Neue Biopharmazeutika: von der Idee zum Prüfarzneimittel

Etablierung einer aseptischen Abfüllung für Kleinstchargen am ITEM

Symposium der Fachgruppe
“Arzneimittelkontrolle/ Pharmazeutische Analytik”
Braunschweig, 11. März 2015

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Fraunhofer **Institute for Toxicology and Experimental Medicine**

Hannover

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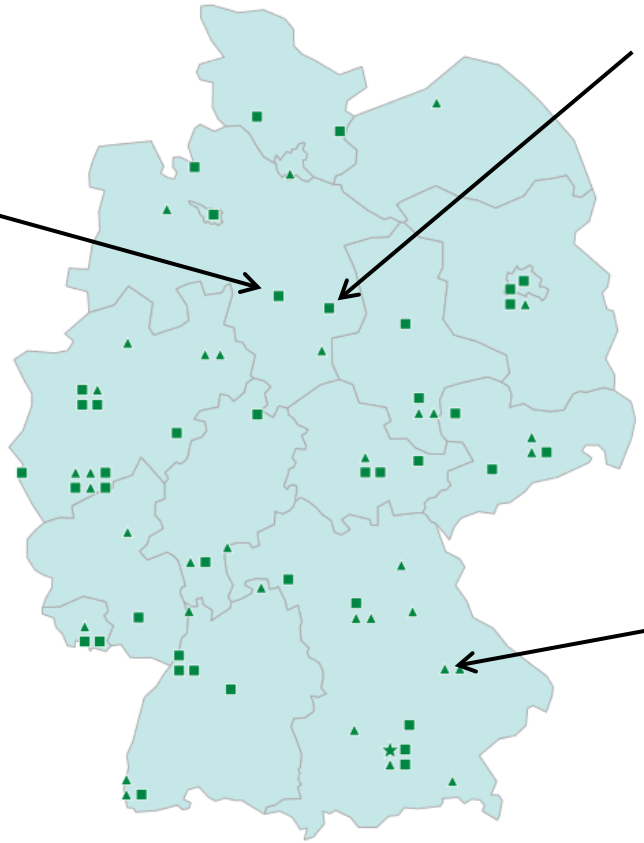

Braunschweig

Pharmaceutical Biotechnology Division

Regensburg

Personalized Tumor Therapy Project group

The ITEM Clinical Research Centre (CRC)

- a new part of the ITEM division of Airway Research -

Focus: Clinical trials phase I (first-in-men) and phase II (proof-of-concept)

Hannover Medical School (MHH) – all indications	Helmholtz-Centre for Infection Research (HZI) – infectious diseases	Fraunhofer ITEM – airway diseases

→ Increasing demand for IMPs for clinical trials

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Pharmaceutical Biotechnology Fraunhofer ITEM

Biopharmaceutical process development in Braunschweig

- 2000 m² lab space for biopharmaceutical process development
- 600 m² clean rooms (A, B, C, D) for early clinical phase manufacture (API + IMP)
- 700 m² offices, 40 persons staff
- Manufacturing license since 1997

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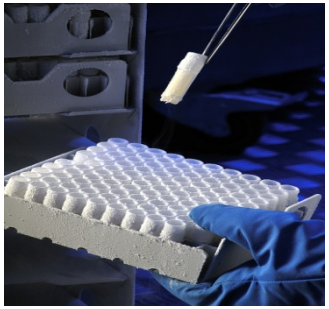
Pharmaceutical Biotechnology: Fields of expertise



- Microbial and animal cell line development
- GMP-manufacture of MCBs and WCBs
- Mammalian and Microbial cell culture development (USP)
- Downstream process development (DSP)
- Analytical method development and validation
- ICH stability studies
- Biopharmaceutical drug substances production platforms
  - Nucleic acids / plasmids
  - Recombinant and monoclonal antibodies
- GMP manufacture of investigational biopharmaceutical drug substances and
- **ASEPTIC FILLING of liquid dosage forms (bags, vials and ampoules)**

