Steam Sterilisation of BFS containers in Autoclaves

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Content

- Regulatory requirements
- Considerations for Choice of Process
- Cycle Design
- Practical case study

Introduction

Aseptic fill vs. Terminal Sterilisation ?

- FDA – Guideline for 'Aseptic Processing' (2004)

"…sterile drugs should be manufactured by aseptic processing only when terminal sterilization is not feasible. However, some final packaging may afford some unique and substantial advantages …… that would not be possible if terminal sterilization were employed."

Introduction

Aseptic fill vs. Terminal Sterilisation ?

- European Pharmacopoeia

”Wherever possible a process in which the product is sterilised in its final container (terminal sterilisation) is chosen.”

“It is recommended that the choice of the container is such as to allow the optimum sterilisation to be applied.”

Introduction

Aseptic fill vs. Terminal Sterilisation ?

- EMEA Guideline (April 2000)

  Decision Trees for the Selection of Sterilisation Methods (CPMP/QWP/054/98)

  ”The use of an inappropriate heat-labile packaging material cannot in itself be the sole reason for adoption of aseptic processing.”

Introduction

Aseptic fill vs. Terminal Sterilisation of BFS ?

- Aseptic fill

  + most flexible for choice of container /material

  + no investment in autoclave needed

  - filling in grade A zone with min. grade C* background
  - extensive environmental monitoring
  - media fills twice a year
  - restrictions in fill time, interventions etc.

  * using grade B clothing

Introduction

Aseptic fill vs. Terminal Sterilisation ?

- Terminal sterilisation
  + filling in grade C or even grade D
  + less environmental monitoring
  + no media fills
  + longer fill time
  - investment in autoclave needed
  - more careful selection of suitable polymer materials

Introduction

Aseptic fill vs. Terminal Sterilisation ?

- It is well recognized that Blow-Fill-Seal is an excellent technique for aseptic processing….

  ….but due to it's superior flexibility in container design and low risk for particulate contamination, it is also
  a most suitable technique for filling containers that should undergo terminal sterilisation

BFS International Operators Association

Aseptic fill vs. Terminal Sterilisation ?

	API Heat Stable	API Heat sensitive
Standard container	Terminal sterilisation (Aseptic fill)	Aseptic fill
Advanced container	Terminal sterilisation or Aseptic fill	Aseptic fill

Regulatory Demands

- If a terminal sterilisation process have been choosen;
  - what should be included in the regulatory submission for a new product ?

Regulatory requirements for Moist Heat Sterilisation

FDA – Guidance for Industry; *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (1994).

- Description of the Process and Product
- Thermal Qualification of the cycle
- Microbiological Efficacy of the Cycle
- Container Closure and Packaging Integrity
- Bacterial Endotoxins Test and Method
- Sterility Testing Methods and Release Criteria

Regulatory requirements for Moist Heat Sterilisation

EU GMP (Eudralex)– Annex 1 (2008)

- ”All sterilisation processes should be validated”
- ”….its efficacy in achieving the desired sterilising conditions in all parts of each load to be processed should be demonstrated by physical measurements and by biological indicators where appropriate.”
- ”…the whole of the material must be subjected to the required treatment and the process should be designed to ensure that this is achieved”
- ”Validated loading patterns should be established for all sterilisation processes”

Regulatory requirements for Moist Heat Sterilisation

USP/NF

- Minimum demand 10^{-6} probability for microbial survivors
- ”Overkill” approach – typical reduction to 10^{-12} or $F_0 = 12$, (normally 121.1ºC for 12 min)

Ph Eur

- Minimum 121.1ºC for 15 min
  - ”Other combinations of time and temperature may be used …….”

Design Considerations

- How to design your moist heat process and choose appropriate equipment ?

