Understanding the Basic Aseptic Process Simulations

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Understanding the Basic Aseptic Process Simulations

- **Aseptic Process Simulations, also known as Media Fills**
  - Simulate a product fill by using a liquid growth media in place of the product
  - How should they be designed?
  - What processes are required?
  - Who should participate in the media fill?
  - What is the frequency?
  - Duration of the media fill?

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- **Aseptic Process Simulations (APS), also known as Media Fills**
  - Number of vials per run
  - Line speed
  - Environmental conditions
  - Media used?
  - Incubation temperatures
  - Inspection requirements
  - Interpretation of the results

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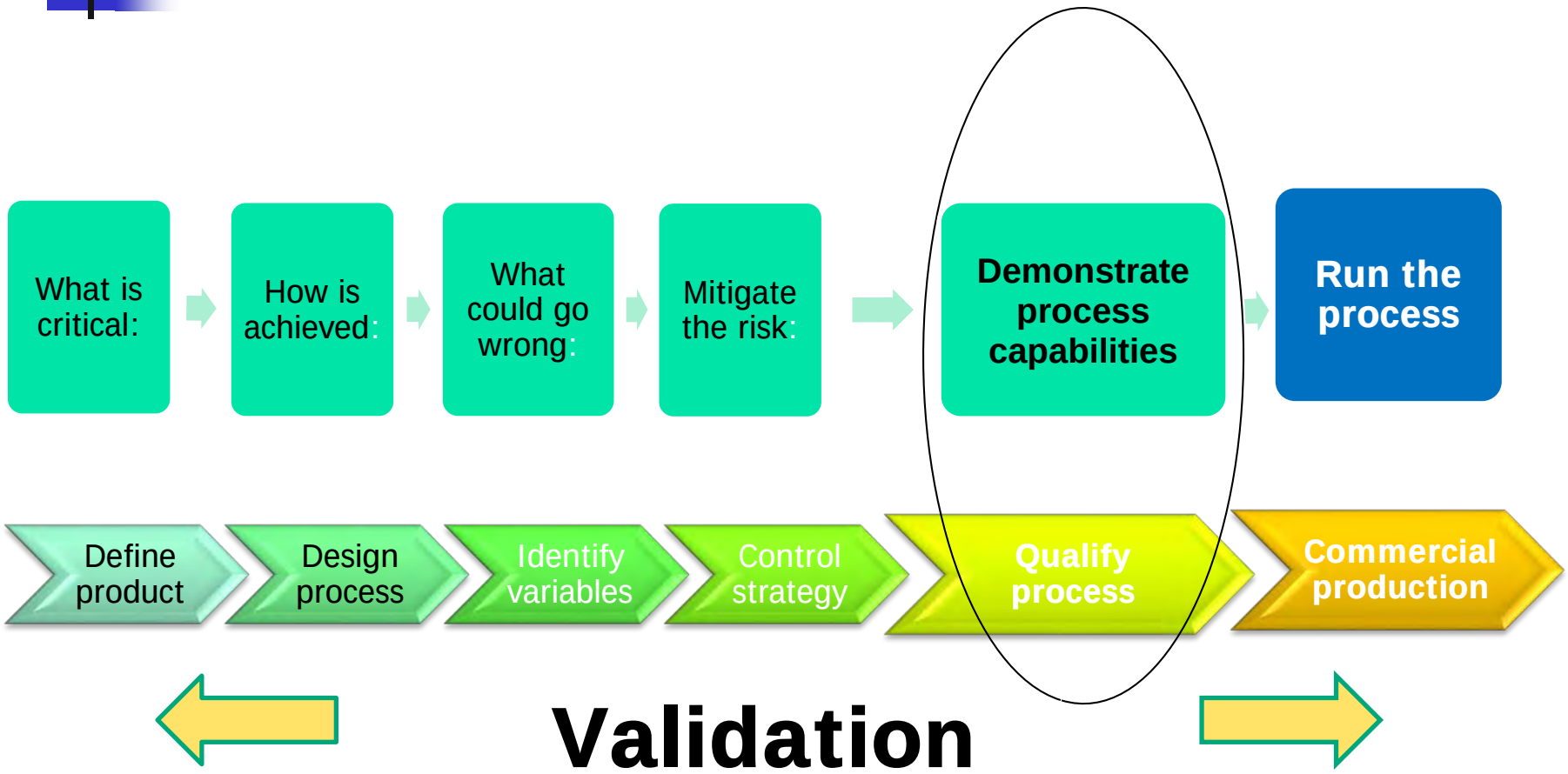