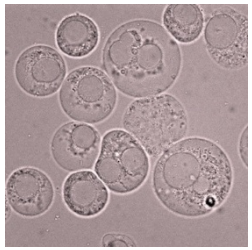
Process Chain

Cell line development | USP | DSP | Formulation | Fill&Finish

Cell line development at ITEM

Plasmid/e mit GoI

DNA-Transfer in Wirtszellen



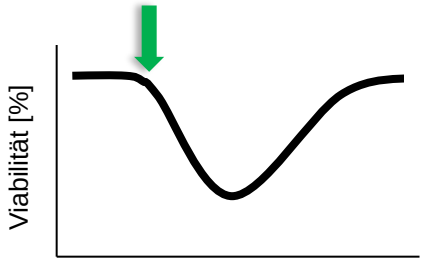
Wirtszellen

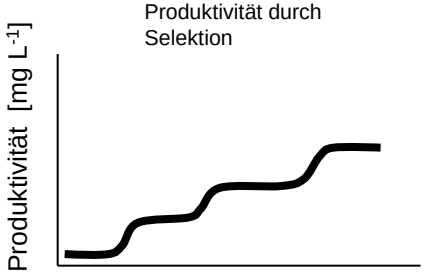
z.B. CHO-K1, CHO-DG44, HEK293, etc.

Selektion der stabilen Zellen (Antibiotika, MTX)

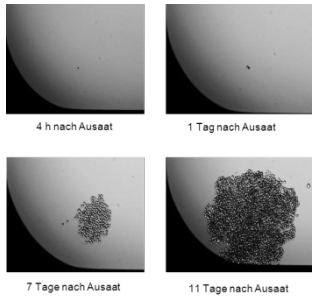
\+

evtl. **Amplifikation** des GoI (MTX)





Einzelzellklonierung nach FDA suggestion limiting dilution + clone picking



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Process Chain

Cell line development | USP | DSP | Formulation | Fill&Finish

Process development at ITEM

USP

- Auswahl des Produktionsklons
- Auswahl/Modifikation des Produktionsmediums
- Entwicklung der Feedingstrategie
- Entwicklung des seed trains
- Prozessentwicklung (pH, Temperatur, CO_2, pO_2, seed density)
- Prozessentwicklung im 1 L-Maßstab (DoE)

DSP

- Generische IgG Aufreinigungsplattform (DoE)
- 3 Chromatographieschritte
- Capture (Protein A)
- Cation exchange chromatography (CIEX)
- Anion exchange chromatography (AIEX)
- Analytische Methoden:

  Content assay, SDS-PAGE, IEF, DNA, HCP, Protein A-ELISA, SE-HPLC, and OD

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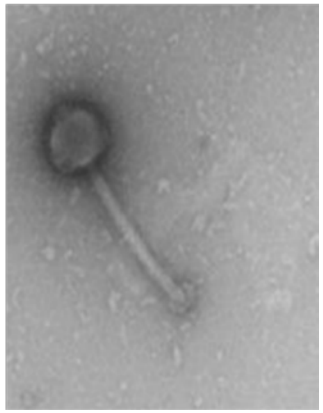
Process Chain

Cell line development | USP | DSP | Formulation | Fill&Finish

Challenges



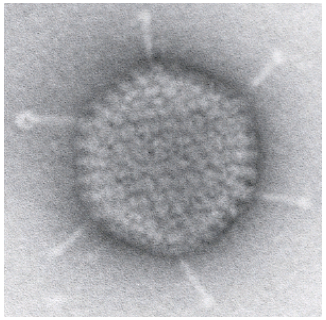
Staph. aureus bacteriophage

- Outsourcing of F&F difficult

  → Biosafety reasons (*BL2!)

