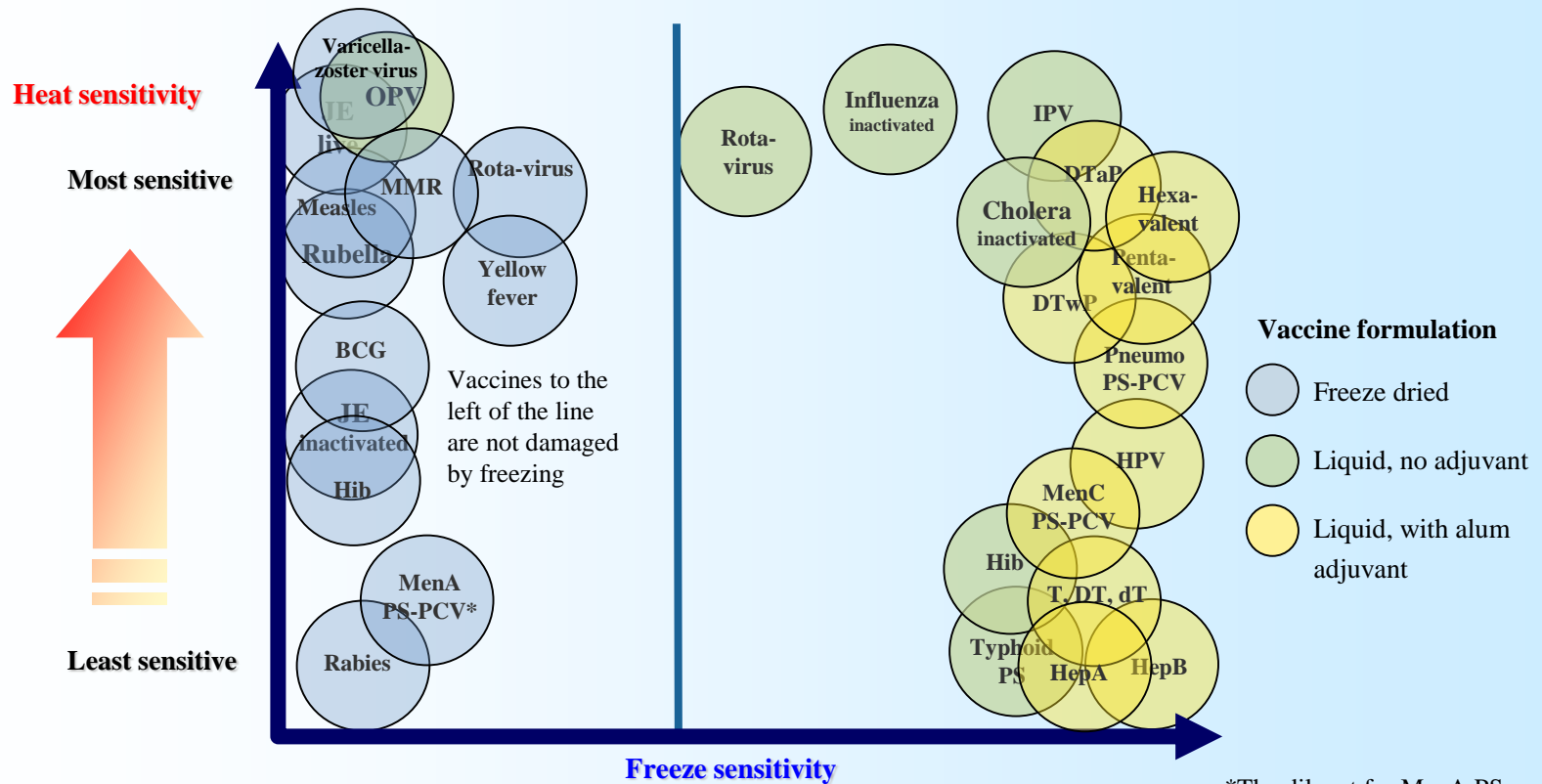
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Parameters Influencing BioProducts during Fill & Finish