Design considerations

- Can Overkill approach be applied ?
- Limitations in temperature (API + container) ?
- Choice of material for container
  - Standard PE grades normally not suitable
  - Heat resistant PE grades exists
  - Most PP grades can allow ≥ 121 ºC
- Example - F_0 15 can be achieved by
  - ➢121 ºC for 15 min or
  - ➢112 ºC for 122 min or
  - ➢108 ºC for >5 h

Choice of Autoclave

Problem:

- When heating up a flexible container, the internal pressure will try to expand the volume of container (i.e. risk for deformation !)
- $P_{int} = P_{H_2O} + P_{air}$
  - P_{H_2O} = saturated steam pressure
  - P_{air} = pressure increase due to the 'Ideal-gas' law
- In a traditional vacuum autoclave $P_{cmb} = P_{H_2O}$!

Choice of Autoclave

Solution:

- Air / Steam mixture autoclave
  (Counter pressure autoclave)
- Can apply a counter pressure to balance the internal pressure in the container
- This has to be relative to the actual temperature
- Homogeneity and heat transfer is achieved by fans creating high turbulence in the chamber

Choice of Autoclave

Advantages of Air/Steam autoclaves;

- Counter pressure gradually increased when temperature increases
- A constant pressure applied during Sterilisation phase
- Gradually decreasing pressure during cool-down, which also allows efficient drying
- Air / Steam autoclaves can be utilised also for other type of sterilisation processes where a dry product is required after processing

Case study

- How to design and validate a autoclave process for a blister packed BFS ampoule ?

Case Study

Background – Product to be sterilised

- BFS ampoule in PP (Polypropylene)
- Two sizes – 10 and 20 mL
- Absolutely no deformation allowed
- Packed in a Blister pack and that must guarantee also a sterile outside of the ampoule
- Should be completely dry after processing
- Minimum sterilisation target $F_0 = 15$

Case Study

Background – Autoclave and load considerations

- Counter Pressure Autoclave
- Three fans in the ceiling + dual heat exchangers
- Process controlled by reference sensors
- Individual control of each section of the chamber
- Load pattern designed to allow free space between each layer of product
- Ampoules autoclaved in upright position to facilitate drainage of condensed steam
- Minimum load = ½ pallet, maximum = 3 pallets

Development of Process

International Operators Association

As a base a standard process-programme from the supplier was used

- Heating with dry air to a temperature below 100º C
- Final heating to sterilisation temperature 121º C by combined steam and air mixture
- Sterilisation at constant conditions at 121º C until F0 target reached
- Drying phase in combination with a slow cooling down
- Final cooling phase to below 40º C

Development of Process

First step is further development and fine-tuning of Process parameters to achieve a perfect process

- Establish design for the reference sensors
- Establish ramp-up speed for temperature and pressure
- Establish temperature for exchange of phase
- Establish counter-pressure at exposure phase
- Establish conditions for drying phase
- Establish ramp-down speed for temperature and pressure
- Fan speed in different phases

Development of Process

- In total more than 20 test runs were needed
- The development work is extremely important to gain knowledge of how the combination of the autoclave and the actual product interacts together
- This information is mandatory to lay down the process-programme to be used for the validation
- It is also valuable to have this understanding if some deviations will occur in the future

Validation

Consists of 5 important steps;

- Installation Qualification
- Operational Qualification
- Thermo mapping study
- Performance Qualification
- Process Validation Batches

Operational Qualification

Some examples of critical tests

- Empty chamber temperature distribution
- Fan speed and rotation
- Media consumption
- Cooling capacity
- Calibration of sensors
- Verification of process control programmes

Thermo mapping studies

To get full understanding of temperature variations in the load

- Identify potential cold spots
- Identify potential hot spots (where applicable)
- Study different load patterns
  - this is especially important for air/steam processes
- Utilise maximum number of sensors

Thermo mapping studies

In the actual case;

- Two Kaye Validator equipments were used
  - each one offered 36 sensors
- Five possible load patterns were evaluated
  (½, 1, 1½, 2 and 3 full pallets)
- Both ampoule sizes tested individually
- Biological indicators were also applied in the load