  → Toxicological data (often) not available in early drug development stages

  → Batches typically too small



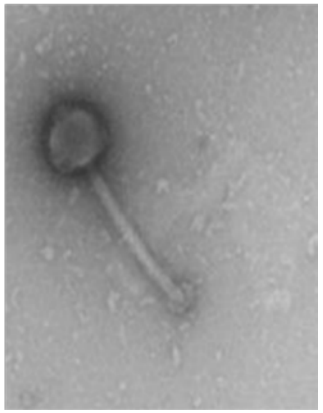
Adenovirus*

- Defining suitable primary containment incl. stopper

  → Significant loss of API in bulk solution depending on the stopper material

  → Additional time-consuming studies required

Challenges



API

Formulated Bulk

Cell line development

USP

DSP

Formulation

Fill&Finish

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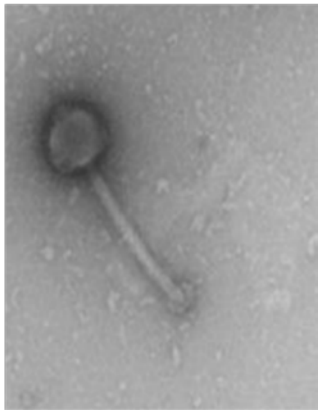
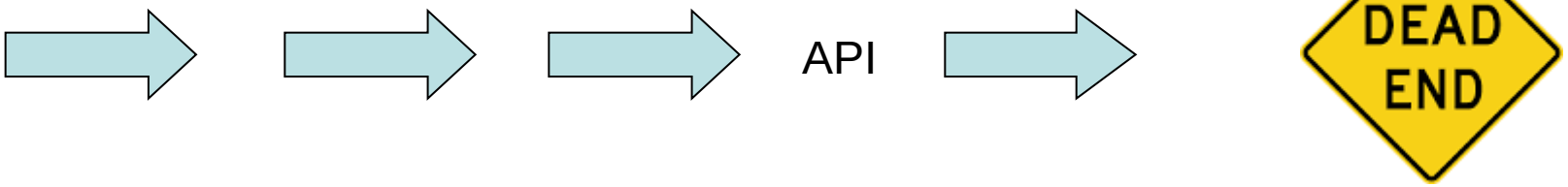
Challenges





Cell line development

USP

DSP

Goals and Approach

The goal:

Cost effective access to small batches of aseptically-filled biopharmaceutical IMPs

The filling line approach:

- a basic/standardized process
- based on ready-to-fill primary packaging/glass containers/ampoules
- use of standard formats
- high quality glass (as primary containment)

User requirements for Fill & Finish

- Implementation of the F&F facility as an extension to an existing API manufacturing facility
- Space constraints (no space for washer and sterilization tunnel)

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User requirements for Fill & Finish

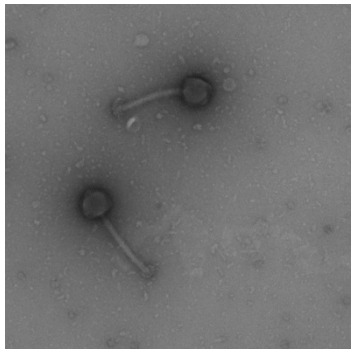
- Budget constraints

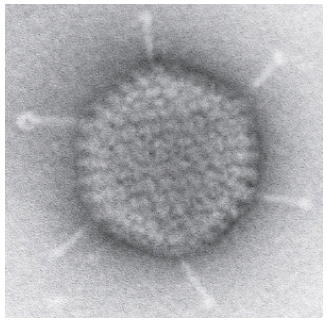
→ Costs for washer and sterilization tunnel disproportionately high for prospective usage

User requirements for Fill & Finish

- Fill of highly potent drug substances (e.g. protein toxins) and biosafety level 2 substances (e. g. viruses)

→ Filling machine and clean room resistant to decontamination gassing (H_2O_2)





User requirements for Fill & Finish

- Highly sensitive biopharmaceutical drug substances ((glyco-)proteins, nucleic acids)

→ N_2 gassing before/during fill

User requirements for Fill & Finish

- Flexibility in primary packaging and volumes

→ vials, ampoules

→ 1 - 50 ml, 1 - 30 ml

- Fully automated filling of small batches

→ clinical trial material / stability studies

→ between 400 and 20.000 objects per day

The ITEM solution

- Primary packaging
- Manufacturing process
- Filling machine
- Operation sequences

The ITEM solution

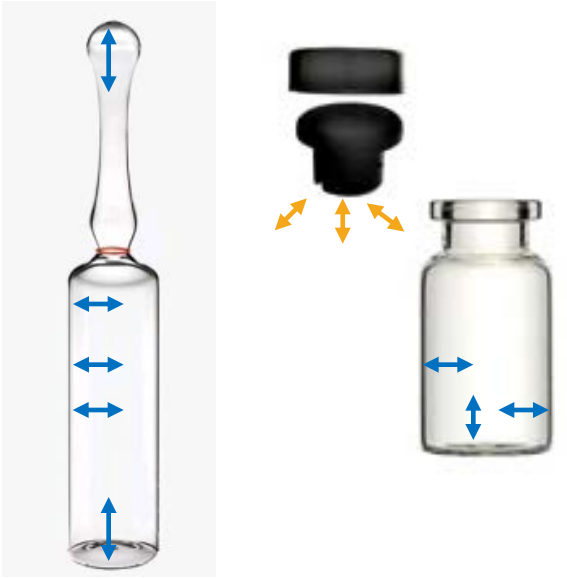
- Primary packaging

→Presterilized ready-to-fill vials and burn-up ampoules

- Manufacturing process
- Filling machine
- Operation sequences

Why glass ampoules?