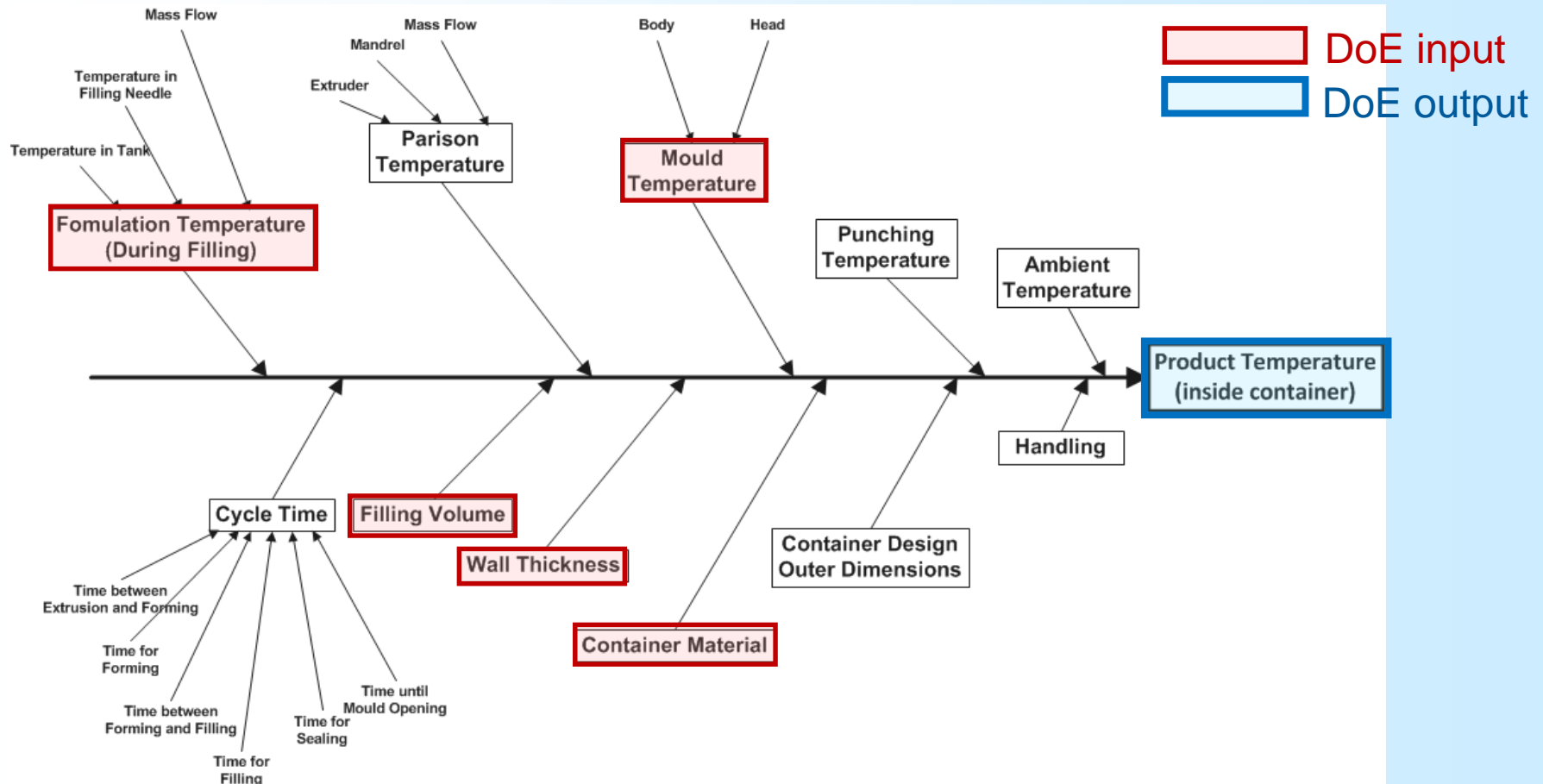
Temperature Sensitivity Vaccines



¹² Darin Zehrung
Next-Generation Vaccine Delivery
Technology Meeting
Geneva, Switzerland, Feb. 2014

*The diluent for MenA PS-PCV contains alum adjuvant and is freeze sensitive.