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- **Asepsis (FDA Aseptic Process Guidance)**
  - A state of control attained by using an aseptic work area and performing activities in a manner that precludes microbiological contamination of the exposed sterile product

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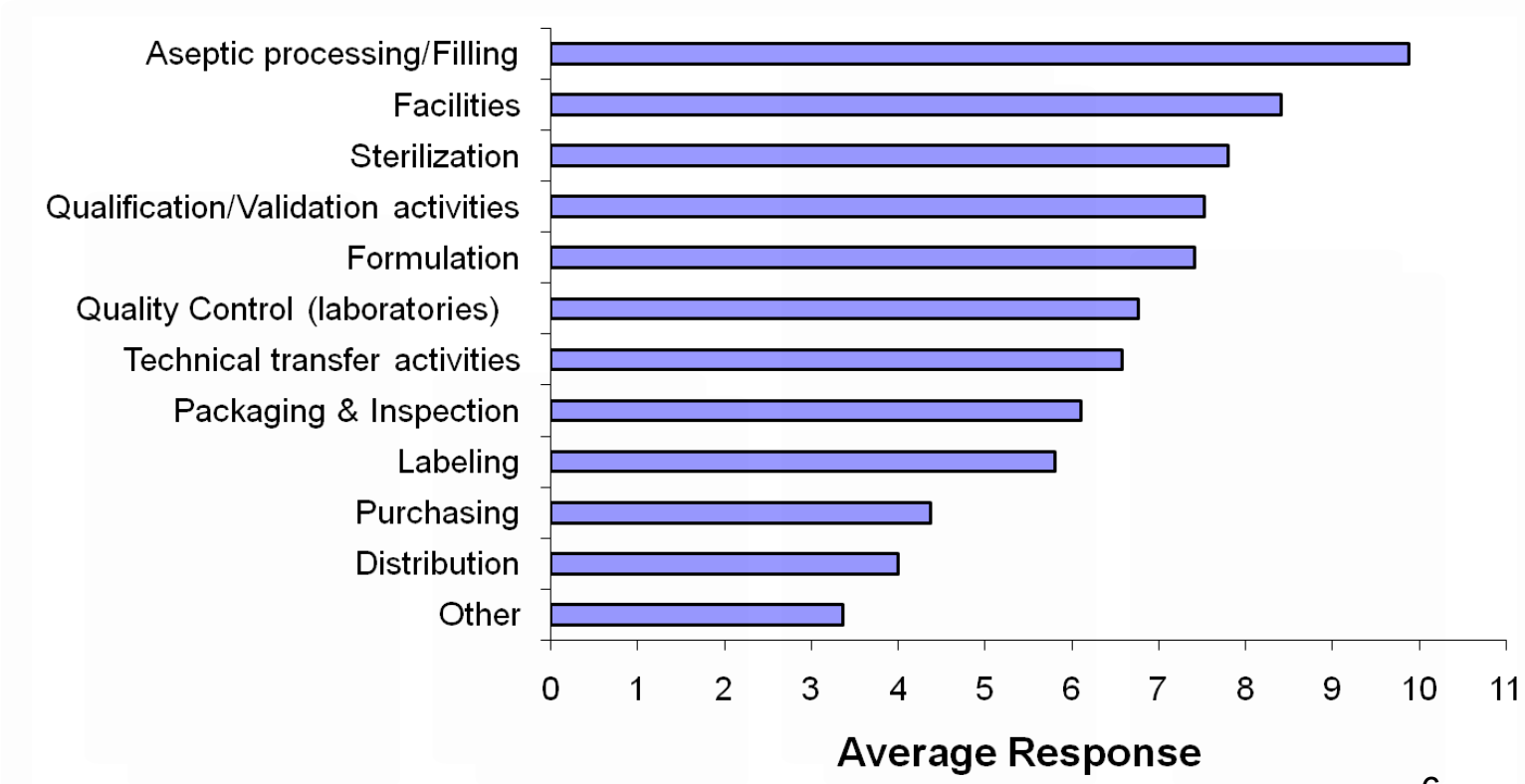
- **What is the Highest Process Risk**