Thermo mapping studies

The results from Thermo mapping showed that;

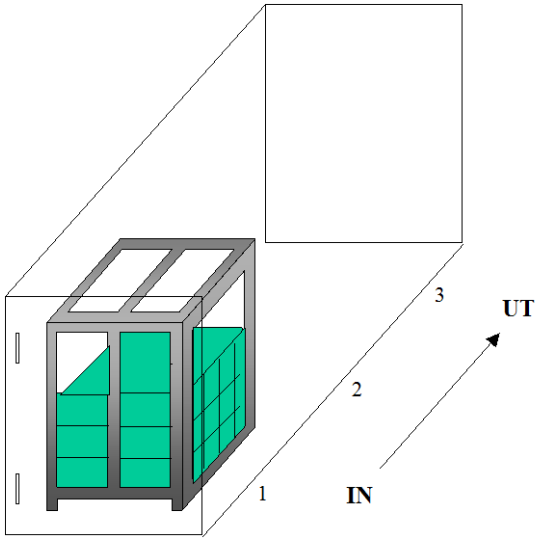
- No significant cold or hot spots were detected
- 20 mL ampoules required longer process time
- 1½ pallet was the most critical load pattern
- No deformation of the ampoules occurred
- No risk for leakage after processing
- It was found to be some very small amounts of condensate on the inside of a few blister packs after end of process

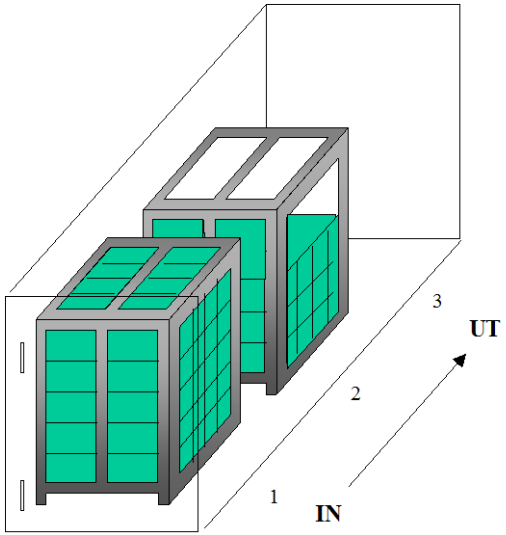
Thermo mapping studies

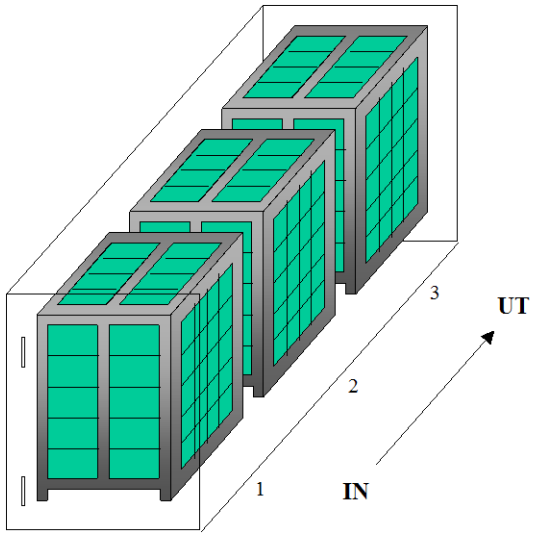
The results from Thermo mapping where then used to establish the conditions for PQ tests

- The recommendation for number of sensors were 36 for maximum load, and 12 for minimum load
- For each thermo sensor also two Biological and one Chemical indicator should be used (”Sensor Package”)
- Process parameters confirmed and criteria for evaluation of each process established
- Number of qualification runs to include in PQ

