GMP for Sterile Pharmaceutical Products

Now we will look at different methods of sterilization, specific approaches in barrier technology, blow/fill/seal technology and quality control

Part 3

Sterile Production

Methods of sterilization

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Sterilization

- Terminally sterilized by heat in final container whenever possible
- When not possible - alternative method of terminal sterilization following filtration and/or aseptic processing.
- Use of moist or dry heat, by irradiation with ionizing radiation (noting that ultraviolet irradiation is not normally an acceptable method of sterilization), by ethylene oxide (or other suitable gaseous sterilizing agents), or by filtration with subsequent aseptic filling of sterile final containers
- Heat sterilization is the method of choice

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Sterilization

- Minimal microbial contamination of starting materials
- Bioburden monitored before sterilization
- All sterilization processes should be validated
- Particular attention in case sterilization method is not in accordance with pharmacopoeial standards or other national standards, or when it is used for a preparation that is not a simple aqueous or oily solution, for example, colloidal suspensions

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Before adopting a sterilization process:

- Demonstrate the suitability for the product
- Prove its efficacy in achieving the desired sterilizing conditions in all parts of each type (physical measurements and by biological indicators)
- Validated loading patterns
- Whole of the material subjected to the required treatment
- Verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment - records kept of the results

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- Biological indicators: (an additional method of monitoring the sterilization process)
  - For additional monitoring
  - Stored and used according to the manufacturer's instructions
  - Their quality checked by positive controls
  - Avoid any transfer of microbial contamination from them
- Differentiate between "to be sterilized" and "sterilized" product
- Each basket / tray clearly labelled (material, batch number etc)
- Autoclave tape can also be used

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- Sterilization records available for each sterilization run
- Sterilization records approved as part of the batch-release procedure

Can you name the different methods of sterilization?

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Different methods of sterilization include:

- Terminal sterilization:
  - Heat (Dry heat and moist heat)
  - Radiation
  - Gas and fumigants أبخرة
- Aseptic processing by filtration

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Terminal sterilization

Sterilization by heat (general aspects)

- Record each heat-sterilization cycle - equipment of suitable accuracy and precision, e.g. on a time/ temperature chart. Reviewed and approved as part of the batch release
- This temperature probe situated at the validated coolest part and temperature checked against a second independent probe
- May also use chemical or biological indicators (in addition)
- Whole of the load to reach the required temperature (Validated time) - no contamination of a sterilized load

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Sterilization by moist heat

- Monitor temperature and pressure (and time)
- Control instrumentation independent of monitoring instrumentation and recording charts
- Validated automated control and monitoring systems used
- Register system and cycle faults and observed by the operator
- If a drain at the bottom of the chamber – consider recording the temperature at this position
- Regular leak tests on the chamber

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- Use sealed containers or wrapped in a material that allows the removal of air and the penetration of steam but prevents recontamination after sterilization
- Specially designed autoclavable stainless steel containers allow steam to enter and air to leave
- Suitable quality steam (chemical, microbiological and endotoxin analysis of condensate and physical examination of steam (such as dryness, superheat, and non-condensable gases); no additives at a level that could cause contamination (product or equipment)
- Steam tested regularly – SOP, specification, review results

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Autoclave

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Bowie Dick test

What is it?

When is it done?

How do you know whether it "Passes" or "Fails"?

What action do you take when it fails?

- Detection of air leaks
- Steam penetration
- In adequate air removal for vacum assisted sterilizer

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Some points to consider

- Vacuum and pressure hold tests
- Bowie Dick test
- Use of Biological Indicators and SAL
- Heat distribution studies
- Heat penetration studies
- Loading patterns
- Quality of steam
- Calibration op sensors
- Coolest part of the load
- Dwell time
- D- value(Decimal reduction time)
- Z- value
- F0-value
- Variation in temperature in a sensor [illegible] sensors

