Validation of aseptic fill process

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I. Regulatory Background
II. Media fill – Method
III. Media fill – Design
IV. Media fill – Evaluation
V. Extruder Challenge Test

Which guidelines are available?

- **China,** Chinese GMP revised in 2010 Annex 1
- **EU,** EudraLex Volume 4 EU-GMP Guide Annex 1
- **FDA,** Guidance for Industry – Sterile Drug Products produced by aseptic processing
- **USP 1116,** Operational Evaluation of the Microbiological status of Aseptically Filled Products in Clean Rooms and Other Controlled Environments.
- **PIC/S,** PI 007-2 Recommendation on the Validation of Aseptic Processing
- **Japan,** Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing

What answers can we find?

- What to do?
- When to do?
- How to do?
- How many units?
- Specifications?
- Which nutrient Medium?

What to do?

Chinese GMP:	***Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill).***
EU-GMP:	***Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill).***
FDA:	***An aseptic processing operation should be validated using a microbiological growth medium in place of the product.***

When to do?

Chinese GMP:	***Process simulation tests should be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC-system, equipment, process and number of shifts. Normally process simulation tests should be repeated twice a year per shift and process, one batch at least in each time.***
EU-GMP:	***Process simulation tests should be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC-system, equipment, process and number of shifts. Normally process simulation tests should be repeated twice a year per shift and process.***

When to do?

FDA:

When a processing line is initially qualified, individual media fills should be repeated enough times to ensure that results are consistent and meaningful…
…We recommend that at least three consecutive separate successful runs be performed during initial line qualification…
…Subsequently, routine semi-annual qualification conducted for each processing line will evaluate the state of control of the aseptic process.

How to do?

Chinese GMP:	***The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps which may affect the aseptic result.***
EU-GMP:	***The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps.***
FDA:	***Media fill studies should closely simulate aseptic manufacturing operations incorporating, as appropriate, worst-case activities and conditions that provide a challenge to aseptic operations.***

How many units?

Chinese GMP: *The number of containers used for media fills should be sufficient to enable a valid evaluation.*

EU-GMP: *The number of containers used for media fills should be sufficient to enable a valid evaluation.*

FDA: *The number of units filled during the process simulation should be based on contamination risk for a given process and sufficient to accurately simulate activities that are representative of the manufacturing process.*

Specifications?

Chinese GMP:	***When filling more than 10,000 units:*** ***(1) 1 contaminated unit should result in an investigation;*** ***(2) 2 contaminated units should result in revalidation , following investigation.***
EU-GMP:	***When filling more than 10,000 units:*** ***a) 1 contaminated unit should result in an investigation;*** ***b) 2 contaminated units are considered cause for revalidation, following investigation.***
FDA:	***When filling more than 10,000 units:*** ***-- 1 contaminated unit should result in an investigation.*** ***-- 2 contaminated units are considered cause for revalidation, following investigation.***

Which nutrient medium?

Chinese GMP:	***Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilisation of the nutrient medium.***
EU-GMP:	***Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilisation of the nutrient medium.***
FDA:	***In general, a microbiological growth medium, such as soybean casein digest medium, should be used. Use of anaerobic growth media (e.g., fluid thioglycollate medium) should be considered in special circumstances.***

