Sterilization and Quality Assurance Procedures

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The essence of quality assurance is demonstrating that you are really doing what you say you are doing.

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Standard of Sterility

- <1> Injections
  - Parenteral articles are prepared….to ensure they meet pharmacopeial requirements for sterility, pyrogens,...
  - Sterility Tests – Preparations for injection meet the requirements under Sterility Tests <71>

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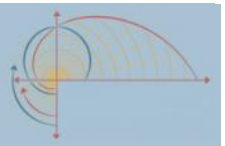
What is “Sterility”?



- “Free from bacteria or other microorganisms”
  - *American Heritage's Definition of Sterility*
- “Within the strictest definition of sterility, a specimen would be deemed sterile only when there is complete absence of viable microorganisms from it.”
  - *<1211> Sterilization and Sterility Assurance of Compendial Articles*
- Is it possible to demonstrate complete absence of microorganisms from a CSP?
- Absolute sterility can’t be demonstrated without the complete destruction of every article from the lot of CSPs.

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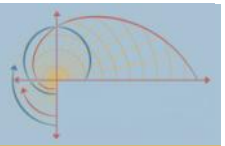
Critical Concepts of Sterilization



- Sterility Assurance Level (SAL) is the probability of a non-sterile item making it through the validated sterilization process.
- Items terminally sterilized by moist or dry heat, irradiation, or chemical sterilants have a SAL of 10^{-6}
  - ***1 nonsterile item per 1 million items sterilized***
- Items prepared aseptically prepared with a 0.22 micron filter have a SAL of 10^{-3}
  - ***1 nonsterile item per 1 thousand items sterilized***

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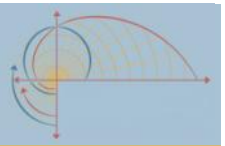
Verification of Accuracy and Sterilization



- The quality (sterility and accuracy) of the CSP is directly related to ensuring that methods used to compound the sterile preparation achieve the desired goal of purity, potency and sterility.
- CSPs that require some form of terminal sterilization:
  - either by filtration
  - Steam
  - ionizing radiation (not the subject of this session)

  MUST be verified to ensure that each CSP is void of microbial contamination.

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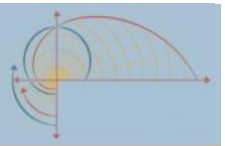
Verification of sterilization



- High-risk level compounding must achieve sterility
  - (nonsterile ➡ sterile)
- Methods of sterilization
  - Autoclave or Dry-Heat oven sterilization cycles
    - Autoclave (121°C for 12-30 min @ 15-20 PSI)
    - Dry-heat
      - 150°C (300°F) for 2.5 hours
      - 140°C (285 °F) for 3 hours
    - Use of Biological Indicators (BIs)
  - Filtration methodology
    - FDA approved/challenged filters
    - Filter integrity testing
  - Ionizing radiation

The stated temperatures and cycle times must be independently qualified by user

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Responsibility of Compounding Supervisor

- The licensed healthcare professionals who supervise compounding shall be responsible for determining that the selected sterilization method both sterilizes and maintains the strength, purity, quality, and packaging integrity of CSPs.
  - *See Methods of Sterilization under Sterilization and Sterility Assurance of Compendial Articles 1211*

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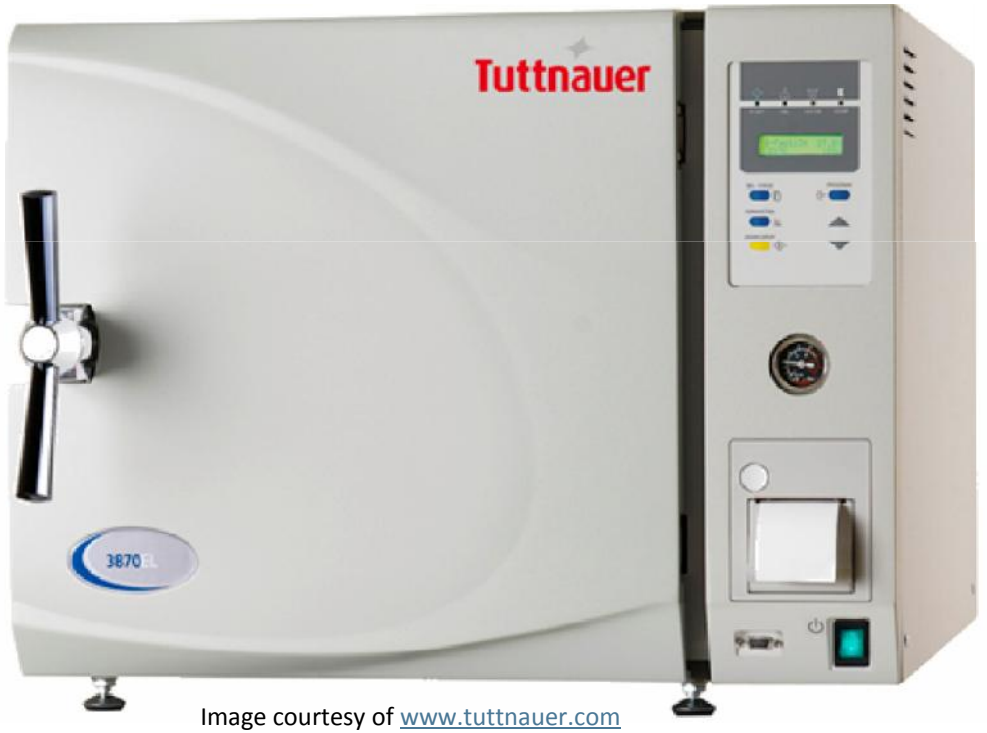
Methods of Sterilization

- Sterilization method must both sterilize and maintain the strength, purity, and packaging integrity
- Methods
  - Steam
  - Dry Heat
  - Filtration



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Steam (Moist Heat) Sterilization

- Autoclaves are used to sterilize heat-stable oil-free liquids, glassware, utensils and medical instruments.
- Lethality is achieved by denaturing proteins of microorganisms.
- Equipment must have systems to control temperature and cycle time.
- The item is exposed to saturated steam under high temperature and pressure conditions.

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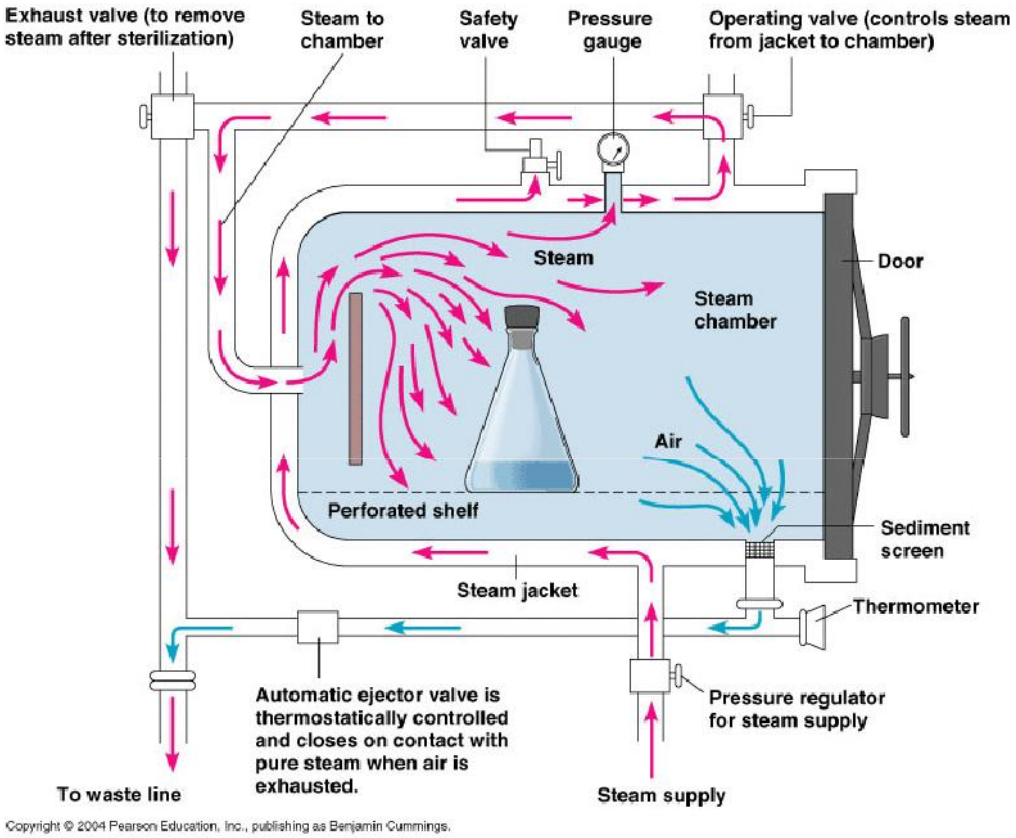