Many parameters influence the temperature of the formulation inside the BFS-container

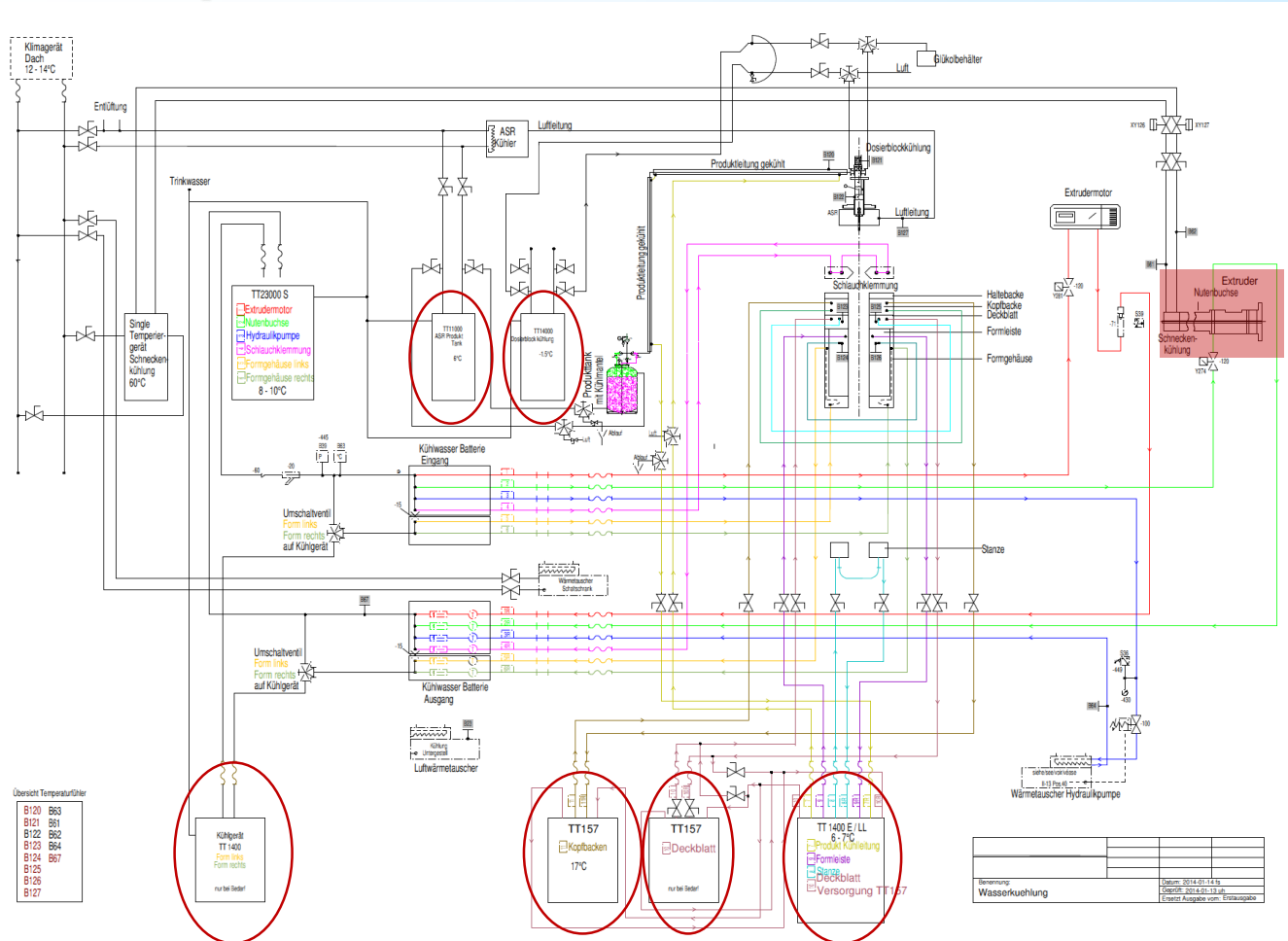


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P&ID optimized for CoolBFS®



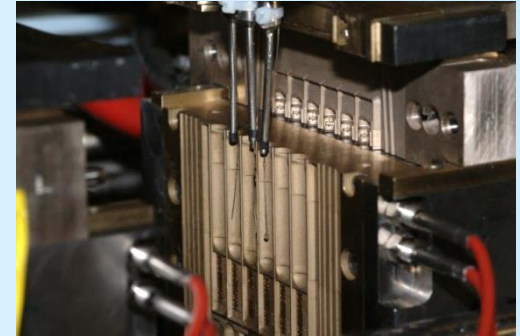
Extruder

Coolant:
5 x water
1x glycol

Temperature regulator