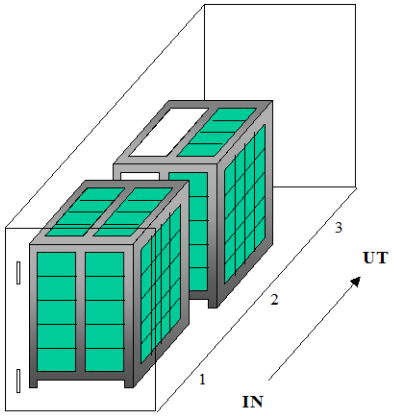
Load Patterns



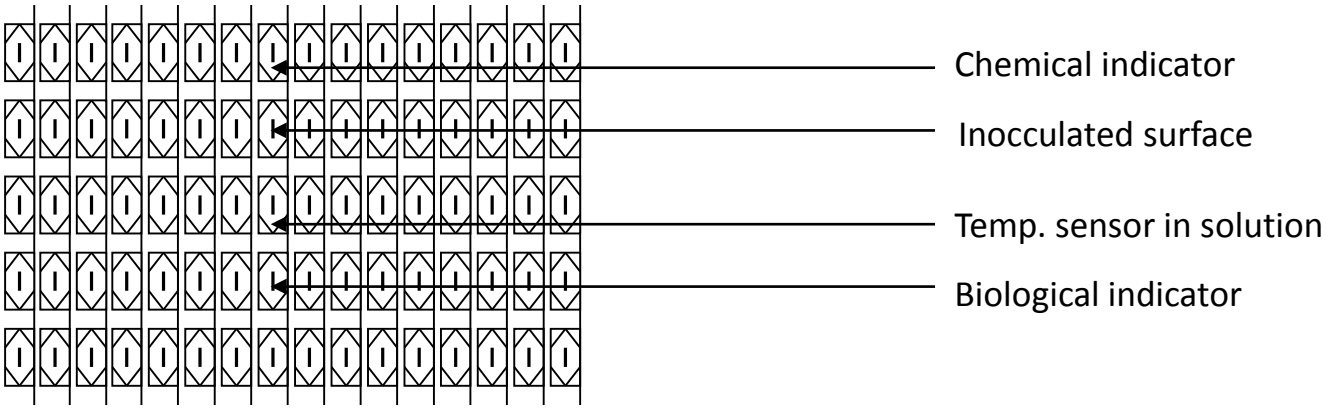




Alternative load pattern evaluated



Example of ”Sensor package”



Process Qualification

Aim to verify the reproducibility for the Process

- For 20 mL ampoules – 3 runs for each of the three load patterns (minimum, middle and maximum)
- For 10 mL ampoules only 3 runs of maximum load (same reference sensor to be used)
- $\Rightarrow$ in total 12 runs

Results of the Process Qualification

All runs fulfilled the acceptance criteria except for one run where F_0 = 15 was not achieved in one position !

Since no explanation could be found, this was seen as normal variation in the process, and therefore it was decided to increase the control limit for F_0 to 20 for coming routine production

A final version of the SOP for the autoclave process were issued

Process Validation Batches

- Normal commercial production batches
- Since the products are considered to be similar this meant 3 batches of each 10 and 20 mL
- The batches were of course run by ordinary well trained production personnel according to BPR and the final version of the SOP
- After approval of these batches the final Validation Report was issues and approved

Critical parameters to evaluate

- Time to reach phase transition 1 (air to air/steam phase)
- Time to reach phase transition 2 (into exposure phase)
- Total heat up time
- Time in exposure phase
- Pressure ramp during different phases
- Drying and Cooling performance

Some Final Words

- A concept paper to establish a harmonised guideline for the selection of sterilisation processes, were presented by EMA in 2014
- ”*Guideline on the sterilisation of the medical product, active substance, excipient and primary container*”
- A draft for public consultation was sent out in april 2016 (EMA/CHMP/CVMP/QWP/BWP/850374/2015)
  - the intention is to further clarify recommendations for Sterilisation of medical products
  - When (if) approved, this document should replace the ”Decision tree” from 1998, (CPMP/QWP/155/98)

Thanks for your attention !

Any questions or comments ?