http://www.acad.polyu.edu.hk/~mmktlau/ME429/autoclave_2.gif

How to load an autoclave

Image: http://ehs.unc.edu/

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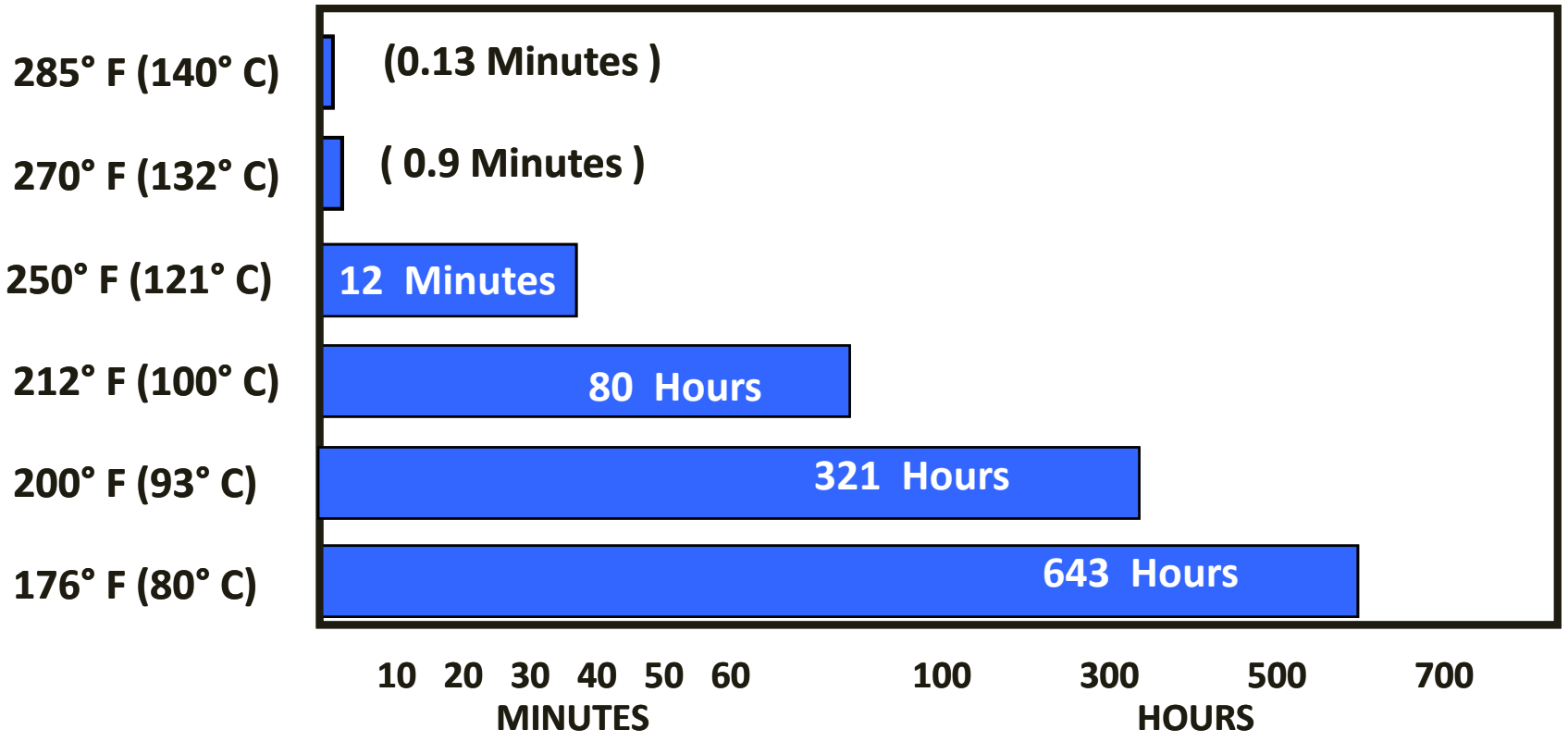
Time to Achieve Equivalent Microbial Lethality at Different Exposure Temperatures



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Chemical and Biological Indicators

- Biological Indicator (BIs) are systems that use a heat-resistant spore-forming microorganism (*B. stearothermophilus or similar)*
- Biological Indicators (BIs) are used to determine whether a sterilizer has delivered a lethal (effective) cycle.
  - They should be used with every cycle and in conjunction with time-temperature data generated from the sterilizer
- Autoclave tape does not meet this requirement.

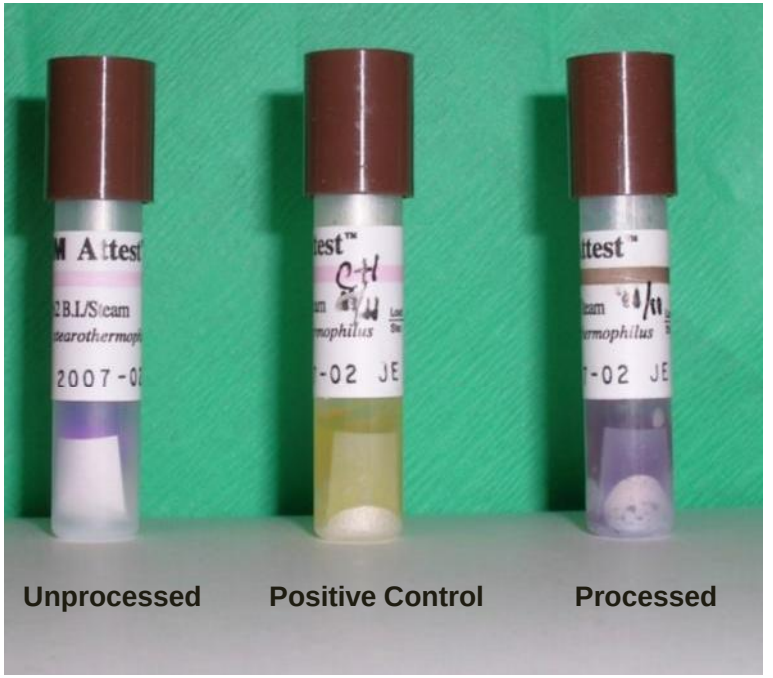

Image adapted from: Autoclave Training; University of Kentucky. 2005.

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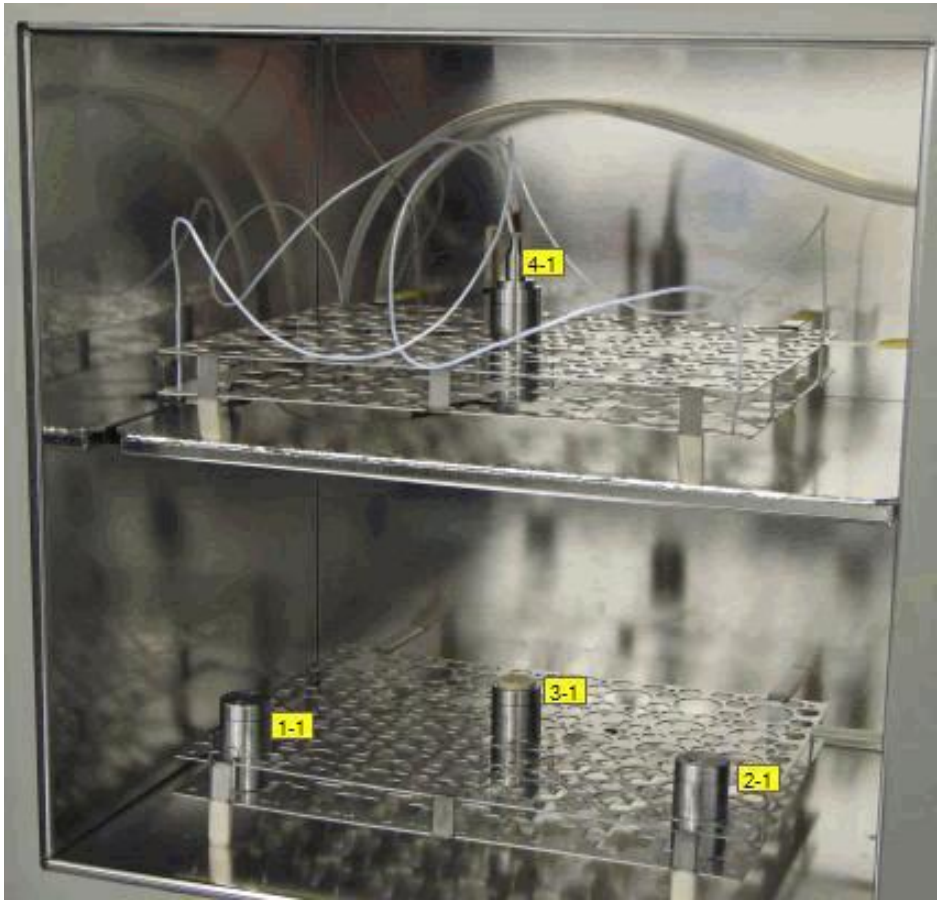
Steam Sterilization (continued)

- The effectiveness of steam sterilization is verified:
  - Using confirmation methods such as temperature sensing devices-thermocouples
- Temperature mapping
  - Hot and cold spots



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Steam Sterilization (continued)

- Biological Indicators
  - Need to incubate after exposure to steam cycle to determine effectiveness.