Methods for temperature measurement inside and outside the container

1. Temperature measurement within the mould
(Thermocouples: Type K \varnothing 0.25mm / Type T \varnothing 0.5mm)



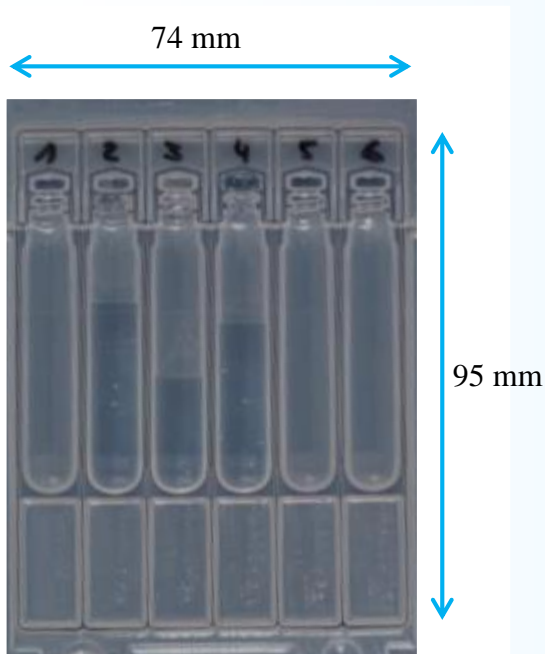
2. Temperature probes
(inside ampoule and surface)
(testo 935 & temperature probes TE type K)