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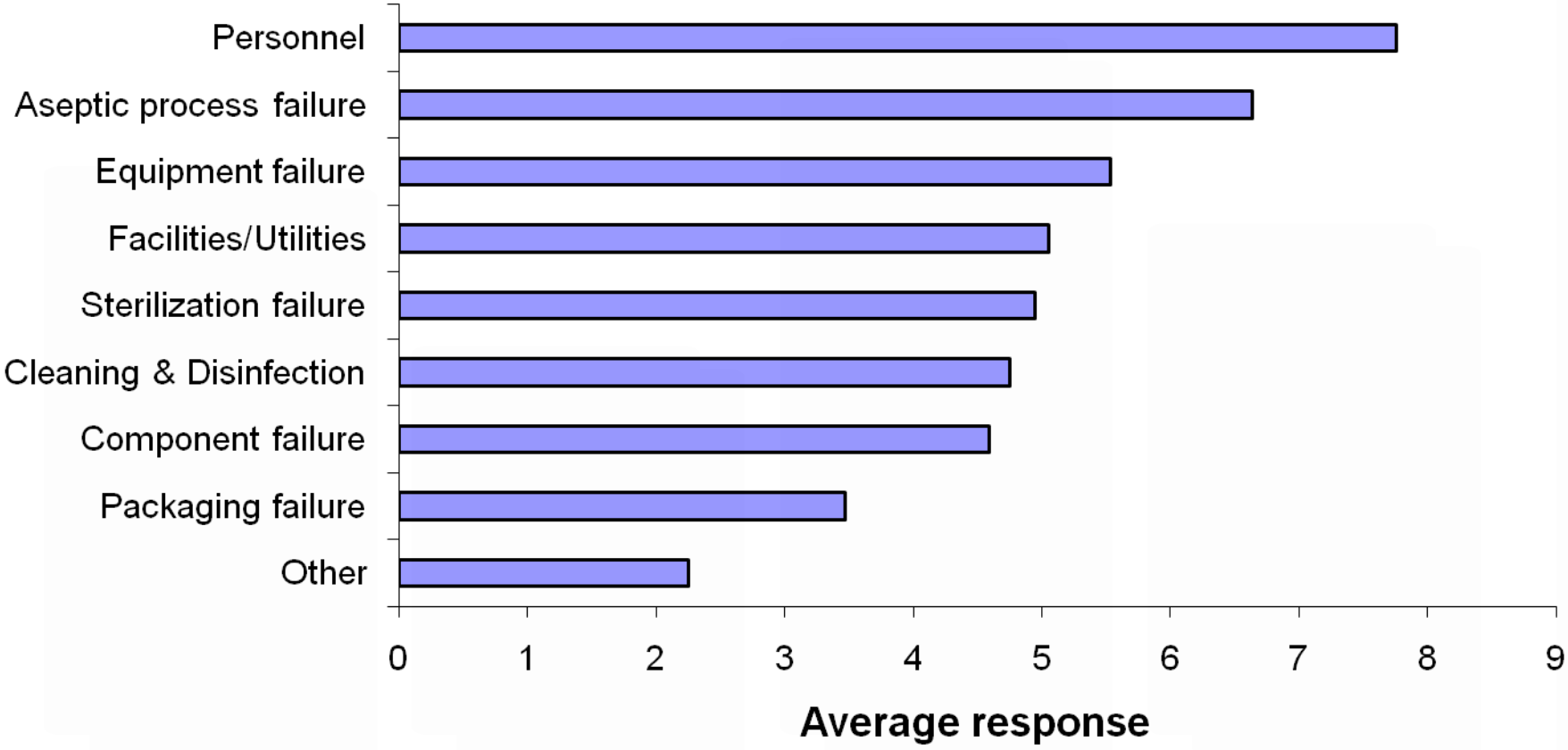
- **Risk to the Product**



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Aseptic Processing

- Part of the overall validation method
- Challenges the capability of the process
- It is a simulation of the aseptic process from the point of sterilization to closure of the container, substituting a microbiological growth medium for the sterile product.

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- To demonstrate the capabilities of the process
- Assess the impact of changes made to the process which might impact the sterility of the product.
- Can identify weaknesses in the process which might contribute to contamination

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- **Aseptic Processing**
  - Process must work before it can be validated
  - Do not use ASP to validate a bad practice
  - Not a training activity, only trained personnel should participate
  - Ensure it is not used to qualify the operators

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- **Risk in Aseptic Processing**
  - Is the risk Actual or Perceived?
  - Who or which group defines risk?
  - Does your Risk Assessment SOP use the proper criteria to assess the risk?
  - How is it evaluated, high, medium and low?
  - Likelihood of detecting a contaminated unit?
  - What's the contamination rate?