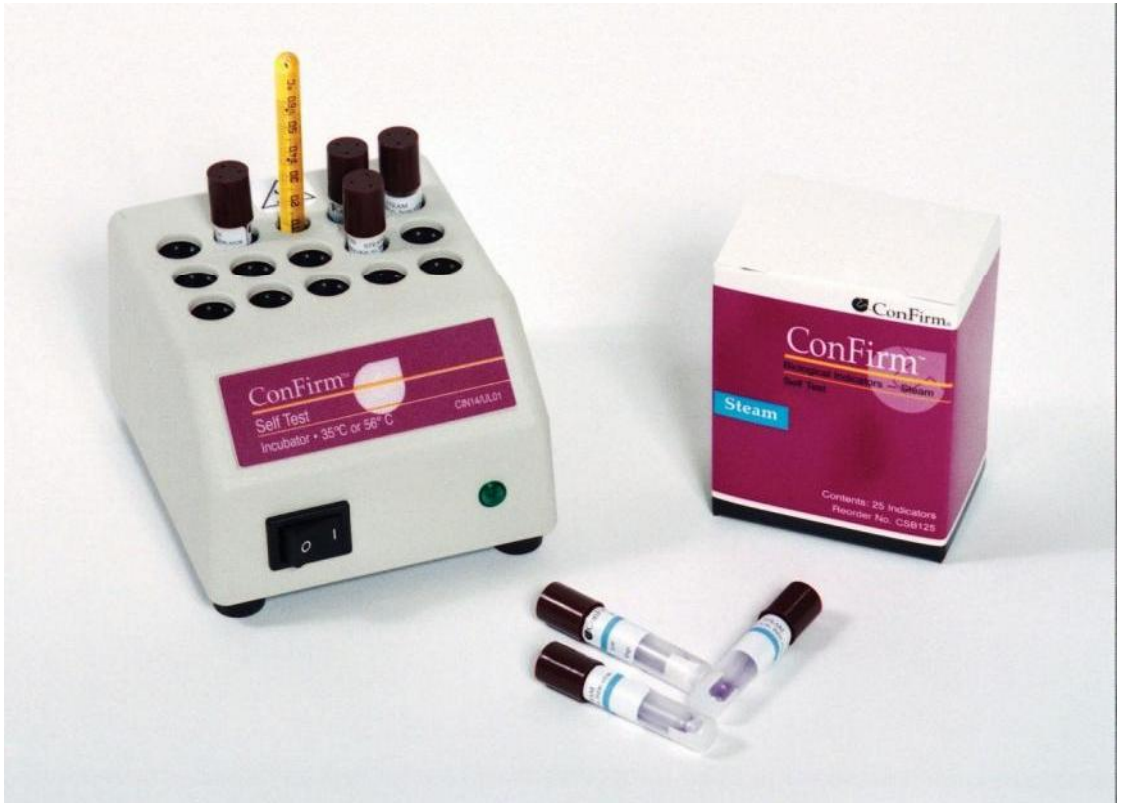

Image courtesy of http://www.confirmmonitoring.com/spore.asp/

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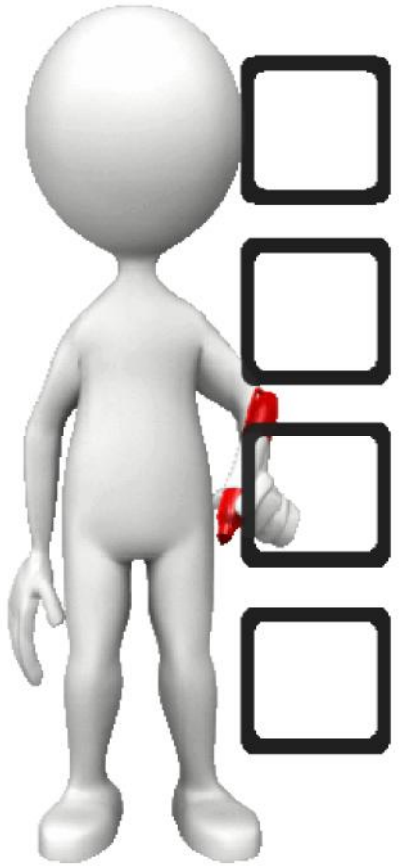
Inspector Evaluation Metrics: Steam Autoclave

- Who operates the equipment?
  - See training records
- How is the equipment operated?
  - See PnPs or SOPs on its use
- How do you know the autoclave cycle was effective?
  - What system is used to control temperature and cycle time
    - Print out of time/temperature
  - Typical temp: 121°C for at least 12 minutes (drug dependent)
  - What type of monitoring and controlling sensors are used (e.g., mercury-in-glass thermometer, thermocouple, RTD, pressure gauge)?
  - Use of biological indicator (tape is not acceptable)
- How is the equipment maintained, cleaned, services, and calibrated



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Dry Heat Sterilization and Depyrogenation

- Used for oils and powders
- Designed to provide heated filtered air evenly distributed throughout the chamber by a blower device (air must circulate around items)
- Requires higher temperature and long exposure times
- Oven should be equipped with a system for controlling temperature and exposure period
- Effectiveness must be verified using appropriate biological indicators and temperature sensing devices

http://sterisure.com/product

http://www.despatch.com/lac.aspx

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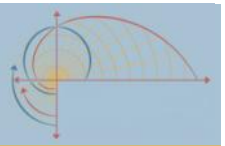
Dry Heat Depyrogenation



- Used on equipment made of glass or metal
  - Rinse with Sterile Water prior to use
- Requires a much higher temperature than sterilization: 250°C for 30 minutes
- Validation of a depyrogenation cycle requires inoculation of bacterial endotoxin
- A three log reduction of E. Coli endotoxin is required to have an effective depyrogenation cycle

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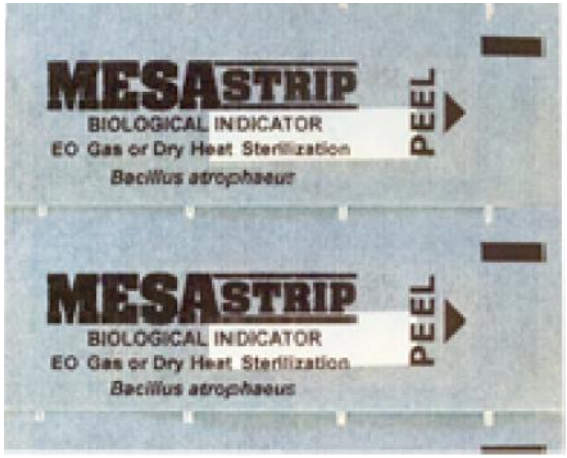
Chemical and Biological Indicators

- Biological Indicator (BIs) are systems that use a heat-resistant spore-forming microorganism (*Bacillus atrophaeus or similar)*
- Biological Indicators (BIs) are used to determine whether a sterilizer has delivered a lethal (effective) cycle.
  - They should be used with every cycle and in conjunction with time-temperature data generated from the sterilizer
- Autoclave tape does not meet this requirement.



http://www.mesalabs.com/mesastrip/

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Biological Indicators

Sterilization Method	BI microorganism	BI incubation
Steam	Geobacillus stearothermophilus	Seven days at 50-55°C
Dry-Heat	Bacillus atrophaeus	Seven days at 30-35°C
Dry-Heat Depyrogenation	Inoculate glassware or vials with a minimum of 5,000 EU of E. coli lipopolysaccharide. All inoculated glassware placed must demonstrate, at minimum, a three-log reduction in endotoxin.	N/A

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Polling Question

The use of biological indicators is not required with each batch of drug that is terminally sterilized by either steam or dry-heat?

1. True
2. False

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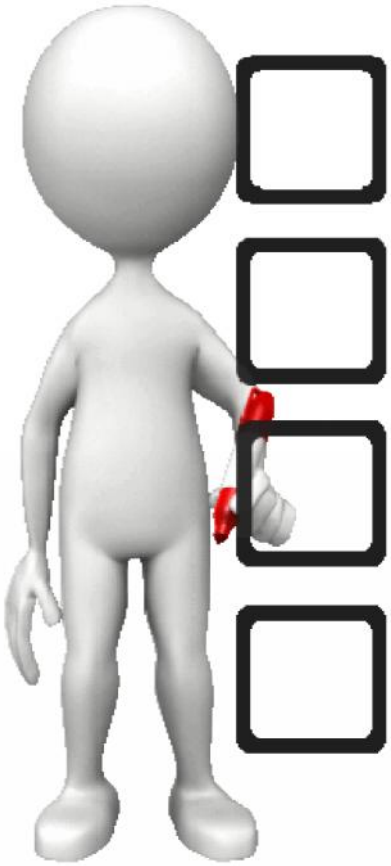
Inspector Evaluation Metrics: Dry Heat Oven

- Who operates the equipment?
  - See training records
- How is the equipment operated?
  - See PnPs or SOPs on its use
- How do you know the dry-heat cycle was effective?
  - What system is used to control temperature and cycle time?
    - Print out of time/temperature
  - Typical temp: 250° C for at least 30 minutes (drug dependent)
  - What type of monitoring and controlling sensors are used (e.g., mercury-in-glass thermometer, thermocouple, RTD, pressure gauge)?
  - Use of biological indicator (tape is not acceptable)
    - Different BI for steam vs. dry heat
- How is the equipment maintained, cleaned, services, and calibrated?



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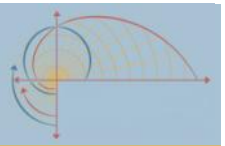
Inspector Evaluation Metrics: Sterilization



Selected Work Practices	Inspector Evaluation Metrics
Sterilization-Steam (autoclave) and Dry-Heat Oven Sterilization methods	• Inspect equipment ✓ Maintained, clean and located in a suitable area? • Are compounded solutions pre-filtered prior to autoclaving? • How are the supplies wrapped/packaged prior to sterilizing? • Equipment has controls for controlling temperature and cycle time ✓ Evidence: Print-out of time/temperature? ✓ Linked to batch? • Are biological indicators used during the cycle (one time or every time?) • Are written CSP specific steam autoclave and dry-heat over PnP maintained?