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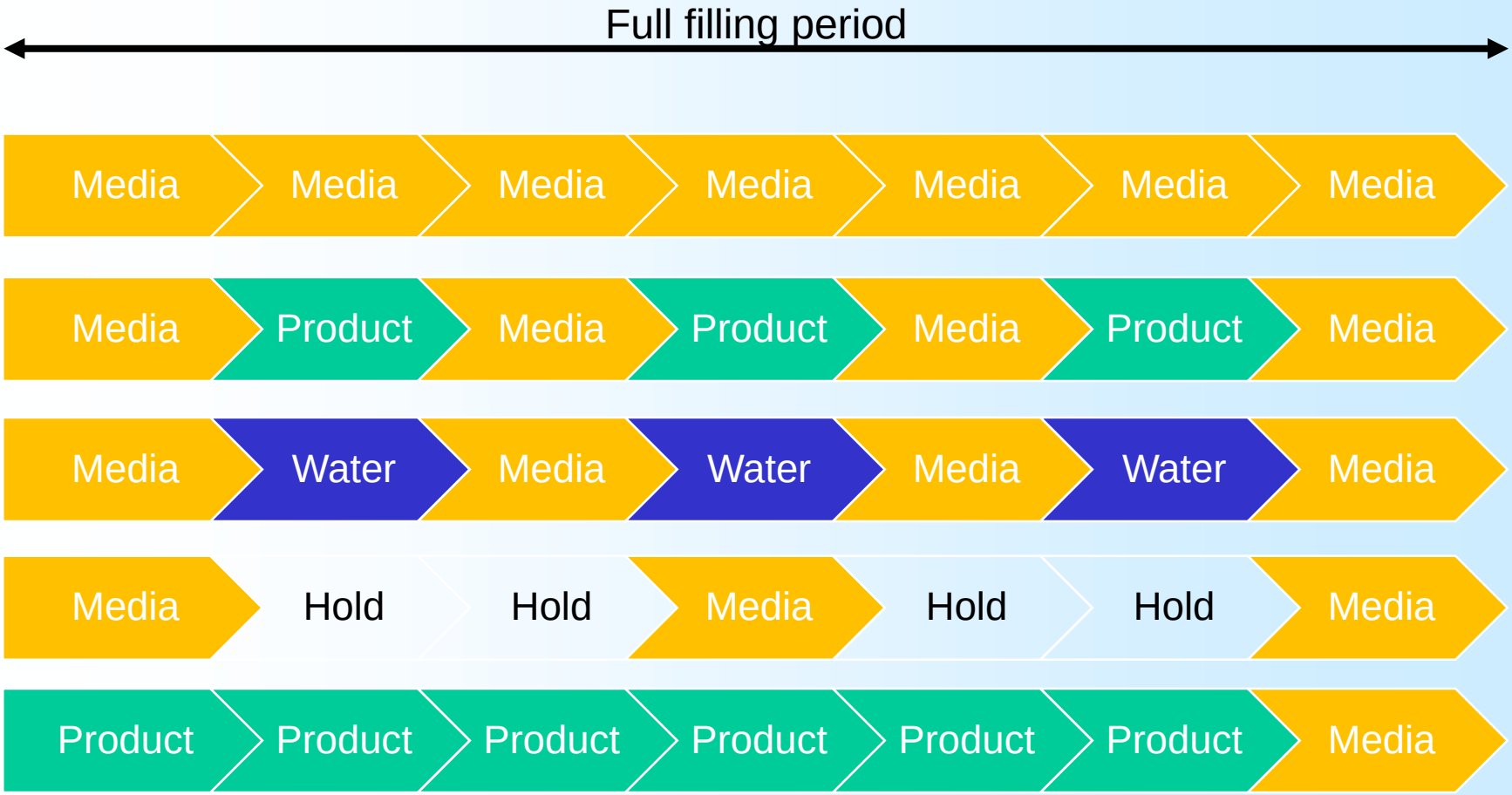
Different methods for media fills



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Worst case parameters

If machine is used as shared equipment, worst case parameters should be defined:

- Longest fill duration
- Widest container opening
- Longest exposure time of open container

Interventions

- Interventions must be clearly defined and classified regarding contamination risk, frequency…
- Interventions must be covered during media fill
- Duration of media fill to allow performing all defined interventions
- Proper documentation of interventions required (batch records)

Interventions

Example for classification of interventions

Minor interventions

Major interventions

Critical interventions

Other points to consider

- Shift regimes to be considered
- Fill level of units sufficient for complete wetting of inner surface
- Fill level of units to allow sufficient oxygen for supporting microbial growth
- Max. holding time to be considered
- All integral units to be incubated

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Incubation / storage

Different possibilities e.g.:

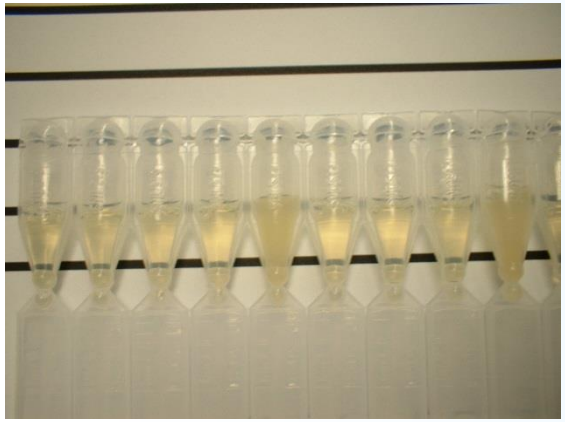
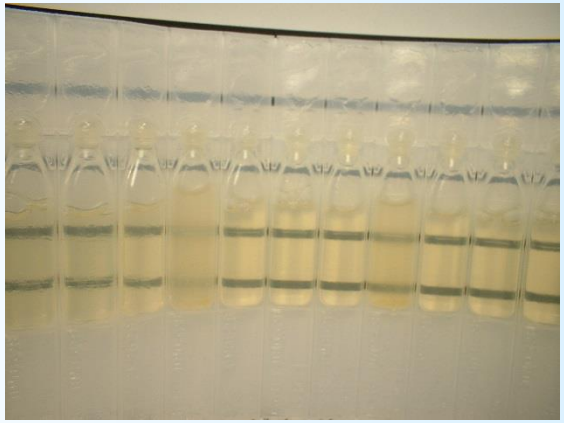
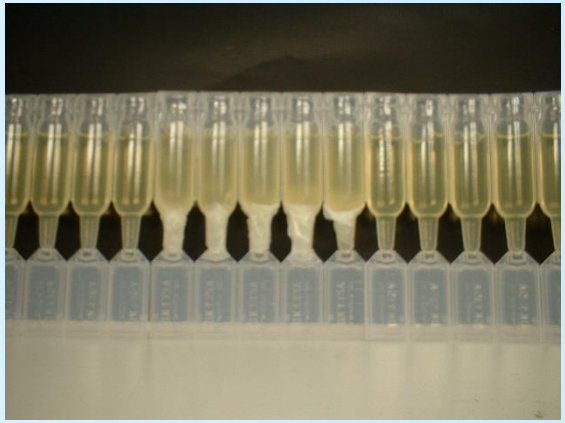
- **14 days at 20-25°C**
- **7 days at 20-25°C and 7 days at 30-35°C**
- **Heat up period to be considered**