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- **Media Fills evaluate all parameters associated with the validation of the aseptic process**
- **Risk Points associated with media fills**
  - Facility design
  - Materials of construction
  - HVAC validation
  - Terminal HEPA. ULPA or SULPA

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- **Risk Points Associated With Media Fills**
  - Choice of filling equipment
  - Gowning
  - Environmental monitoring
  - Cleaning and sanitization
  - Autoclave validation
  - SIP of hold tanks and process lines

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- **Process Design**
  - Assess the following
    - Personnel flow
    - Process flow
    - Component/Equipment flow
    - Product flow
    - Waste flow
    - Differential pressure to adjacent rooms
    - First Air concept

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- **Process Design**
  - Training/Qualification of aseptic personnel
    - Small scale media fill in a LAF or BSC
    - Demonstrate competence in the following
      - ✓Aseptic techniques
      - ✓Airflow and First-Air concepts
      - ✓Cleaning and sanitization
      - ✓Introducing items into the Grade-A area
      - ✓Basic gowning for the LAF/Hood

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- **Process Design**
  - Training/Qualification of aseptic personnel
    - Training per SOP and/or computer based
    - Hands on training in the fill room
    - Water fill/dynamic filling conditions
    - Initial clean room activity as support person

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- **Process Design**
  - Training/Qualification
    - Do we validate the process?
    - Do we qualify the personnel?
    - Or is it a combination of both?

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- **Process Design**
  - Training/Qualification
    - How do we qualify, demonstrate competency, for 6-set up operators if there are only 2-media fills per year?
    - Can a Subject Matter Expert qualify operators to perform the task with out participating in a media fill?

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- **Process Design per TR-22 Personnel Qualification**
  - Personnel working in the clean room should be capable of adequately performing job function, properly trained in work function, and qualified to perform those functions. The requirements for qualification of personnel should be written in a formal procedure and the results documented.

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- **Process Design per TR-22 Personnel Qualification**
  - Initial Qualification
    - Demonstrate proficiency in aseptic technique by successfully performing qualification test entailing manual media manipulation not associated with APS

-OR-

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- **Process Design per TR-22 Personnel Qualification**
  - Initial Qualification
    - Participate in a successful aseptic process simulation run in which they perform the same functions to the extent that they will perform it during actual production.

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- **Process Design per TR-22 Personnel Qualification**
  - Periodic Qualification
    - Participate in a successful aseptic process simulation run in which they perform the same functions to the extent that they will perform it during actual production at least once per year.

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- **Personnel Qualification Requirements**
  - Personnel are allowed to support non critical filling operations, prior to participating in a media fill
  - Personnel working in the critical areas must participate in a successful media fill once per year
  - Filling personnel are required to gown qualify once per year

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- **Personnel Qualification Requirements**
  - The appropriate department will submit a notification of the individuals requiring participation in a media fill to management
  - If individuals do not participate in a timely fashion, they will be disqualified from the aseptic processing areas

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- **Media Fills**
  - Do not rushing into initial media fills until all parameters have been completely evaluated, assessed and understood
  - For initial facility Performance Qualification
  - Requires a minimum of 3 consecutive successful media fills
  - A failed media fill during this phase of qualification will significantly impact the timelines of the project

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- Media fills must be conducted over a time period, the same as or longer, than routine processing time
- For changes to the facility and process
- Routine re-qualification
- Is the process well understood?
  - How detailed are the airflow studies
  - How many water fills have been run to evaluate the system
  - For new equipment, how does one become a SME

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- Performed at least twice per year, based on filling configuration
- A failure on a semi-annual media fill will require a minimum of 1, and possibility 3 consecutive successful media fills after corrective actions have been completed
  - Is there definitive cause or defined root cause for the failure?