3. IR Thermography
(IR Thermography Camera: Optris PI200)



Key experimental equipment



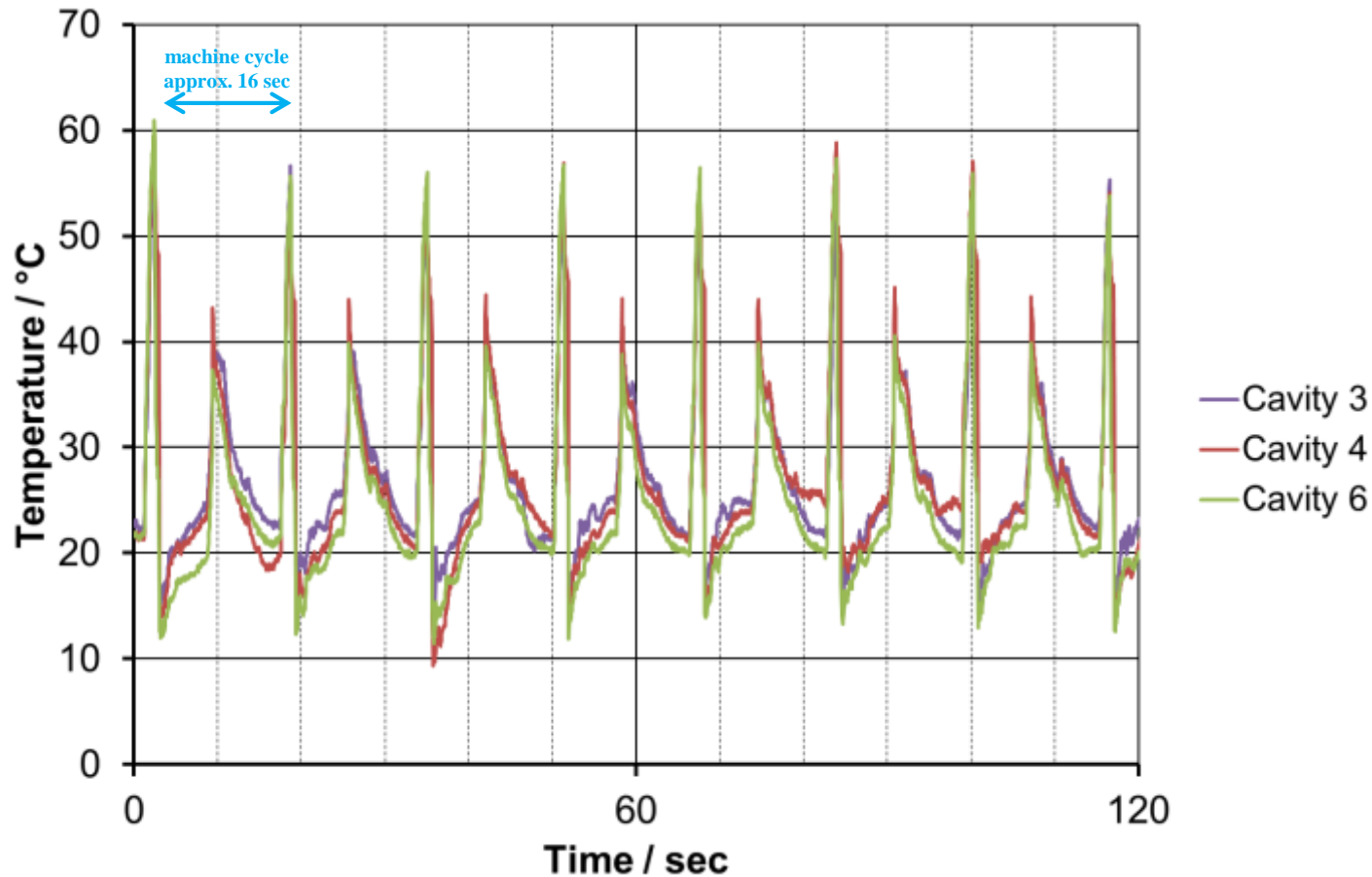
Ampoules with different filling volumes

- BFS-Equipment: bottelpack 3012
- Containers: 2,3 ml Ampules, 6 cavities
- Formulation: Water
- Materials: Two Purell LDPEs
- Thermocouples: Type K \varnothing 0.25mm /
Type T \varnothing 0.5mm
- IR Thermography Camera:
Optris PI200