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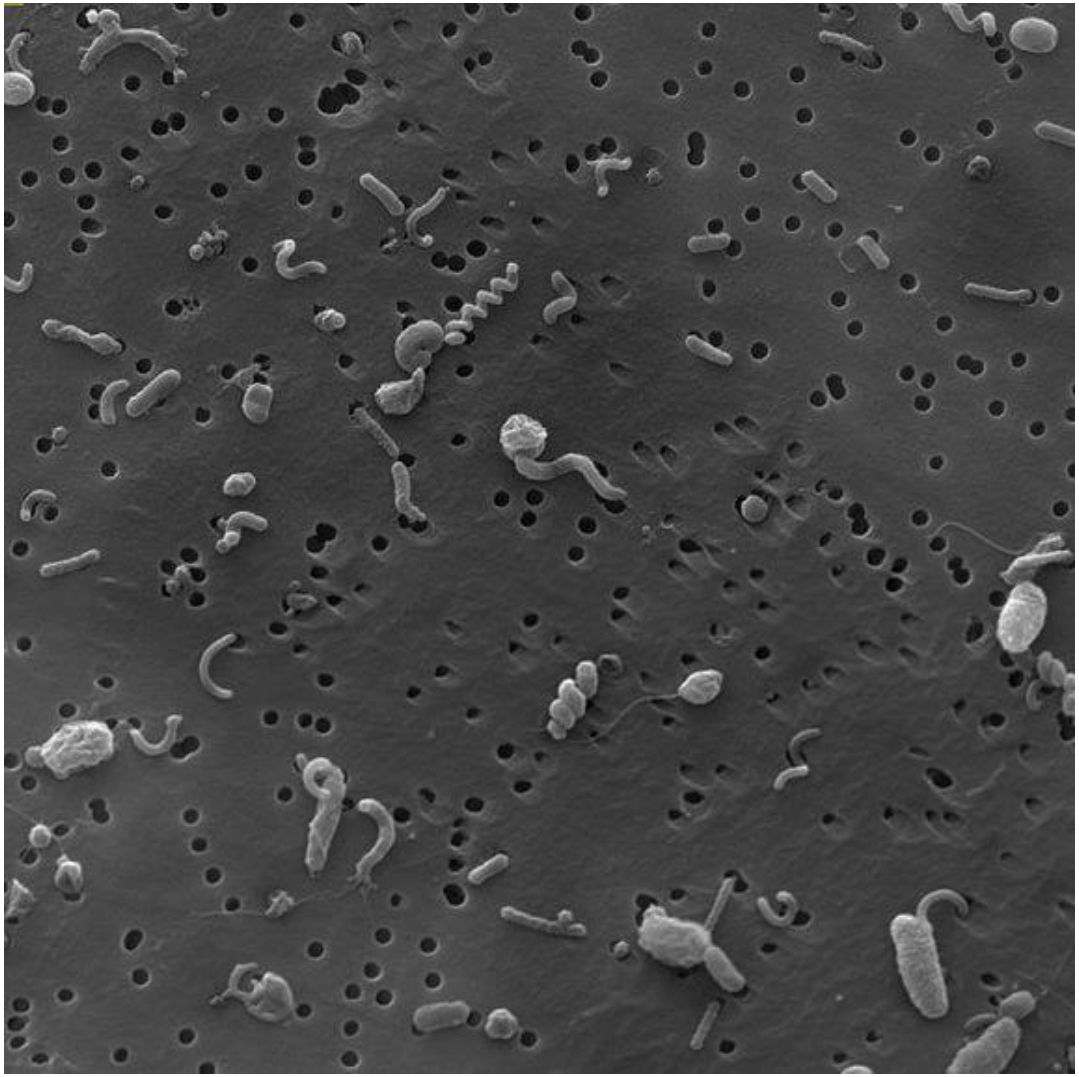
Filtration



An electron microscope image of a bacterial community, on a filter.

Image courtesy of http://www.livescience.com/18397-marine-microbes-big-implications.html

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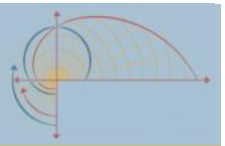
Filtration



- Process for removing particulate matter from a liquid
- Removes particles by entrapment in the channels of the filter, adsorption to the filter by chemical or electrical attraction, by sieving, or size exclusion
- Most frequently, filters work by a combination of these mechanisms
- SAL for sterilizing a solution by filtration is normally accepted as 1:1000 (10^{-3})

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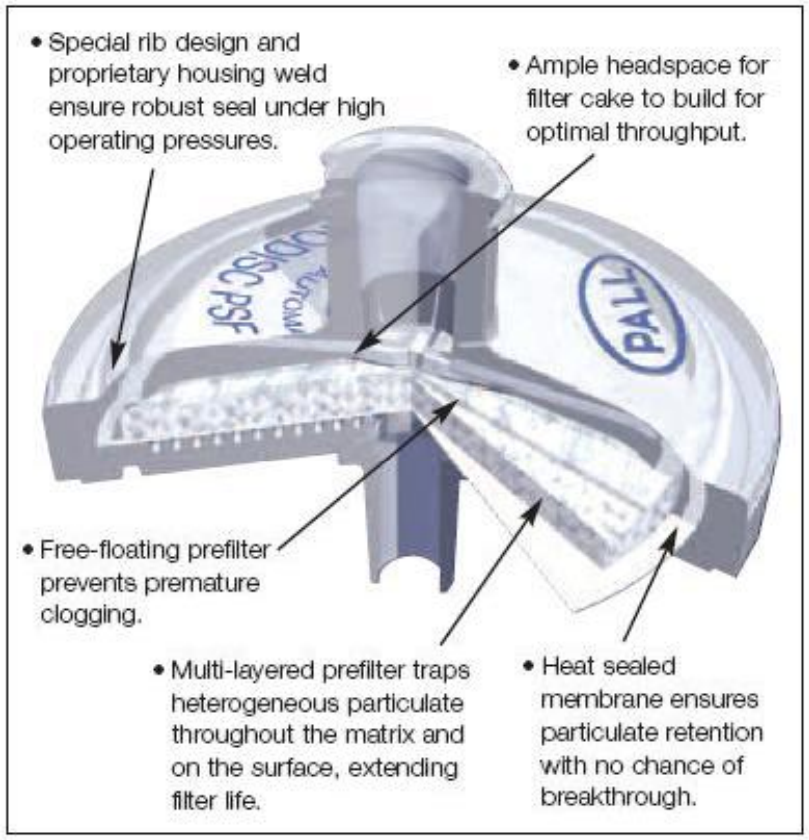
Filtration

- Sterile filters used to sterilize CSPs shall be:
  - Pyrogen-free and have a nominal porosity of 0.2 µm or 0.22 µm
  - Certified by the manufacturer to retain at least 10^7 microorganisms of a strain of Brevundimonas diminuta per cm^2 of filter surface area
- The filter dimensions and liquid material to be sterile-filtered shall permit the sterilization process to be completed rapidly, without the replacement of the filter during the process.



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Filters

- Size and configuration should accommodate the volume being filtered to permit complete filtration without clogging
- 25 mm disk filter should filter no more than 100 mL
- Filter and housing should be physically and chemically compatible with the product to be filtered and capable of withstanding the temperature, pressures and hydrostatic stress imposed on the system

Image courtesy of http://www.millipore.com

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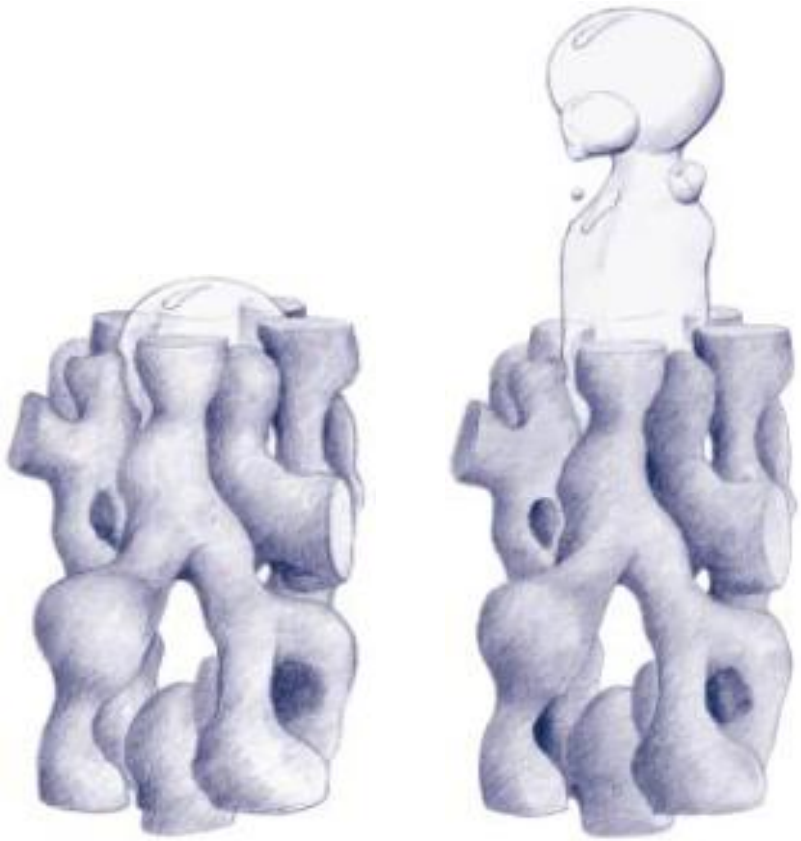
Bubble-Point (Filter Integrity Test)

- A test to ensure the integrity of filters used for sterilizing compounded solutions.
- The Bubble Point Test is based on the fact that liquid is held in a capillary tube by surface tension.
- The minimum gas pressure required to force liquid out of the tube is a direct function of tube diameter