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- Is there a plausible or probable cause?
- Does the story line make sense?
  - ✓ Source of the contamination identified
  - ✓ Movement of contamination from the source to the operator, filling equipment and/or surface
  - ✓ Vector into the vial determined
  - ✓ Identified how to eliminate the source
  - ✓ Confirmed CAPA was effective through additional sampling/testing

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- **Designing a Process Simulation**
  - Determine the number of vials required for the APS
    - Less than 5000, same number of units as product fill
    - Between 5000 and 10,000, same number of units as product fill
    - More than 10,000, only require 10,000

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- **Designing a Process Simulation**
  - Determine process to be simulated
  - Select filling components and media
  - Fill volume must be sufficient to coat the entire surface of the interior or the vial
  - Determine if nitrogen is required and replace with compressed air
  - Interventions required
  - Qualified personnel required

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- **Designing a Process Simulation**
  - Maximum and minimum personnel in the fill room
    - Do personnel that just stand in the clean room and do not participate in the fill, count in the maximum number?
    - The expectation is the maximum number represents operational personnel

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- **Designing a Process Simulation**
  - Define line speed and fill parameters
  - Some companies use components at expiration
    - This is a validation function
    - Does not have to be performed on each media fill

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- **Designing a Process Simulation**
  - Is the room conditions for media fills the same as product fills?
  - Most companies say yes, but the answer is actually no
    - Most companies perform media fills post shutdown

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- Post shutdown, a sporicide is used for re-start cleaning/sanitization
  - ✓ Is the sporicide left on the floors/walls?
  - ✓ Routinely it is not
  - ✓ Some companies perform a 3X cleaning/sanitization sequence post shutdown
  - ✓ Therefore, media fills might be performed under best case conditions

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- ✓ The sequence of application is important
- ✓ Sanitizer left on the walls/floors for product fills must be the same as media fills
- ✓ The sequence should be
  - Clean
  - Sporicide
  - Cleaner/Sanitizer (LpH and Decon-Quat/Cycle)
  - Alcohol on all filling surfaces and windows

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- **Set-Up filler Operations**
  - Operators/Mechanics set up the filling equipment for aseptic processing
  - Perform aseptic connections from the bulk to the fill line
  - Purge the system to remove any air
    - The volume purged must represent routine product filling operations
  - If the purge volume is discarded for products, then it does not have to be incubated as part of the media fill

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- **Filling Operations**
  - Fill time must represent production runs
  - Run the fill line at the routine speed in addition to the rate at which would be considered the most challenging
    - The smallest vials at the fastest speeds
    - The largest vials at the slowest speeds
  - If the hold tank is emptied during product fills, the media fill must reproduce this

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- **Filling Operations**
  - Perform routine environmental monitoring that represents routine product operations
    - Setup viable air and particulate tests
    - Changing plates
    - Yeast/mold and anaerobic monitoring if applicable

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- **Filling Operations**
  - For lyophilized products
    - Pre-chill shelves if applicable
      - ✓This is significant when using standard hinge door
    - Transfer vials into the freeze dryer
      - ✓Manually carrying the trays
      - ✓Lyo cart
      - ✓Auto loading system

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- **Filling Operations**
  - For lyophilized products
    - Partial vacuum must be pulled
    - Define dwell time in the freeze dryer
    - Shelves must collapse to close the vials
    - Unload vials
    - Place vials back on the line to be capped

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- **Hold Times**
  - Sterile empty tanks
  - Media in bulk tank
  - Sterilized commodities
    - Use components at expiration?
  - Vials in the dry heat tunnel
  - Commodities on the fill line
  - Partially stoppered vials on the line

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- **Media Fill Conditions**
  - Maximum personnel in the fill room
    - Are all personnel involved in filling operations?
    - Do some operators stand there for a defined time, period such as QA personnel?
      - ✓Are they considered media fill qualified?
      - ✓What are they qualified to do?
    - Is the maximum number the most risky?

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- **Media Fill Conditions**
  - Minimum personnel in the fill room
    - Operators are doing more work per person
    - Are the personnel moving faster to get the work done?
    - Does this pose more risk to the process?
    - You don’t know until you validate it
    - Therefore maximum and minimum personnel are required per media fill

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- **Media Fill Conditions**
  - Temperature and Relative Humidity (RH)
    - Are media fills performed under upper and lower conditions?
    - Most companies do not take this into account
      - ✓ Lower temperatures/RH do not pose any significant microbial risk

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- Temperature conditions
  - Higher temperatures and RH
    - ✓ Perspiration
    - ✓ Increased personnel monitoring positives
    - ✓ Comfort of the operators
    - ✓ There can even be a significant difference when using disposable verses re-useable gowns

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- **Media Operations**
  - How closely does the media fill mimic the product fill?
  - If a video of a product and media fill was reviewed, how easy would it be to tell the difference by only evaluating personnel movement during operations?