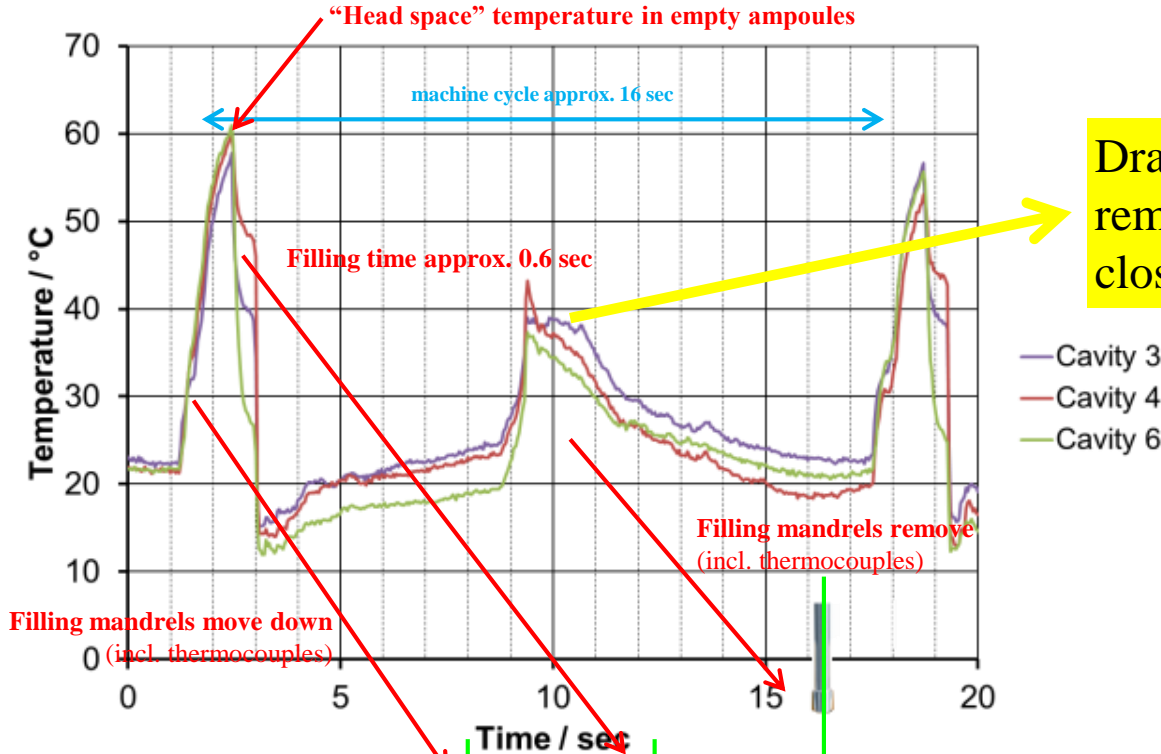
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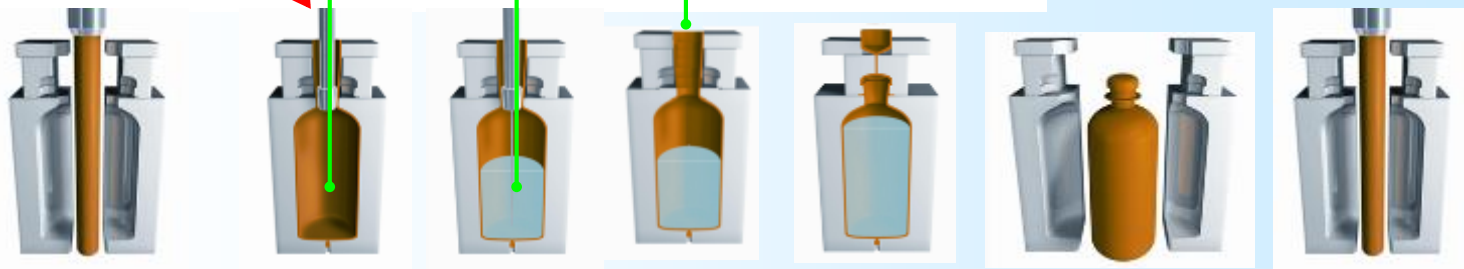
Overview 3 cavities, 7 cycles



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Drawback: Thermocouples removed from product prior to closing