Evaluation/Examination

- To be performed or at least supervised by QC personnel
- Examination to be done by educated, trained and experienced personnel
- Proper ambient conditions required
- Proper documentation required
- Growth promotion test to be demonstrated for medium

Evaluation/Examination



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Why to do an extruder challenge test?

FDA Aseptic Guideline – Appendix 2 BFS Chapter B

Data gathered during such studies should ensure that BFS containers are sterile and, if used for parenteral drugs, nonpyrogenic. This can generally be achieved by validating that time temperature conditions of the extrusion process are effective against endotoxin or spore challenges in the polymeric material.

Literature available

- Leo, F., Poisson, P., Sinclair, C. S., & Tallentire, A. (2004). Evaluation of Blow/Fill/Seal Extrusion through Processing Polymer Contaminated with Bacterial Spores and Endotoxin. PDA Journal of Pharmaceutical Science and Technology.
- Birch,C.J., Sinclair, C.S.(1998). BFS Extrusion of Contaminated Polymer. BFS-News 9_98;
- Molin, O. (1999). Extruder Challenging Test for verifying Production of Sterile and Endotoxin Free Polypropylene Ampoules. BFS-News 3/1999
- Poisson, P.(1999). Spore Polymer Challenge of the ALP Model 624 BFS Machine. BFS-News 3/99.
- Rommelag (2015). Design Space Verification for extrusion process

Questions to be asked

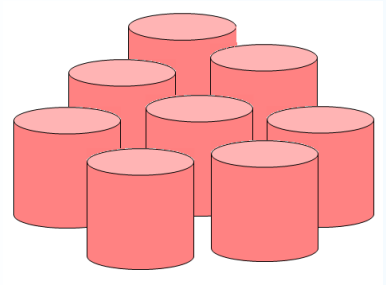
- Is there a reduction of endospores within the BFS-extrusion process?
- What are the parameters influencing the process?
- Can the reduction-effects be ranked?
- Is the extrusions-process equivalent to sterilization?