- one single surface material for potential interaction with formulation components
- no additional rubber component with potential effects through:
  - selective adsorption / modification (inactivation/aggregation) of formulation components
  - leachables/extractables
  - rubber aging effects (particles)
- Standardized / generic media fills



Why glass ampoules?

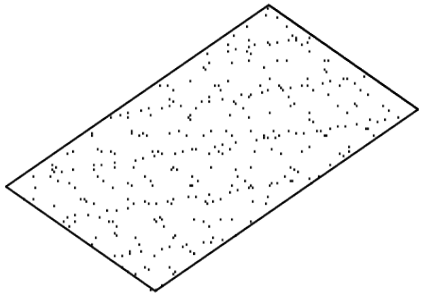
Facilitated stability assessment

→ Fast access to preliminary stability data (≥ 3 months)

→ **Time:** fast step sequence from drug substances to clinical grade drug products

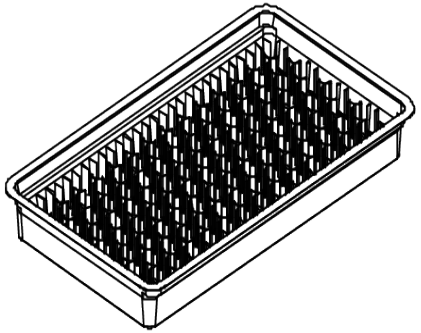
→ **Costs:** Reduction of costs per ampoule

Presterilized ready-to-fill vials
- packaging description

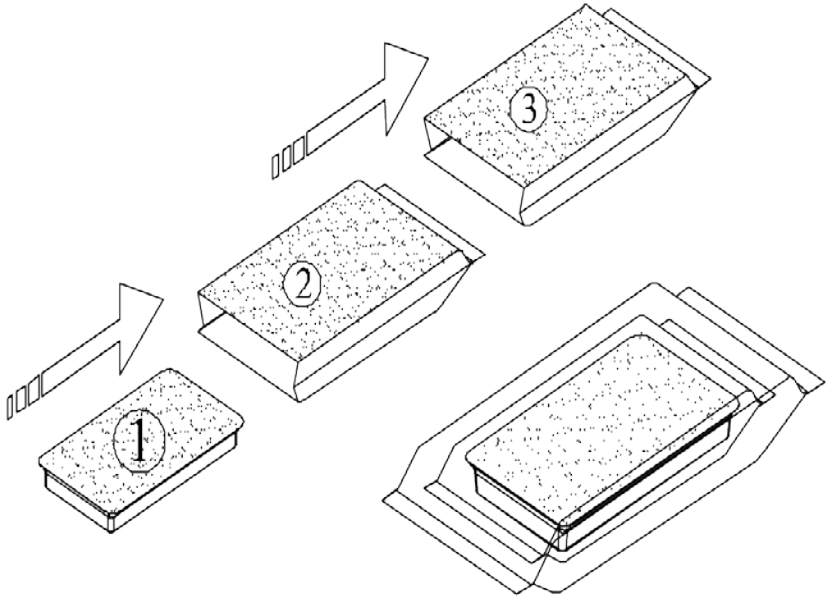


Tyvek lid

Glass vials (type I)