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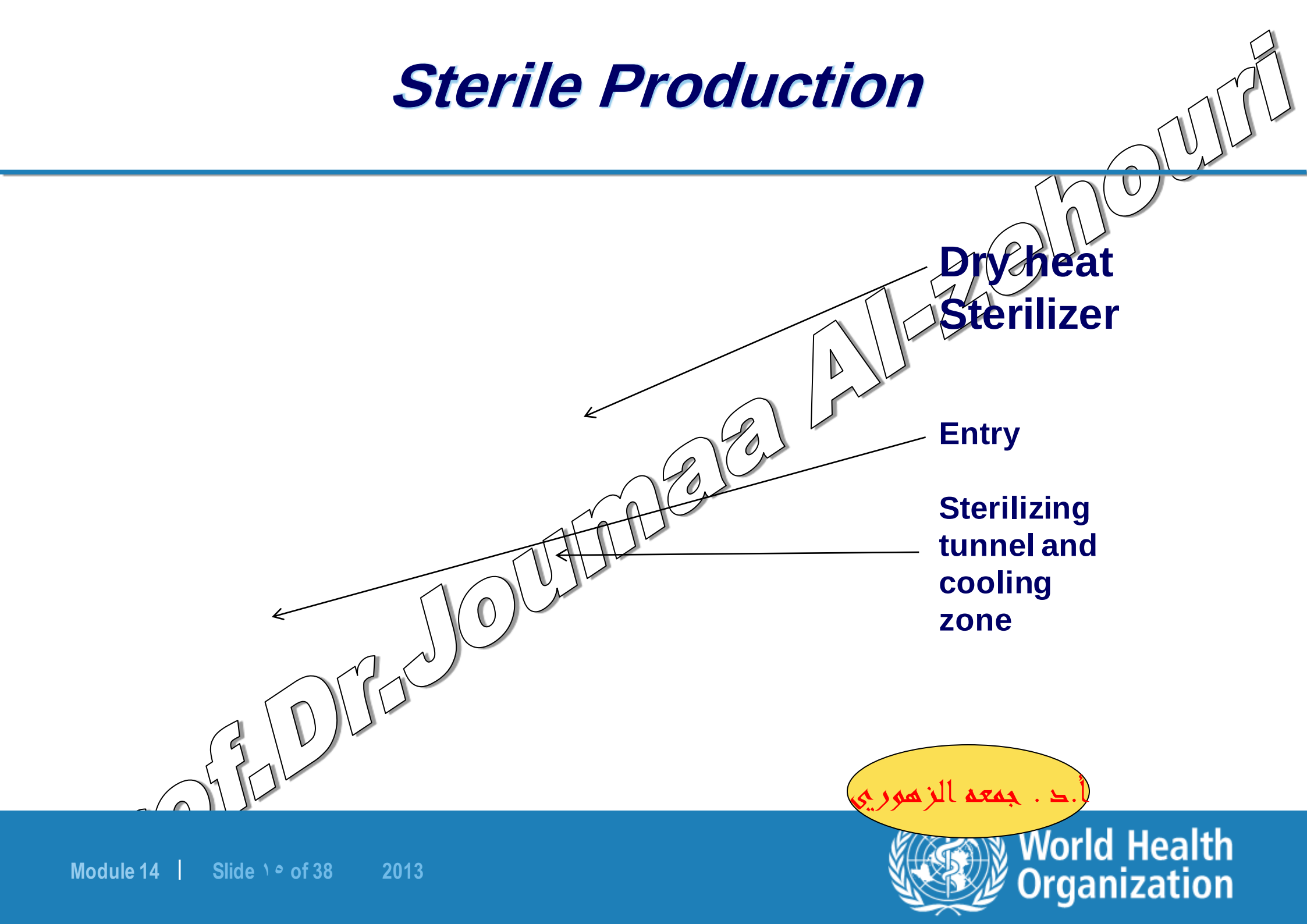

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Sterilization by dry heat

- Suitable for non-aqueous liquids or dry-powder products
- Air circulation within the chamber
- Maintain positive pressure to prevent the entry of non-sterile air
- Air supplied through a HEPA filter
- For pyrogen removal – validate through challenge tests using endotoxins

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Sterilization by radiation

- For heat-sensitive materials and products and only allowed if no negative effects on the product has been confirmed
- Manufacturer is responsible when done by an outside contractor
- Radiation dose to be measured. Sufficient number of calibrated, independent dosimeters used, quantitative measurement - read shortly after exposure
- Colour discs to differentiate/indicate before and after sterilization
- Ultraviolet irradiation is not an acceptable method for terminal sterilization

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- Validated procedures followed
- Considered variations in the density of the packages
- Material-handling procedures followed to prevent any mix-up of irradiated and non-irradiated materials. (Each package should carry a radiation-sensitive indicator to show whether or not it has been subjected to radiation treatment)
- The total radiation dose administered within a predetermined period

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Sterilization by gases and fumigants (E.g. hydrogen peroxide vapour). *Ethylene oxide should be used only when no other method is practicable.*

- This method used only for finished products where there is no suitable alternative

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- Proof of no damaging effect on the product and that degassing reduces any residual gas and reaction products to defined acceptable limits as specified in specifications