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- **Media Operations**
  - Unfortunately it is extremely easy
    - Gowning is exactly per SOP
    - Operators move slower
    - Sanitize gloves more frequently
    - Ensure compliance to First-Air
    - More attention to detail by operators
    - Little to no deviation by personnel during media fills

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- **Media Operations**
  - Why is this the norm?
    - More personnel scrutinizing the process from the outside
    - Because every vial is a test
    - For product fills, at a minimum, 20-vials are tested for sterility

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- **Media Operations**
  - It should be the opposite
    - Since only 20-vials are tested for sterility testing, more attention to detail should occur during product fills
    - Or at least the same critical eye on the process

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- **Media Operations**
  - A company fills 100K vials over 20 hours
  - For media, they fill 10,001 vials covering the same 20 hour period per the regulatory guidelines
  - Does the media fill represent product fills?
  - The number of vials required for media fills is only 10K even if you fill 100K – 200K.
  - This is not statistically valid or reasonable

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- **Media Operations**
  - How do companies accomplish this?
  - They fill for short periods and take long breaks with no activity in the clean room
  - In many cases they simulate interventions
    - How closely does the simulated intervention compare to the actual
    - Does it take the same time?
  - What value is this as to understanding a fill of 100K vials

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- Consider this proposal for fills over 10,000
  - Define a sliding scale as to the number of vials required for media fills
  - Fill sufficient vials to represent the process and activity in the room
    - ✓ Setup of the filling equipment
    - ✓ Shift change and breaks
    - ✓ Environmental activity
    - ✓ All interventions
    - ✓ Maximum and minimum personnel

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- Fill sufficient vials to represent the process and activity in the room
  - ✓ This would not require taking long breaks which are not value added
  - ✓ Would require a minimum number of vials to be filled after each intervention
  - ✓ Comply with total vials up to 10K
  - ✓ This could be considered more representative of the process

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- **Interventions**
  - Manipulation or activity that occurs within the critical Grade-A/B areas to keep the filling operations running or to fix problems with the filling line
  - How are interventions defined or categorized?
    - Routine/Non-Routine
    - Critical/Non-Critical
    - Inherent/Corrective

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- **Interventions**
  - Occur during most production runs
  - Most will be included in each media fill
  - Intervention procedures must be clearly defined in applicable SOP
  - Define requirements for stopping and starting of the fill line for routine interventions
  - Some interventions may not require line stoppage

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- **Interventions**
  - Design the process to minimize the number of interventions
  - Is the equipment/intervention even part of the process anymore?
  - Assess how to prevent, reduce or eliminate the interventions
    - Can the intervention be engineered out?
    - Is it possible to change the process to eliminate the intervention?

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- **Interventions**
  - All interventions must have airflow studies associated with it
  - Does the intervention interfere with the First Air to the process
  - Can the airflow be changed to keep the process in First-Air?

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- **Interventions**
  - The operator sanitizes their gloves and performs the intervention using sterile instruments like forceps or stainless steel rod
    - The process remains in First Air
    - Little or no risk to the process

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- **Interventions**
  - The operator puts on sterile sleeves and gloves prior to performing the intervention
    - The sleeves and gloves are not considered sterile since the operator moves through a Grade-B area to perform the intervention in the Grade-A area
    - Medium/Low risk to the process

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- **Interventions**
  - Personnel sanitize their gloves and performs the intervention.
    - Interferes with First Air to the process
    - Medium/High risk
    - In this case, there is a variable
      - ✓ If a support person opens the cabinet door, than the risk remains the same
      - ✓ If the aseptic operator opens the cabinet door, and performs the intervention, then the risk becomes High

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- **Interventions**
  - Divided into two categories
    - Mechanical
      - ✓ There is a physical problem that can be minimizes and/or eliminated through engineering
    - Intrinsic
      - ✓ Associated with the inherent nature of the process
      - ✓ These are items that can't be resolved by engineering

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- **Interventions**
  - Common mechanical interventions
    - Stopper jam caused by catch point in the hopper, bowl or rail
      - ✓ Evaluate for imperfections in the metal
      - ✓ Bowls need to be tuned
      - ✓ Increase vibration rate
    - Vial jam in the scrolls
      - ✓ Connection point not aligned
      - ✓ Defects in the scroll over time

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- **Interventions**
  - Common mechanical interventions
    - Vials tip over on the turntable
      - ✓ Evaluate for scratches and refinish
    - Vials fall over on the conveyor
      - ✓ Do not use silicone to prevent this
      - ✓ Check conveyor for grooves or wear
      - ✓ Change conveyor if significant imperfections are observed

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- **Interventions**
  - Common Intrinsic interventions
    - While manually loading vials, several fall over
    - While loading stoppers, one falls and jams in the track
    - While performing an intervention, operator causes a vial to fall over

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- **Interventions**
  - Evaluate the interventions and perform a risk analysis
    - Are the proper tools available to perform the interventions?
      - ✓How short/long are the forceps?
      - ✓Can the forceps be modified to make the intervention easier.
      - ✓Use custom curved or angled forceps
      - ✓Is there a SOP for use of forceps?