Tray: no glass to glass contact



- Tray sealed with Tyvek sheet
- Tray protected by a double steribag

The Fraunhofer ITEM solution

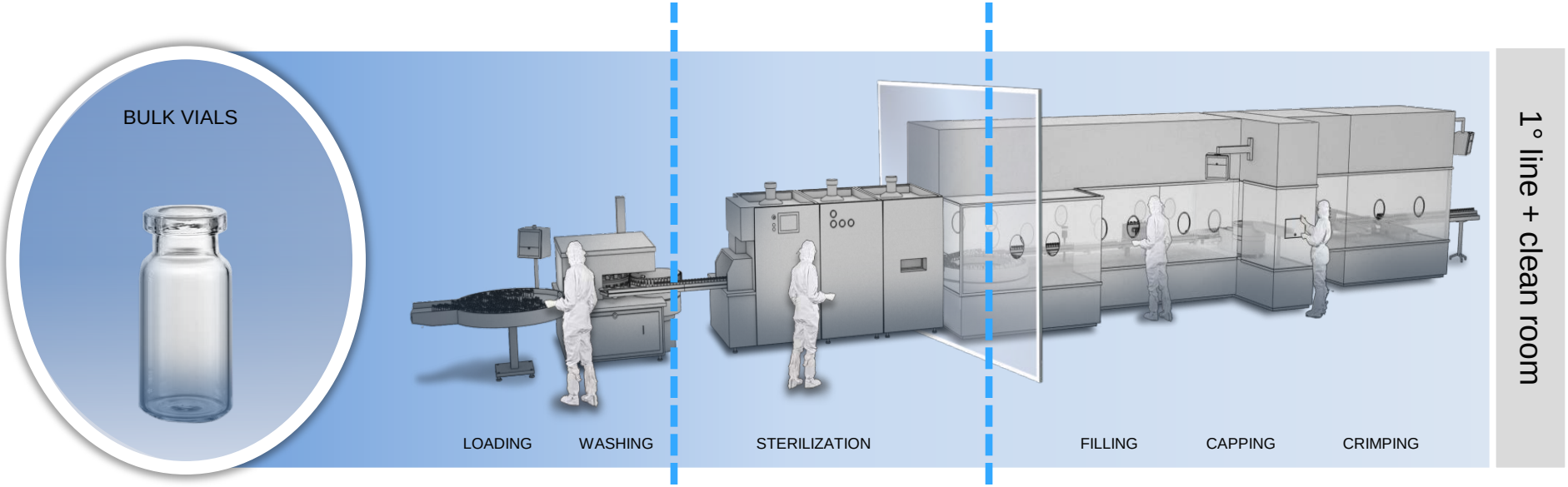
- Primary packaging
- Manufacturing process

→ **fill-and-seal unit; no in-line washer and sterilization tunnel**

→ **reduction of space requirements and investments**

- Filling machine
- Operation sequences

Basic zone requirements for traditional aseptic filling line



Zone 1 (ISO 8):

Loading of primary packing material and washing

Zone 2 (ISO 7/LAF):

Sterilization / depyrogenation

Zone 3 (ISO 7/LAF):

Filling / sealing

*additional line for bulk ampoules

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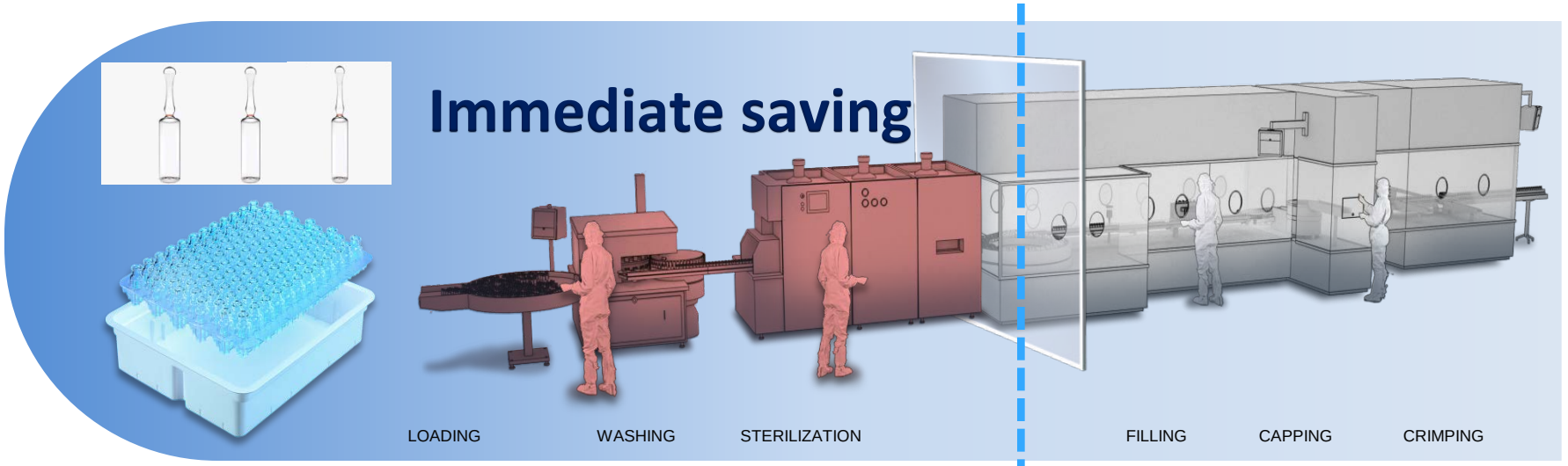
Ampoules and ready-to-fill vials approach for an aseptic filling line