- Direct contact between gas and microorganisms – ensure avoiding the presence of organisms enclosed in materials such as crystals or dried protein. Consider the nature and quantity of packaging materials

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Sterilization by gases and fumigants (E.g. ethyleneoxide and hydrogen peroxide vapour)

- Before exposure to the gas - equilibrium with humidity and temperature
- Biological indicators (BIs)
  - Use to monitor each cycle
  - Stored and used appropriately
  - Checked by positive controls
- Records include time, pressure, temperature, humidity, gas concentration (chart). Records to be part of the batch record
- Store under ventilated condition after sterilization

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Aseptic processing and sterilization by filtration

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Aseptic processing and sterilization by filtration

- Objective to maintain the sterility of a product that is assembled from sterile components – therefore conditions such to prevent microbial contamination

- Maintain sterility of the components and the product by controlling:
  - environment;
  - personnel;
  - critical surfaces;
  - container/closure sterilization and transfer procedures;
  - the maximum holding period of the product before filling into the final container; and
  - the sterilizing filter

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Aseptic processing and sterilization by filtration

- Certain solutions and liquids cannot be sterilized in the final container
- These can be filtered through a sterile filter of nominal pore size 0.22 micron (or less), or with at least equivalent microorganism-retaining properties
- Into a previously sterilized container
- Where possible use also some degree of heat treatment
- When sterilization in the final container is possible then filtration alone is not considered sufficient

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- A double-filter layer or second filtration through a further sterilized microorganism-retaining filter immediately prior to filling is recommended - as close as possible to the filling point.
- Filters should not shed fibres. No asbestos-containing filters used

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- Filter integrity verified before and after use (e.g. bubble point, diffusive flow or pressure hold test
- Filter used for one working day - unless otherwise validated
- Filter not to remove ingredients from product; not releasing any substance into the product

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- Integrity of critical gas and air vent filters, as well as other filters
- Validate time and pressure for a known volume of bulk solution
- Significant differences during manufacturing investigated

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Isolator technology

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Isolator technology

- Minimize human interventions in processing areas and thus contamination. (Risk: Puncture and leakage)
- Different designs. (Also single-door, double-door, and fully-sealed transfer devices)
- Required air quality in and around (background) of the isolator
- Greatest chance of contamination during transfer of materials into and out of the unit
- Background at least Grade D

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Isolator technology

- Used only after appropriate validation which covers e.g.:
  - Quality of the air inside isolator
  - Quality of air outside (background) the isolator
  - Sanitization of the isolator
  - Transfer process
  - Isolator integrity.
- Routine monitoring of isolator which includes frequent leak testing of the isolator and the glove/sleeve system

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Blow/fill/seal technology

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Blow/fill/seal technology

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- Purpose-built machines - one continuous operation
- Aseptic production - Grade A air shower and installed in Grade C
  - Grade A or B clothing used
  - Comply with the viable and non-viable limits at rest
  - Comply with viable limit in operation
- When used for the production of products which are terminally sterilized - installed in at least a Grade D environment

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Particular attention to:

- equipment design and qualification;
- validation and reproducibility of cleaning-in-place and sterilization-in place;
- background clean room environment;
- operator training and clothing; and
- interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

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Quality Control and sterility testing

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Quality control

- Review BPRs, environmental quality records with sterility tests
- Injectable products – WFI, intermediate, finished product - monitored for endotoxins. Validated pharmacopoeial method
- Failures investigated - necessary action should taken
- Rapid microbiological methods can be used if validated and a comparative assessment was done

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Quality control

- Sterility test is only the last in a series of control measures
- Validated test to be used for the product(s) concerned.
- Samples taken to be representative of the whole of the batch e.g.
  - aseptically prepared – samples from beginning and end of the batch and after any significant interruption of work
  - heat sterilized in their final containers - from that coolest part of the load
- Sterility assured through:
  - validation of the sterilization cycle (terminally sterilized products)
  - "media simulation" or "media fill" runs (aseptically processed)

Sterile Production

Quality control

- Review BPRs, environmental quality records with sterility tests

water for injection

- Injectable products – WFI, intermediate, finished product - monitored for endotoxins. Validated pharmacopoeial method
- Failures investigated - necessary action should taken
- Rapid microbiological methods can be used if validated and a comparative assessment was done

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Quality control

- The previous slides only highlight some quality control aspects
- See also the Training Modules on Quality Control laboratories and Microbiology Laboratories

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Case Study and Assessment