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- Are the proper tools available to perform the interventions
  - ✓ Are the scissors straight or off set?
  - ✓ Can a sterile rod be used to remove vials, cap/stopper jams to keep the process in First-Air?
  - ✓ Are sterile tools single or multiple use?
  - ✓ Are the tools sterile and are they stored in First-Air after use?

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- **Interventions**
  - Can an intervention be considered too risky, and therefore cause to end the fill?
  - For example
    - Pump change
    - Needle change
    - Stopper bowl or stopper rail change
  - Most companies perform these type of interventions routinely

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- **Interventions**
  - For media fills, which pump or needle is changed?
  - In most cases it's the ones on far right or left because they are the easiest
  - However, the most difficult and most risky are the center locations
    - Difficult to reach
    - Operator interferes with First-Air to the filling needles
    - Post intervention, are the operators gloves sampled to assess risk?

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- **Interventions**
  - Record intervention start and completion time on a activity sheet
  - Document personnel who performed the intervention
  - What speed should the vials be run at upon restarting the machine
  - How many vials must be cleared after an intervention
    - Is it necessary to discard vials
    - It depends on the intervention

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- **Interventions**
  - Some companies re-produce the intervention based on the number of times it occurs during product fills
    - If the intervention occurs 30 times while filling 100K product vials
    - For media fills, only 10K vials are filled. Therefor, the intervention must be performed 3 times.
    - The same percent as product fills

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- **Interventions**
  - Is the intervention process the item that is validated?
    - If so, then anyone trained on the process can perform the intervention
    - If the intervention is validated, and it can be kept in First Air, then the number of times it is performed is irrelevant.
    - The Risk Factor does not increase with the number if times it is performed.

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- **Interventions**
  - Is the intervention process the item that is validated?
    - If the intervention is not be kept in First Air, then the number of times it is performed can be significant
    - The Risk Factor will increase with the number if times/duration it is performed.

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- **Examples of Inherent (Routine) Fill Interventions**
  - Fallen vial
  - Line speed adjustments
  - Container breakage
  - Stopper/Cap jam
  - EM sample operations
  - Component replenishment
  - Weight adjustments and weight checks

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- **Corrective (Non-Routine) Interventions**
  - Occur infrequently during filling operations
  - Not require for each media fill but required to be performed on a periodic basis
  - Can be performed on a rotational basis
  - Interventions and procedures must be defined in a applicable SOP

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- **Corrective (Non-Routine) Interventions**
  - Since these are not performed on a routine basis, are the operators comfortable at performing the intervention
  - Are these higher risk than routine interventions
  - Should they be performed more than once per year
  - Are they simulated or do they actually occur during media fills

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- **Examples of Corrective (Non-Routine Interventions**)
  - Changing filling needle and/or pumps
  - Leaking at aseptic connections
  - Mechanical issues under filler
  - Changing stopper bowl
  - Loss of vacuum/compressed air

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- **Corrective (Non-Routine Interventions)**
  - Requirements associated with emergency stops of the fill line
  - If non-routine interventions become routine, perform an investigation and correct the problem

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- **New Interventions**
  - Was a deviation initiated for the product fill?
    - What was the outcome and the Risk Factor for the new intervention
  - What is the Change Control process to incorporate them into the
    - Media fill batch record
    - Airflow program
    - Applicable manufacturing SOP
    - Training for operators to perform the new intervention

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- **New Interventions**
  - Is the intervention similar to a current one?
    - May appear comparable, but the airflows can be significantly different
  - Who makes the decision and what criteria is used?
    - Is there an SOP that covers this?
  - What happens if the next media fill is positive based on this new intervention?
  - Risk to the product and the patient?