Reduction in:

Investments

- Clean room
- Washing Machine
- Depyrogenation oven
- Fixtures for machinery
- Additional instrumentation
- Validation cost (time)

Fixed costs

- WFI
- LAF
- Personnel training and revalidation
- Maintenance
- Direct labor

Zone 3 (ISO 7/LAF):

Filling / sealing

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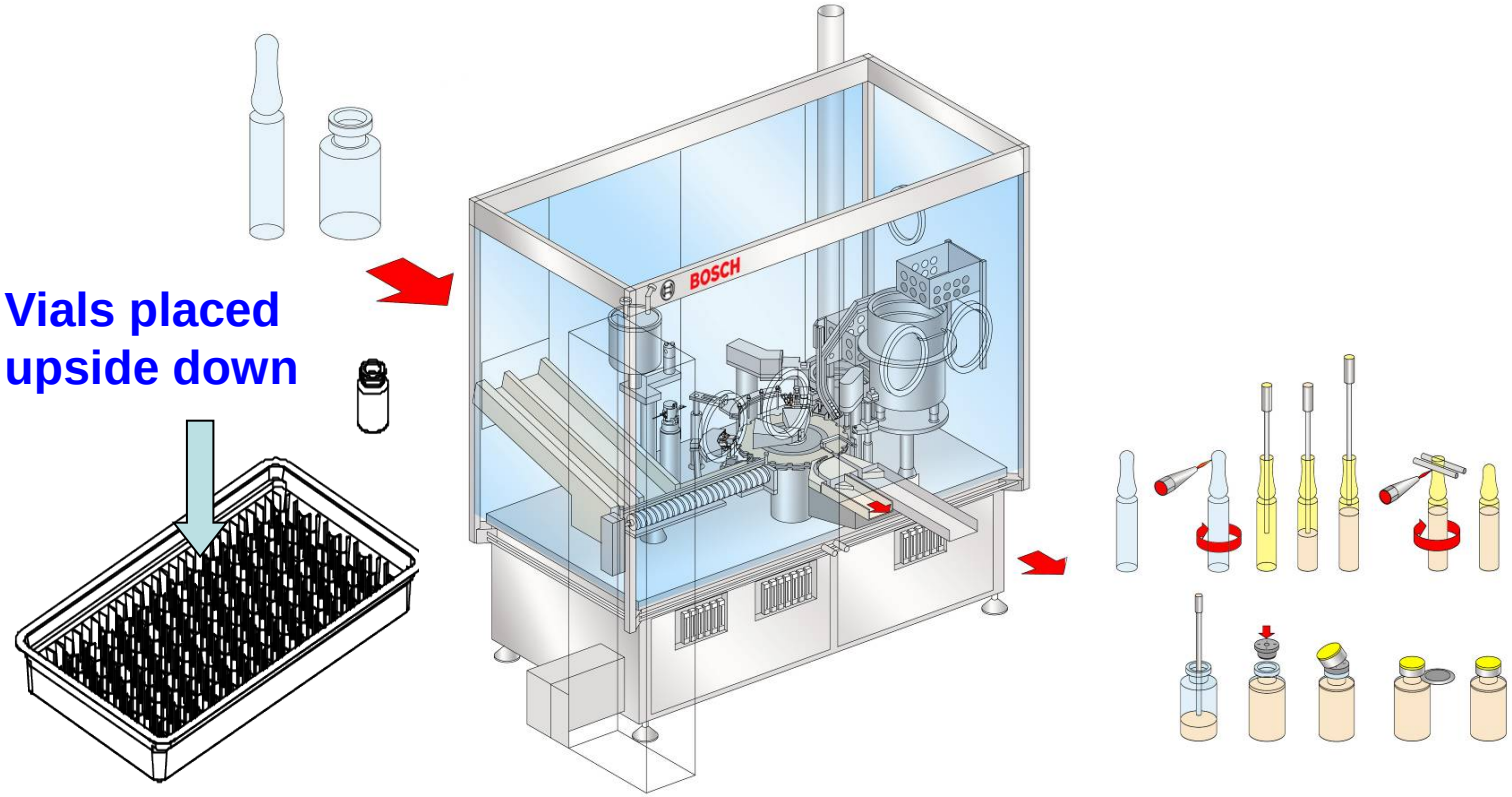
The Fraunhofer ITEM solution