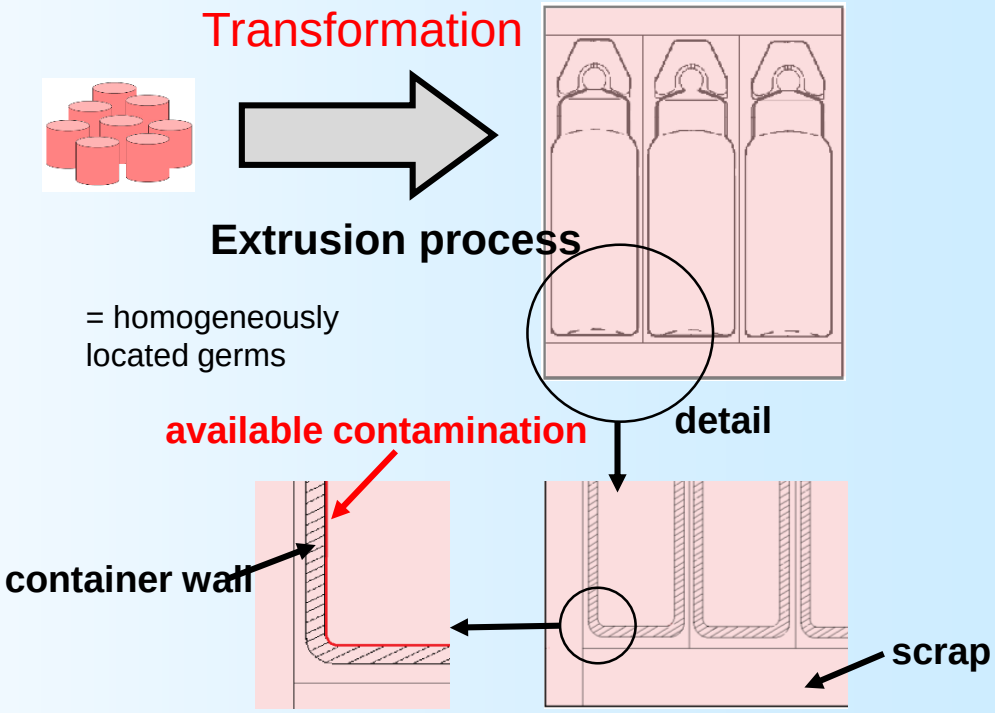
How to perform

1. Contamination of resin (homogenous or spotted)
2. Performing a media fill using worst case conditions:

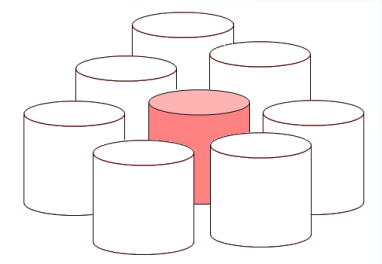
   Lowest possible temperature / highest possible extrusion speed
3. Incubation and evaluation of the produced containers

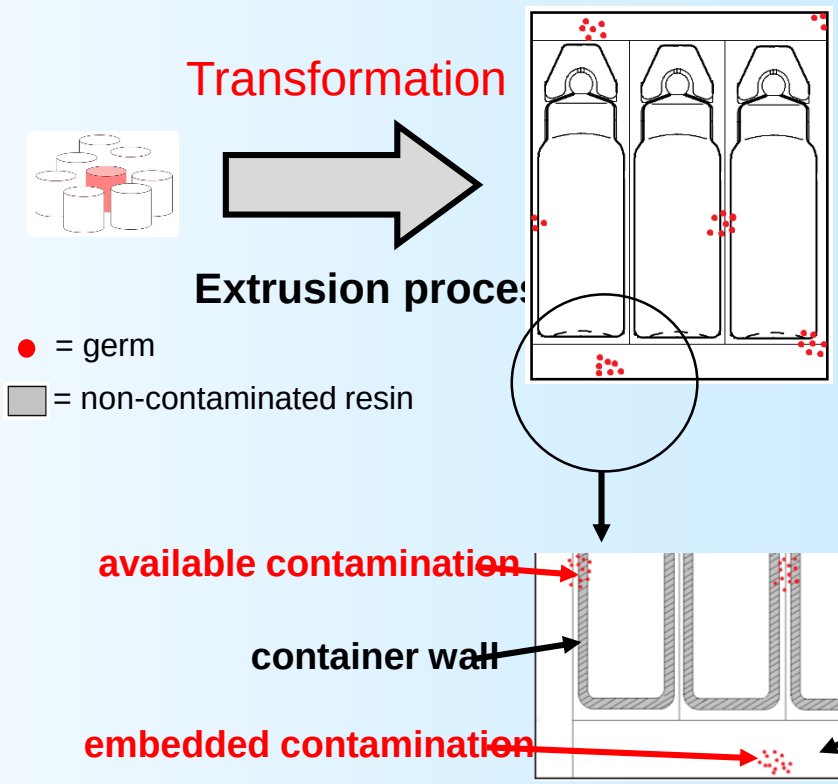
Contamination of resin (Homogenous)





Contamination of resin (Spotted)





Is there a reduction of endospores within the BFS-extrusion process?

- All available literature is stating that there is a reduction of endospores (Bacillus atrophaeus ATCC 9372) during extrusion
- Reduction factors vary 10^2 CFU/g to 10^4 CFU/g

→Yes 

What are the parameters influencing the process?

- Kind of contamination (homogeneous / spot)
- Container design (product-contacting surface)
- Transformation of the contaminated resin surface:

  scrap, outer surface, container wall
- Product of temperature and retention time

Can the reduction-effects be ranked?

- 1. Kind of contamination (homogeneous / spot)
- 1. Transformation of the contaminated resin surface:

  scrap, outer surface, container wall
- 2. Container design (product-contacting surface)
- 3. Product of temperature and retention time

→Yes 

Is the extrusions-process equivalent to sterilization?

- The extrusion process is not equivalent to a sterilization process
- Temperature*Retention Time is too small
- Reduction from 10^2 CFU/g 10^4 CFU/g

→ No 👎

Consequences for BFS-process

- Typical bioburden of resin is found below <10^1 CFU/g resin
- Transport, storage and distribution is critical, for example damaged bags, etc.
- Handling is critical: opening of bags etc.
- Qualification of the supplier
- Appropriate design of the handling system, qualification of the handling system
- SOPs and training of operators

Thank you very much for your Attendance!