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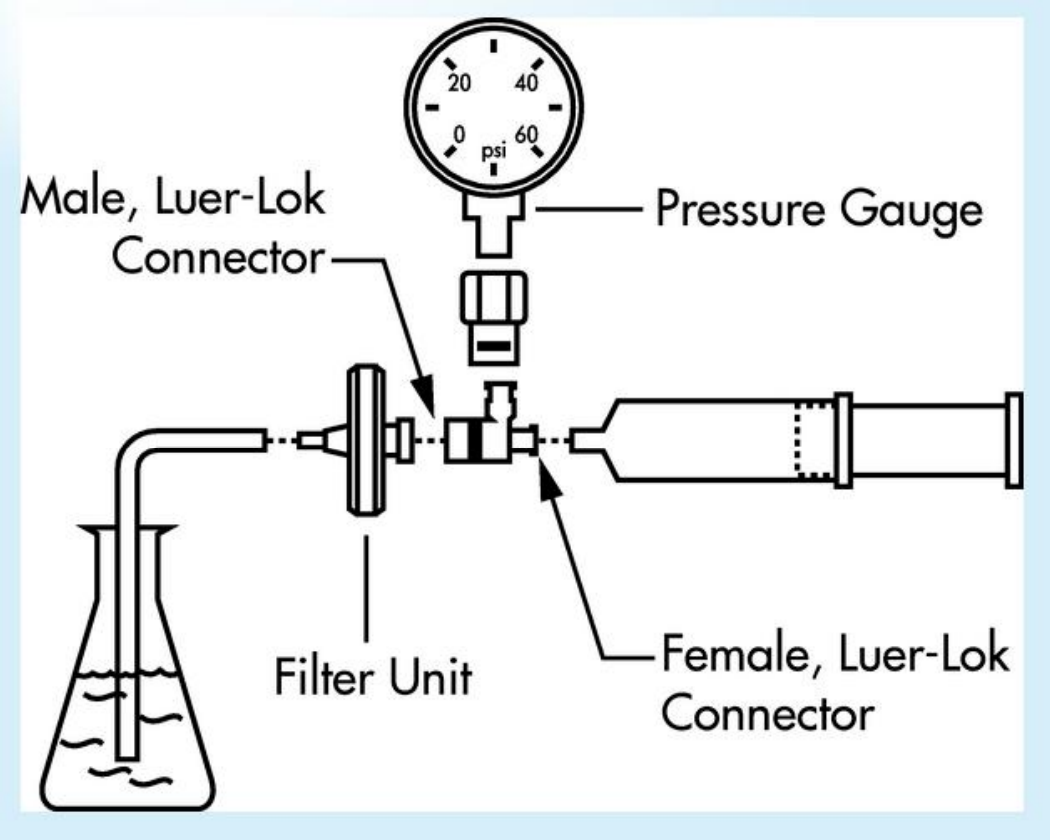
Filter Integrity Testing Millex® / Sterivex™ Integrity Tester



Images courtesy of http://www.millipore.com

Bubble Point Procedure:

1. Wet the filter with the appropriate fluid, typically water for hydrophilic membranes or an alcohol/water mixture for hydrophobic membranes.
2. Pressurize the system to about 80% of the expected bubble point pressure which is stated in manufacturer's literature.
3. Slowly increase the pressure until rapid continuous bubbling is observed at the outlet.
4. A bubble point value lower than the specification is an indication of the following:
   - fluid with different surface tension than the recommended test fluid
   - integral filter, but wrong pore size
   - high temperature
   - incompletely wetted membrane
   - non-integral membrane or seal

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Polling Question

Conducting filter integrity testing can be used as an alternative quality release test to sterility testing?

1. True
2. False

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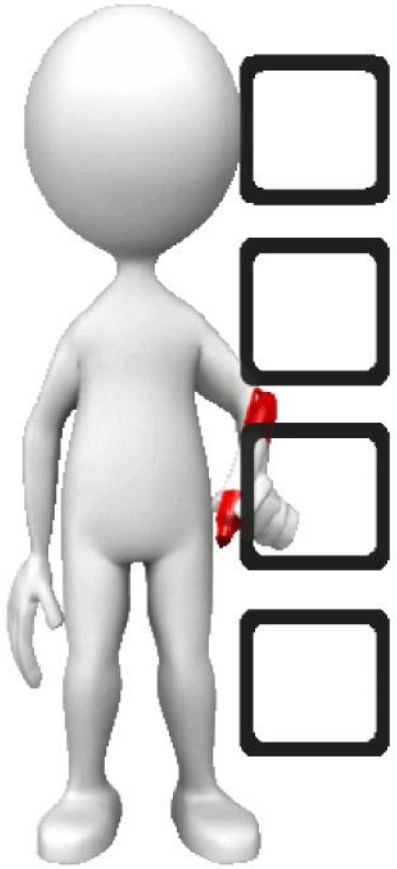
Inspector Evaluation Metrics: Filtration

- Is the filter a sterilizing grade filter?
- How was the filter membrane selected?
  - Aqueous (hydrophilic)
  - Non-aqueous (hydrophobic)
- What is the maximum filtration volume per filter?
  - See PnPs or SOPs on its use
- Are filters used to sterilize solutions integrity tested (Bubble-point)?
- Are there specific written procedures for performing a filter integrity test?



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Probability

"The sterility of a lot purported to be sterile is therefore defined in probabilistic terms, where the likelihood of a contaminated unit or article is acceptably remote."

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Sterility Testing Requirements

- High risk CSPs
  - Batches of more than 25 individual CSPs
  - Any high risk CSP that has been exposed longer than 12 hours at 2º to 8º or longer than 6 hours at warmer than 8º
- All risk level CSPs
  - When USP <797> BUD limits are exceeded

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Sterility Testing

- USP <71> Sterility Tests states:
  - "These Pharmacopeial procedures are not by themselves designed to ensure that a batch of product is sterile or has been sterilized. This is accomplished primarily by method suitability of the sterilization process or of the aseptic processing procedure."
  - Is an industrial test used to detect incidents of gross contamination.
  - It should be recognized that the USP sterility test might not detect microbial contamination if present in only a small percentage of the finished articles in the batch.
  - Current knowledge offers no nondestructive alternatives for ascertaining the microbiological quality of every finished article in the lot.

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Sterility Testing

Table 1: The Relationship between the Probability of Passing the First and Repeat Sterility Tests and the Percentage of Nonsterile Units in the Lot Contamination Rate or Percentage of Nonsterile Units in a Batch						
	0.1	1	5	10	20	50
Probability of passing the sterility test, n = 20	0.98	0.82	0.36	0.12	0.012	<0.00001
Probability of passing the repeat sterility test, n = 20	0.99	0.99	0.84	0.58	0.11	0.002

Cundell AM. "Review of the Media Selection and Incubation Conditions for the Compendial Sterility and Microbial Limit Tests," *Pharm.Forum* **28** (6), 2034–2041.

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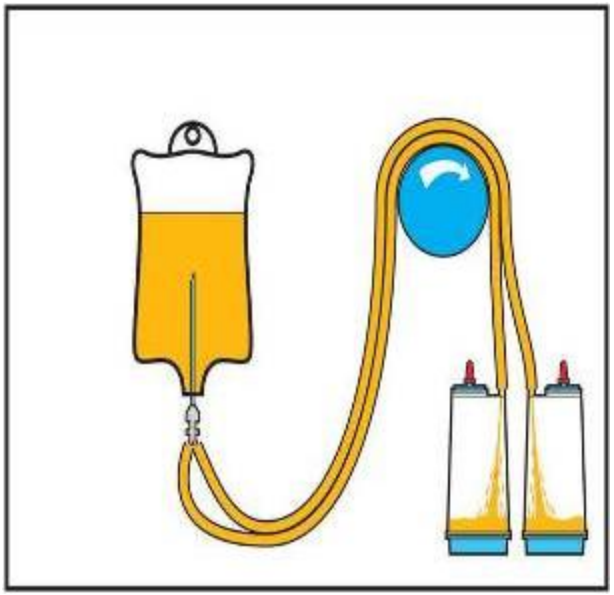
Sterility Testing (Membrane Filtration)



Millipore Equinox Steritest System

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Flow of the Sterility Test

1. Media and Bacteriostasis/Fungistasis Testing (Method Suitability)
2. Eliminate any bacteriostatis/fungistatic properties
3. Determine number of articles, quantity from each, to test
4. Incubate the samples
5. Examine test articles for signs of growth
6. Examine suspect tubes microscopically for signs of growth
7. Subculture if necessary
8. Write the report

Reminder: All Compendial Microbiological Test Methods, including Sterility Tests, are Classical Growth Based Methods

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Polling Question

The preferred method of sterility testing is which of the following?

1. Direct inoculation
2. Filter integrity testing
3. Membrane filtration
4. Something else

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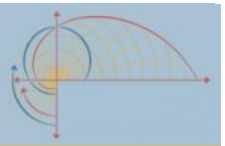
Sterility Testing



- "Passing" a sterility test does not guarantee that every unit in that batch is sterile.
- The use of two types of medias is required.
  - TSB and FTM
- Two incubations are required for the medias
- Membrane filtration is the preferred method of sterility testing
- BUDs are not universal and must be verified by each vendor
- Must be based on sterility testing according to USP 71 or other procedures, methods or processes that have been proven to be equivalent or superior with statistical significance

Challenge external testing labs and vendors on how they accept samples less than the quantities prescribed in USP 71, Table 3.

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Number of Articles to be Tested in Relation to the Number of Articles in the Batch (From USP<71>)

Number Items in Batch	Minimum Number Items to be Tested for Each Medium (unless otherwise justified and authorized)*
Parenteral Preparations	
• Not more than 100 containers	10% or 4 containers, whichever is the greater
• More than 100 but not more than 500	10 containers
• More than 500 containers	2% or 20 containers, whichever is less
For large-volume parenterals	2% or 10 containers, whichever is less
Antibiotic solids	
• Pharmacy bulk packages (< 5g)	20 containers
• Pharmacy bulk packages (≥ 5g)	6 containers
Bulks and blends	See bulk solid products
Opthalmic and other noninjectable preparations	
• Not more than 200 containers	5% or 2 containers, whichever is the greater
• More than 200 containers	10 containers
If the product is presented in the form of single dose containers, apply the scheme shown above for preparations for parenteral use.	
Devices:	
Catgut and other surgical sutures for veterinary use	2% or 5 packages, whichever is the greater up to a maximum of 20 packages
• Not more than 100 articles	10% or 4 articles, whichever is the greater
• More than 100, but not more than 500 articles	10 articles
• More than 500 articles	2% or 20 articles, whichever is less
Bulk Solid Products	
• Up to 4 containers	Each container
• More than 4 containers, but not more than 50 containers	20% or 4 containers, whichever is greater
• More than 50 containers	2% or 10 containers, whichever is greater

*refer to USP <71> for additional information

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Minimum Quantity to be Used for Each Medium (from USP <71>)