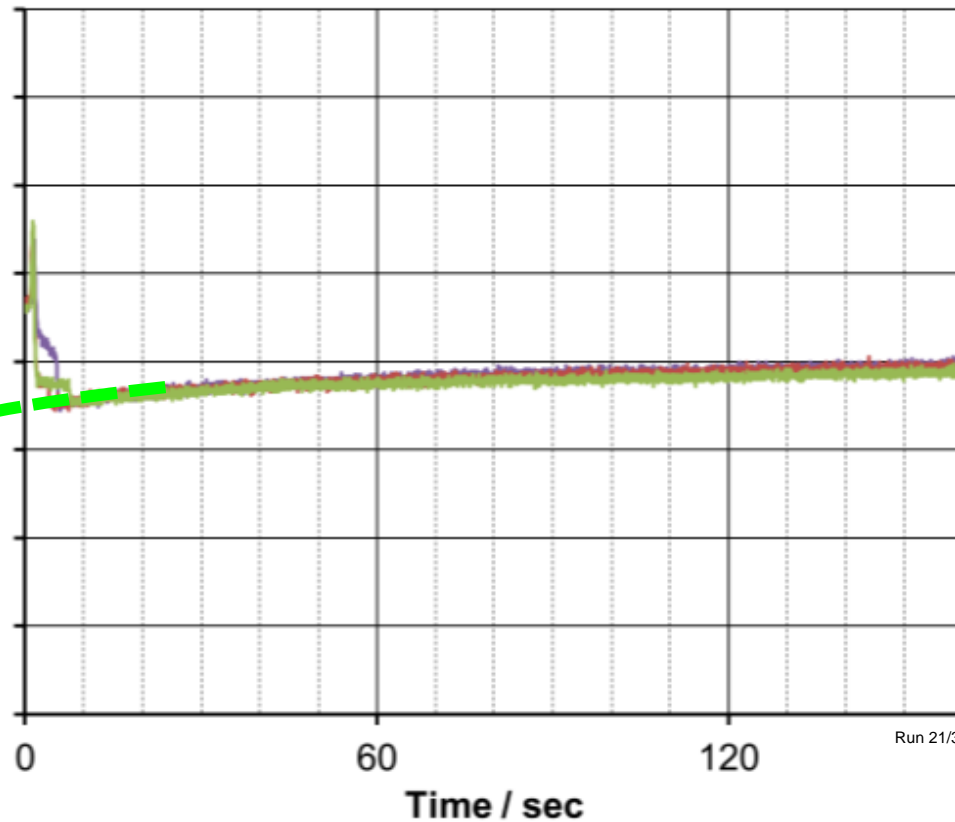
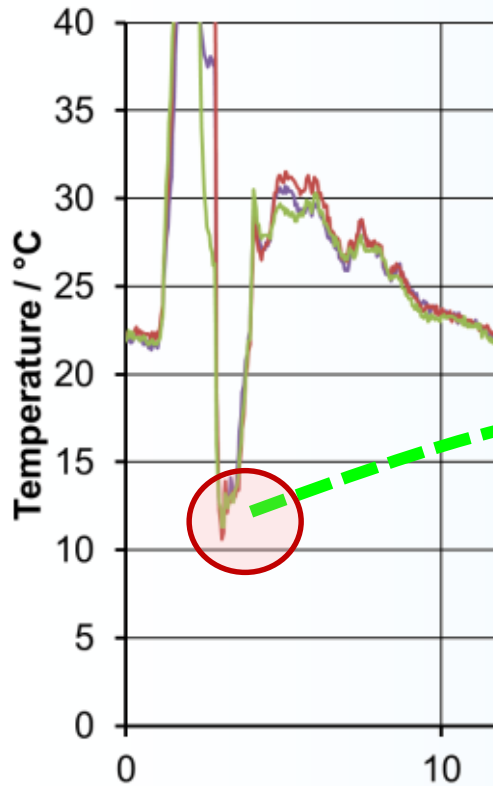


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In mould set-up
(method1)

Piercing set-up (method 2)



The combination of two experimental methods reveals the temperature over time profile