- Primary packaging
- Manufacturing process
- Filling machine: → **customized**
- Operation sequences

Filling machine
for closed ampoules and vials



The Fraunhofer ITEM solution

- Primary packaging
- Manufacturing process
- Filling machine
- Operation sequences

Filling machine basic configuration for pre-sterilized ampoules and vials

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Sequence for vials and stoppers

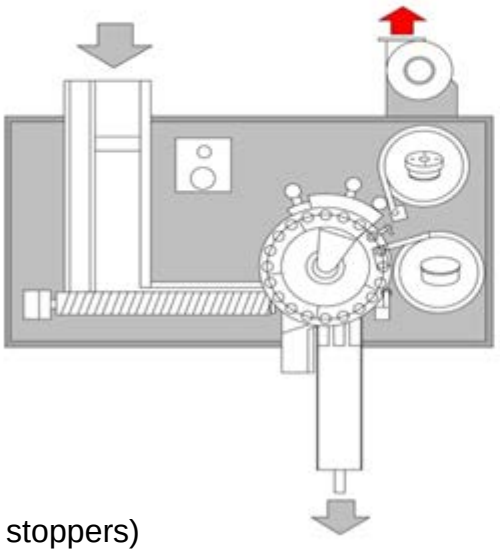
- Stoppers sterilized, double packed
- Vials ready-to-fill / double packed
- Introduced into class B clean room and from there into the RABS (Restricted Access Barrier System) via pizza door
- Unpacking from the Tyvek cover inside the RABS
- Filling and sealing sequence in ARF 1000 (Bosch)

Sequence for ampoules

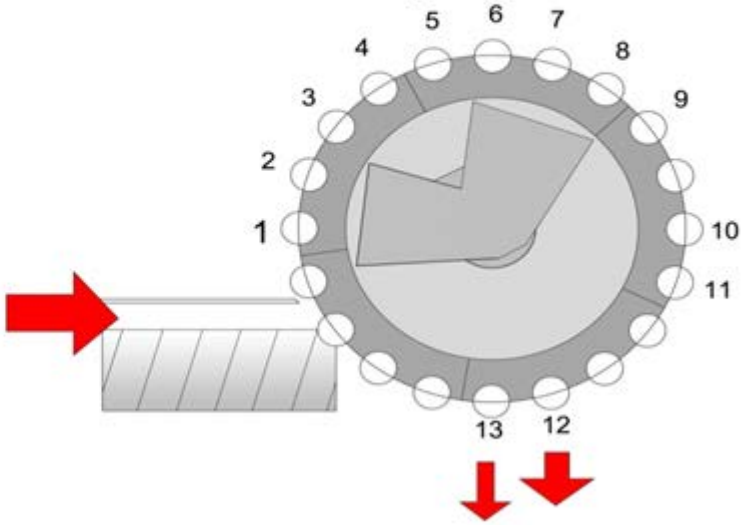
- Loaded in a nest
- Cleaning
- Drying
- Double-packed
- In house sterilization /depyrogenization (121 C)
- Transferred into class B clean room and loaded into the filling line via pizza door (→ class A)
- Unpacking from the Tyvek wrap inside the RABS
- Filling and sealing sequence filling machine

Operation sequence – combined filling machine

ARF 1010 / 1020



combi version
- closed ampoules
- open ampoules
- injection vials



1. Pre-heating opening
2. Tip opening
3. Burn opening under rotation
4. Pre-gassing
5. Filling
6. Post-gassing
7. Pre-heating closing
8. Closing ampoules (inserting stoppers)
9. Control stoppers
10. Caps placing
11. Crimping
12. Outfeed
13. Reject station

GMP manufacture

- Aseptic process simulation for vials

→ 3 successfull media fills in 2014

- GAA inspection in January 2015

- Manufacturer‘s license for automated aseptic F&F expected in 2015

Summary

Fraunhofer ITEM needed a combined solution to be able to manufacture small batches of investigational medicinal products for clinical trials and stability testing

→ **small combined filling machine in conjuction with pre-sterilized vials and burn-up ampoules provides a fast, flexible and cost-effective solution, enabling Fraunhofer ITEM to offer the complete manufacturing process from cell line development to the final IMP**

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Thank you for your kind attention