Quantity Per Container	Minimum Quantity to be Used (unless otherwise justified and authorized)*
Liquids (other than antibiotics)	
• Less than 1 mL	The whole contents of each container
• 1 – 40 mL	Half the contents of each container, but not less than 1 mL
• Greater than 40 mL and not greater than 100 mL	20 mL
• Greater than 100 mL	10% of the contents of the container, but not less than 20 mL
Antibiotic liquids	1 mL
Other preparations soluble in water or in isopropyl myristate	The whole contents of each container to provide not less than 200 mg
Insoluble preparations, creams, and ointments to be suspended or emulsified	Use the contents of each container to provide not less than 200 mg
Solids	
• Less than 50 mg	The whole contents of the container
• 50 mg or more, but less than 300 mg	Half the contents of each container, but not less than 50 mg
• 300 mg – 5 g	150 mg
• Greater than 5 g	500 mg
Devices	
Catgut and other surgical sutures for veterinary use	3 sections of a strand (each 30 cm long)
Surgical dressing/cotton/gauze (in packages)	100 mg per package
Sutures and other individually packaged single-use material	The whole device
Other medical devices	The whole device, but into pieces or disassembled

*refer to USP <71> for additional information

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Sterility Testing Quick Reference

Key Element	Description
Correct # units	Per Chapter <71>, Table 3
Correct volume /unit	Per Chapter <71>, Table 2
Correct method	• Membrane Filtration: pool all samples and run through single filter • Must have justification if using Direct Inoculation: 1:1 (unit tested and broth used) • Other methods (not in <71>) ***IF*** verification demonstrates equivalence to USP <71>
Method Suitability Testing performed	Determines if the sterility testing method is valid for a particular type of CSP and that the drug does not interfere with the sterility test method
Correct Media Used	• Fluid Thioglycollate Media (FTM) Incubated for 14 days (20-25°C) anaerobic and aerobic bacteria • Soybean Casein Digest Media (SCDM) Incubated for 14 days (30-35°C) for both aerobic bacteria and fungi

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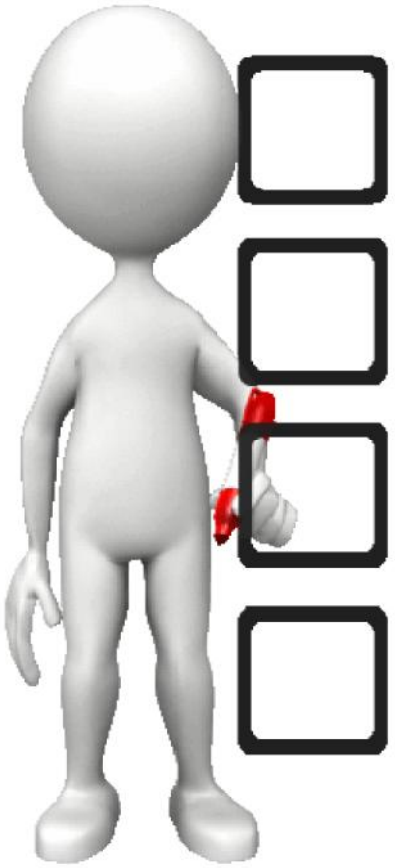
Inspector Evaluation Metrics: Sterility Testing

- Does the pharmacy have detailed policies, procedures, forms or electronic methods of documentation about all aspects of sterility testing?
- Does the pharmacy comply with USP Chapter <71>?
- Does the compounding location have a written procedure for immediate recall of the dispensed CSPs in the event of any evidence of microbial growth in the test specimens?



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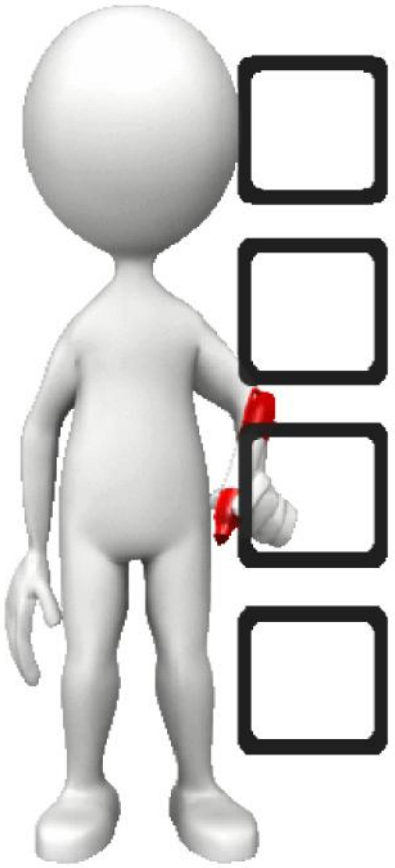
Inspector Evaluation Metrics: Sterility Testing

- CSPs are not dispensed prior to the time their final sterility test results are available.
- Does the compounding location have a written procedure requiring daily observation of the incubating sterility test specimens (if the CSP is dispensed prior to the final sterility test results?
- Does the pharmacy have a procedure for the immediate recall of the dispensed CSPs in the event of any evidence of microbial contamination?



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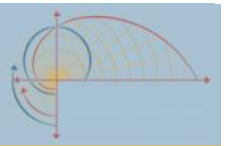
Polling Question



The two media used for sterility testing are:

1. FTM & LAL
2. LAL & TSB
3. TSB & FTM
4. TSA & TSB

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Critical Concepts in Pyrogen Testing

- Endotoxins produced by gram-negative bacteria and found within the cell membrane account for an estimated 99% of the pyrogens found on the surface of medical devices
- The term "pyrogen," literally "heat generating," refers to any substance—microbial or otherwise—which would induce a temperature rise when introduced into a patient

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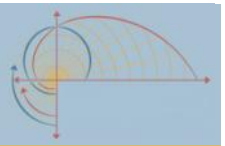
Why is pyrogen testing important?



- Endotoxins are produced by both gram-positive and -negative bacteria and fungi.
  - Endotoxins from gram-negative bacteria are more potent and represent a serious threat to patient safety and well-being.
- Intrathecal CSPs contaminated with endotoxins have been implicated in cases of both septic and aseptic meningitis, in addition to shock and death.
  - The intrathecal space does not have the same immunological and biological defense mechanisms as the intravenous system.

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Why is pyrogen testing important?

- The official endotoxin limits are 5 EU/kg/hr or 350 EU/total body/hour for drugs and biologicals
- Drugs for intrathecal administration have a much lower endotoxin limit:
  - 0.2 EU/kg/hr

Image: Retrieved from Medscape on October 3, 2013.

Official endotoxin limits were established by the FDA

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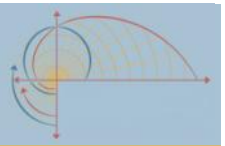
Sources of pyrogens



- The choice of components used in CSPs is a critical step, especially during preparing intrathecal injections.
- Commercially available components from manufacturers are typically sterile and pyrogen-free.
  - Nonsterile components used in high-risk level compounding may not pyrogen-free.
- Water is the main source of pyrogens.
- Endotoxins are a type of pyrogen and are stable over long periods of time.

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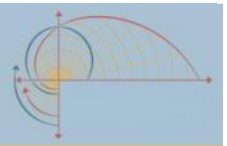
Sources of pyrogens (continued)



- Glassware, devices, or utensils that have been washed with tap water and then used to compound high-risk level CSPs can serve as a reservoir of endotoxins.
  - These pyrogens can be transferred to solutions prepared in beakers or utensils during the compounding process.
- Filtration using typical 0.22 micron filters or moist-heat sterilization will not eliminate endotoxins after introduction into a solution.
  - Pall Posidyne® filter is a 0.2 micron positively charged nylon filter membrane that can retain endotoxins in solution.
- Properly depyrogenating glassware and utensils by using a dry-heat oven can eliminate the introduction of pyrogens.

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Bacterial Endotoxin Test (BET)

- Historically, pyrogen testing of drugs was performed using rabbits.
  - This method took longer and was less sensitive.
- This method was replaced with the LAL method.
  - LAL is an acronym for Limulus Amebocyte Lysate which is based on clotting properties of the horseshoe crab's blood.
- BET or LAL is a test method for estimating the concentration of bacterial endotoxins.

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BET (continued)

- There are several methods of performing this test:
  - Gel-clot technique: gel-clot formed in presence of endotoxin.
  - Photometric
    - Turbidimetric method: presence of turbidity is observed
    - Chromogenic method: color change is observed

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BET Summary

- BET appears simple, but it is a complex procedure and requires method validation for the individual drug being tested.
- BET has several requirements in order to be a validated test. They are:
  - All testing solutions have a neutral pH
  - All testing solutions have a low salt or solute concentration to allow an optimal reaction between the LAL reagent and endotoxins.
- Compounded drugs usually require significant dilution to prevent interference and risk of false-negative results.

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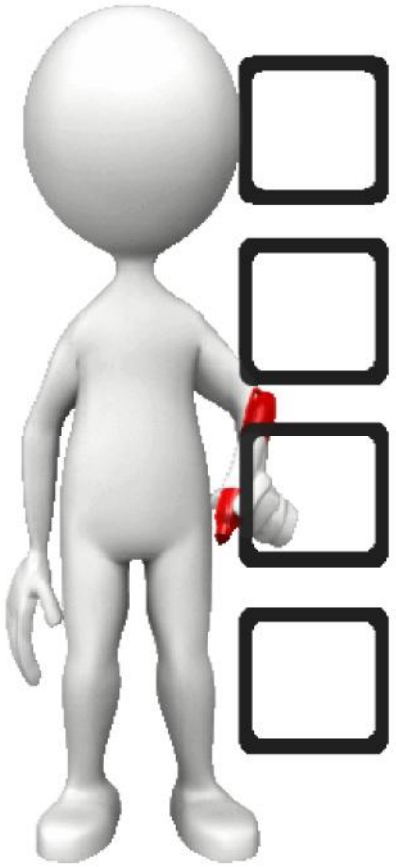
Inspector Evaluation Metrics: Bacterial Endotoxin

- Is bacterial endotoxin (pyrogen) testing on all high risk level CSPs, (except those for inhalation and ophthalmic administration) performed?
- Does the pharmacy have a specific policy and procedure for bacterial endotoxin testing?
  - Does it includes the description of the procedure?
  - Have specific endotoxin unit limits based on USP Endotoxin Test < 85> been developed?