- Ampoule 3
- Ampoule 4
- Ampoule 6

3 examples for main parameters

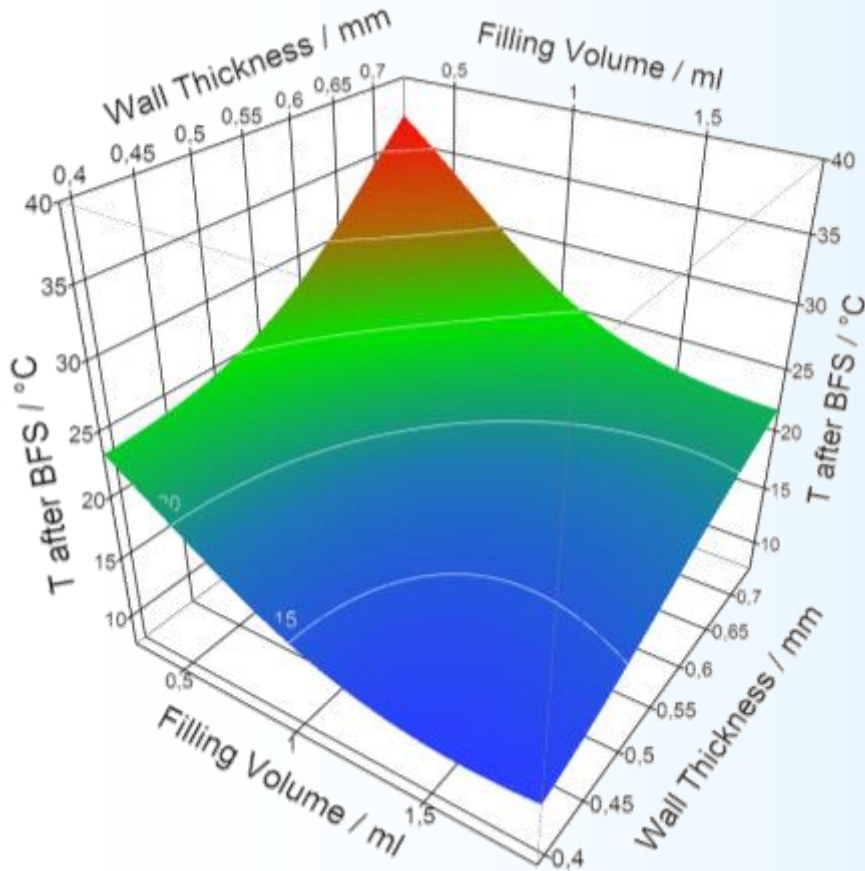
Formulation Temperature

Filling Volume

Wall Thickness

Mould Cooling

DoE data allows tailoring of temperature profiles



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

4 Biotec BFS drug products

rhDNase (Pulmozyme, Genentech) /14/

4 mg/ml formulation, 37°C for 15 min.
Visual inspection, ELISA, CD, UV SEC,
activity assay

Fully active, no aggregates, no permanent changes
to conformational states
2-year refrigerated stability verified

4 Biotec BFS drug products

Attenuated Live-Virus Vaccines (flu vaccine and Rota-Virus vaccine) /15/

0.2 and 2.3 ml

BFS-Process with Purell 1840H

No statistically significant differences in stability compared to conventional filled market products (glass & LDPE container)

2-year (flu vaccine) & 1-year (Rota-Virus) stability verified

There is a biological product in BFS at the market since some years



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- The filling of temperature sensitive products is possible with an adapted BFS machine.
- At time being this is not a generally accepted statement, but must be proofed on a case by case basis.
- A stringent QbD approach revealed the most important parameters to deal with heat sensitive products.
- Main influence parameters are container design, fill volume, wall thickness and formulation temperature.
- BFS can generate some advantages in filling of Biological products.

YES it's possible

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**Thank you very
much for your
Attendance!**