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Polling Question

The reagent for the Bacterial Endotoxins test is which of the following?

1. FTM
2. LAL
3. TSB
4. TSA

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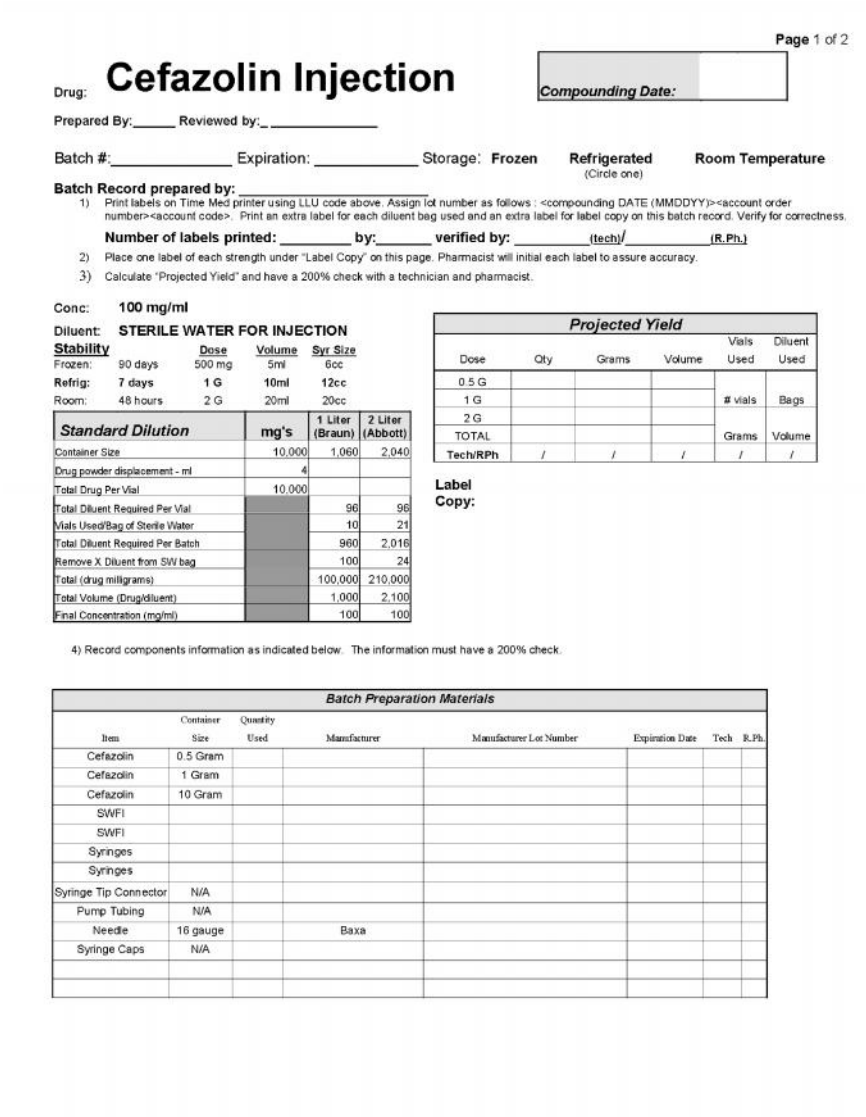
Quality Release Checks And Tests: Documentation



Page 1 of 2

Drug: **Cefazolin Injection**

Compounding Date:

Prepared By:_____ Reviewed by:_ _____

Batch #:_____ Expiration: _____ Storage: **Frozen** **Refrigerated** (Circle one) **Room Temperature**

Batch Record prepared by: _____

1) Print labels on Time Med printer using LLU code above. Assign lot number as follows : <compounding DATE (MMDDYY)><account order number><account code>. Print an extra label for each diluent bag used and an extra label for label copy on this batch record. Verify for correctness.

Number of labels printed: _____ **by:**_____ **verified by:** _____(tech)/_____(R.Ph.)

2) Place one label of each strength under "Label Copy" on this page. Pharmacist will initial each label to assure accuracy.

3) Calculate "Projected Yield" and have a 200% check with a technician and pharmacist.

Conc: **100 mg/ml**

Diluent: **STERILE WATER FOR INJECTION**

Stability		Dose	Volume	Syr Size
Frozen:	90 days	500 mg	5ml	6cc
Refrig:	**7 days**	**1 G**	**10ml**	**12cc**
Room:	48 hours	2 G	20ml	20cc

Projected Yield					
Dose	Qty	Grams	Volume	Vials Used	Diluent Used
0.5 G					
1 G				# vials	Bags
2 G					
TOTAL				Grams	Volume
Tech/RPh	/	/	/	/	/

Standard Dilution	mg's	1 Liter (Braun)	2 Liter (Abbott)
Container Size	10,000	1,060	2,040
Drug powder displacement - ml	4		
Total Drug Per Vial	10,000		
Total Diluent Required Per Vial		96	96
Vials Used/Bag of Sterile Water		10	21
Total Diluent Required Per Batch		960	2,016
Remove X Diluent from SW bag		100	24
Total (drug milligrams)		100,000	210,000
Total Volume (Drug/diluent)		1,000	2,100
Final Concentration (mg/ml)		100	100

Label Copy:

4) Record components information as indicated below. The information must have a 200% check.

Batch Preparation Materials							
Item	Container Size	Quantity Used	Manufacturer	Manufacturer Lot Number	Expiration Date	Tech	R.Ph.
Cefazolin	0.5 Gram						
Cefazolin	1 Gram						
Cefazolin	10 Gram						
SWFI							
SWFI							
Syringes							
Syringes							
Syringe Tip Connector	N/A						
Pump Tubing	N/A						
Needle	16 gauge		Baxa				
Syringe Caps	N/A						

- Does the pharmacy have a written release checks and tests PnP used to evaluate?
- Were the correct ingredients used?
- Were the weights and measures correct?
- Verified by review of batch documentation
- Signatures or initials of compounders can be traced back to signature log
- Date of preparation and specimen label retained and attached to compounding documentation

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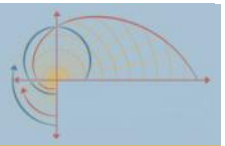
Quality Release Checks and Tests



- Physical inspection provides very basic information about the CSP.
- Primary concern is that the CSP contains the ingredients specified in the original prescription.
- The final preparation still should be evaluated for:
  - Container leaks and integrity: physical examination of the final prepared container visually inspected for leaks, holes or other container-closure breaches;
  - Particulates in solution: physical examination of the solution for the presence of mobile, randomly sourced, extraneous substances other than gas;
  - Solution color, volume, and odor (if possible) and
  - Phase separation (oiling, creaming, or cracking)

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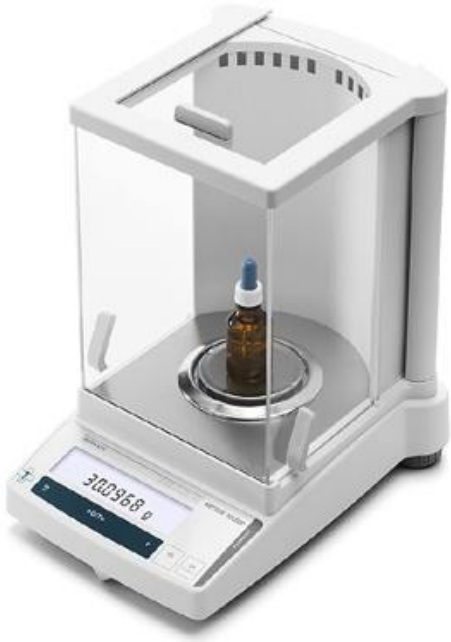
Quality Release Testing: Equipment

- How does the pharmacy ensure that equipment, apparatus, and devices used to compound a CSP be consistently capable of operating properly and within acceptable tolerance limits?
- Are written procedures outlining required equipment calibration, annual maintenance, monitoring for proper function, and controlled procedures for use of the equipment and specified time frames for these activities are established and followed?
  - Routine maintenance and frequencies shall be outlined in these SOPs.



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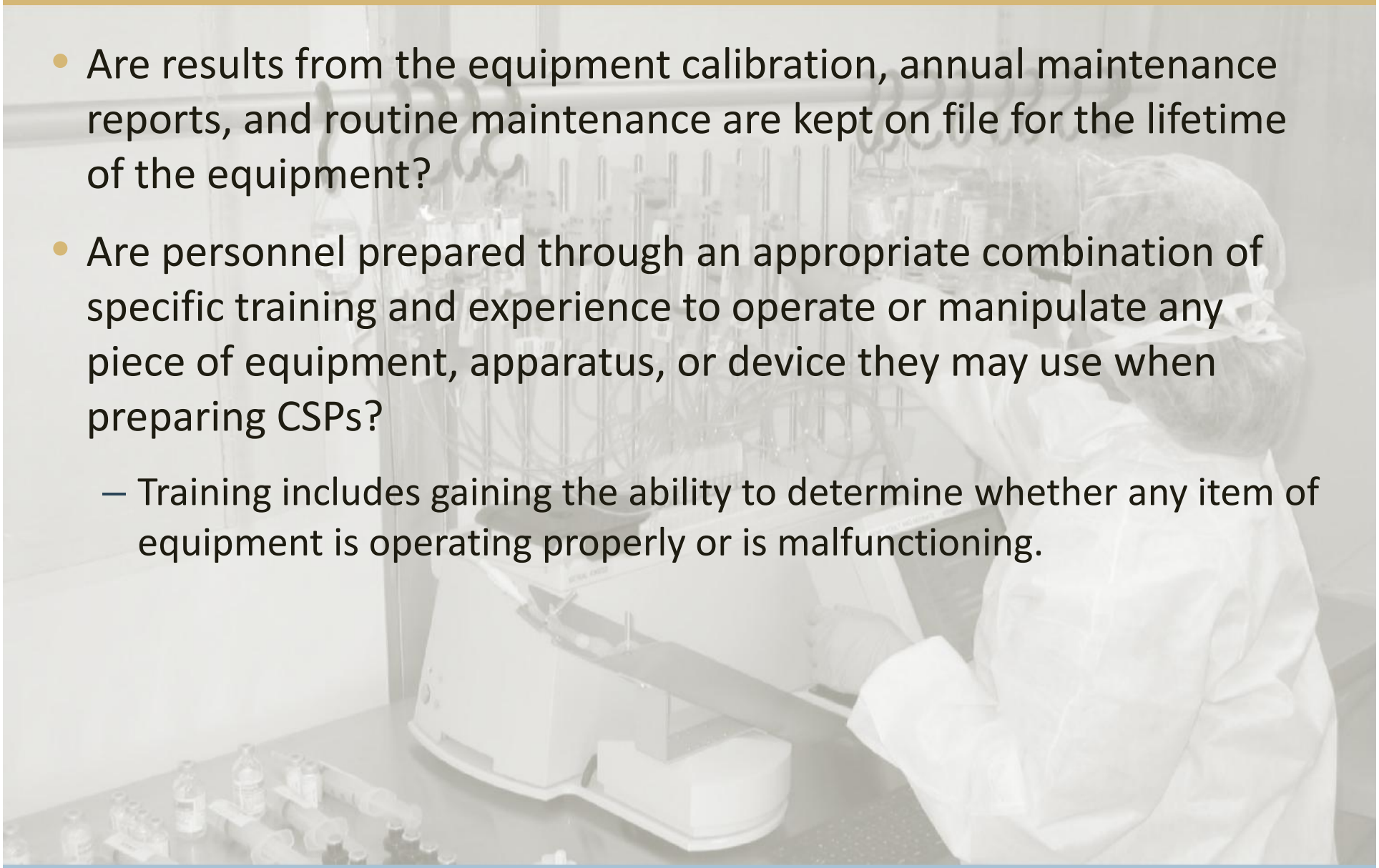
Quality Release Testing: Equipment



- Are results from the equipment calibration, annual maintenance reports, and routine maintenance are kept on file for the lifetime of the equipment?
- Are personnel prepared through an appropriate combination of specific training and experience to operate or manipulate any piece of equipment, apparatus, or device they may use when preparing CSPs?
  - Training includes gaining the ability to determine whether any item of equipment is operating properly or is malfunctioning.

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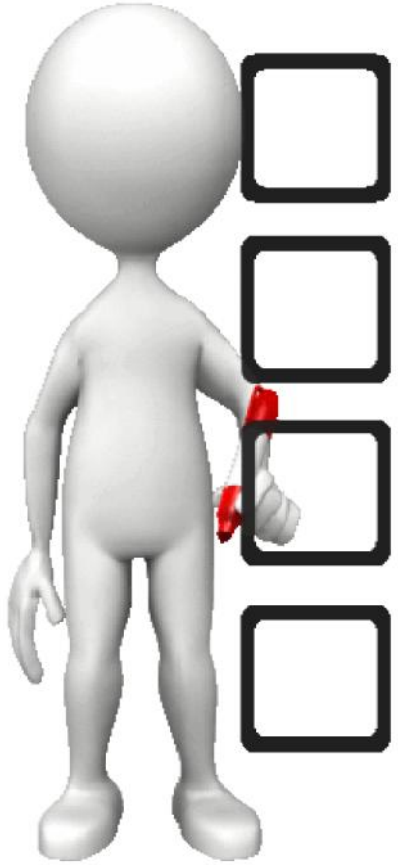
Inspector Evaluation Metrics: Quality Release

- Does the pharmacy a formal written policy for release checks and tests for CSPs?
- Is there evidence that CSPs are inspected for particulate matter?
- Is there evidence that the pharmacy calibrates and maintains their equipment in good working condition?
- Is there evidence that staff are appropriately trained on the use and troubleshooting of equipment?



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Quality Management System

- Does the pharmacy have a formal and written Quality Assurance/Performance Improvement Plan for all aspects of compounding activities?
  - includes specific monitoring and evaluation activities; details on how results are reported; and delineation of the persons responsible.
- Are Adverse events and defects related to CSPs are reported through the FDA's MedWatch and/or Quantros programs?

QUANTROS

Food and Drug Administration
MEDWATCH

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Quality Management System

- Does the pharmacy have a consistent process to document, trend, and ascertain the effectiveness of a corrective action plan to resolve issues when:
  - a desired patient outcome is not achieved;
  - an Action Limit is exceeded;
  - or other operational variance is noted?
- Examples: CAPA, QRE/Incident Report
  - Corrective and Preventative Action
- Does the compounding location have a written procedure requiring notification of the physician and patient to whom a potentially contaminated CSP was administered?

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Example of CAPA Form

Corrective & Preventive Action (CAPA) Plan

Problem

Select type:

- ☐ Existing Problem (may be multiple below)
  - ☐ *Customer Complaint*
  - ☐ Sentinel Event (SE)
  - ☐ Major Incident (MI)
  - ☐ Other
- ☐ Potential Problem

Describe the problem: ☐ **See attached CCF (F-916.a) if customer complaint**

Describe immediate action/s taken to contain the problem (short term corrective action)

☐ Pharmacy Manager notified by ☐ telephone ☐ in person

Completed by:	**Date:**

➡ The section below is filled out by problem solving team manager <insert title/s of appropriate SCP staff>

Root Cause

- ☐ Machines
- ☐ Method
- ☐ Manpower/ training
- ☐ Measurements
- ☐ Materials
- ☐ Milieu/environment

Problem Owner (name/title):

In check boxes to left, describe contributing factors & root cause identified (attach additional sheets as needed)

Completed by:	**Date:**

Permanent Corrective Actions

Actions to correct the root cause to reduce likelihood of reoccurrence ☐ Other attached

Task	**Owner**	**Due Date**

Completed by:	**Date:**

Results

Sufficient time must pass to ensure proper evaluation of corrective action effectiveness

Has the root cause been corrected? ☐ Yes ☐ No ➡ *new corrective action/explanation below (attach additional sheets when needed to adequately explain)*

Standardization of Change

Policy/Procedure/Forms updated ➡ ☐ No ☐ Yes ☐ N/A (document below)

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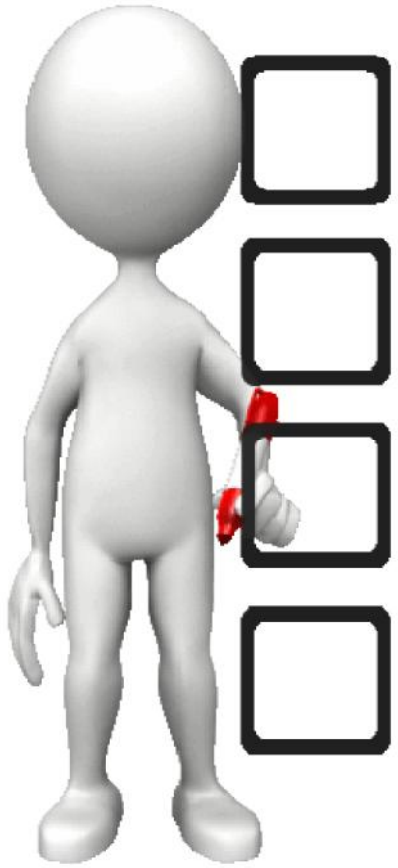
Inspector Evaluation Metrics: Quality Management

- Does the pharmacy a formal and written quality assurance plan?
- Does the pharmacy document patient complaints?
- Does the pharmacy respond appropriately to complaints and is there evidence that an investigation was conducted and resolution documented?



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Patient Counseling

- Does the pharmacy have a training program includes didactic and practical hands on training of patients and caregivers with successful return demonstration of the required skills for administration of CSPs?
- The specific required competencies are formally assessed and patients/caregivers must demonstrate competency before they are allowed to administer CSPs independent of supervision by healthcare professionals?
- Does the pharmacy have a formal training program that ensures that patients/caregivers achieve the required competencies for safe storage, handling, administration, monitoring, emergency actions and disposal of CSPs?
- Does the pharmacy provide written materials to patients/caregivers to supplement verbal training?
- Does the pharmacy have procedures/system in place for patients and caregivers to use to report questions or concerns relative to CSPs they receive from the compounding location?

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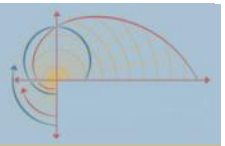
Redispensing CSPs, Storage and Transport



- Common practice in hospitals (also known as recycling)
- Originally assigned BUD dates are not changed and CSPs are not redispensed unless changes are supported by the originally assigned BUD.
- Is there absolute certainty that proper storage conditions have been maintained during the time they were outside of pharmacy's control?
- Is there evidence of a systematic process to evaluate when unopened, returned CSPs are safe to redispense?
- Is there evidence that packaging maintains physical integrity, sterility, stability and purity of CSPs?
- Is there evidence that the storage of finished CSPs and drug components is separate from food storage and from any specimen storage (if occurs onsite)?
- Does the pharmacy have evidence that the methods used to transport CSPs to the patient prevent damage and maintain appropriate temperatures during transit?

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“Absence of Evidence Does Not Equal Evidence of Absence”

Dr. David Hussong

(FDA and the USP Microbiology and Sterility Assurance Expert Committee)

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