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- **Pre Incubation**
  - SOP's in place to qualify inspection personnel
  - Inspectors of the vials must complete extensive training including unknowns in trays
  - Inspectors can be from Manufacturing and/or Quality

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- **Pre Incubation**
  - Turn vials 360 to allow media touch entire interior surface including stopper
  - Incubate right side up or up-side down?
    - There is no preference
  - Most companies incubate right side up

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- **Pre Incubation**
  - Must have accountability for amount of media filled, media remaining in the bulk tank, fill lines, pumps, manifold, purging system, rejects and spills
  - Number of units must be counted and verified, per tray, prior to incubation
  - Critical that this number is accurate

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- **Pre Incubation**
  - The best way to ensure the counts are correct is to fabricate a tray with segregations
    - If all compartments are full the tray holds a defined number of vials
    - Best to make the tray so it is easy to determine the count.
    - For example 250 per tray

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- **Pre-Incubation**
  - Evaluate all vials and segregate them into the following categories
  - Critical Defects
  - Major Defects
  - Minor Defects
  - Integral

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- **Defects**
  - Critical
    - Non-Integral Rejects
    - Defect that will jeopardize patient safety
    - The product unfit for use.
    - May not conform to specification such as sterility and product release assay

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- Critical Defects
  - Cracked vial
  - No stopper
  - Dimple in the glass
  - Container closure not integral
  - These vials will be enumerated and rejected

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- **Critical Defects: Crack in glass**

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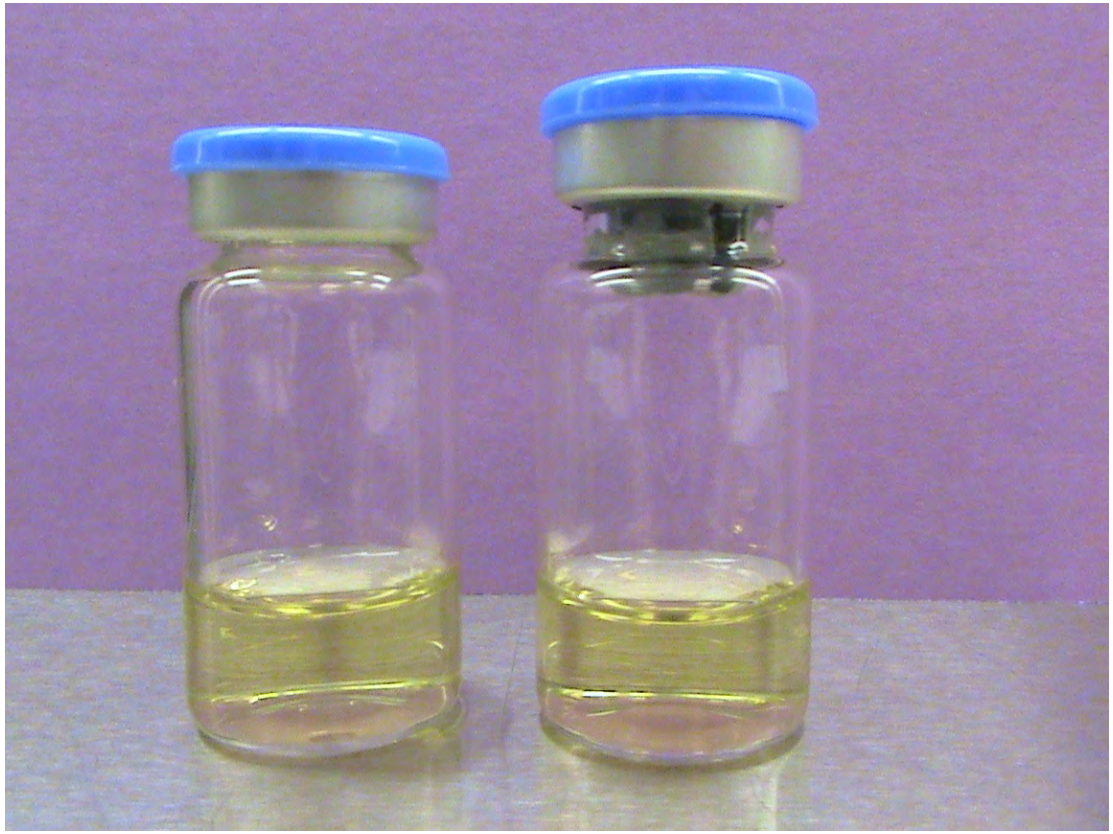
- **Critical Defects: No stopper**



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- **Critical Defects: Stone in glass**

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- **Defects**
  - Major
    - Impair package functionality
    - May lead to loss of performance
    - May cause personnel injury
    - Empty or broken containers

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- **Major Defects: Tear in cap**

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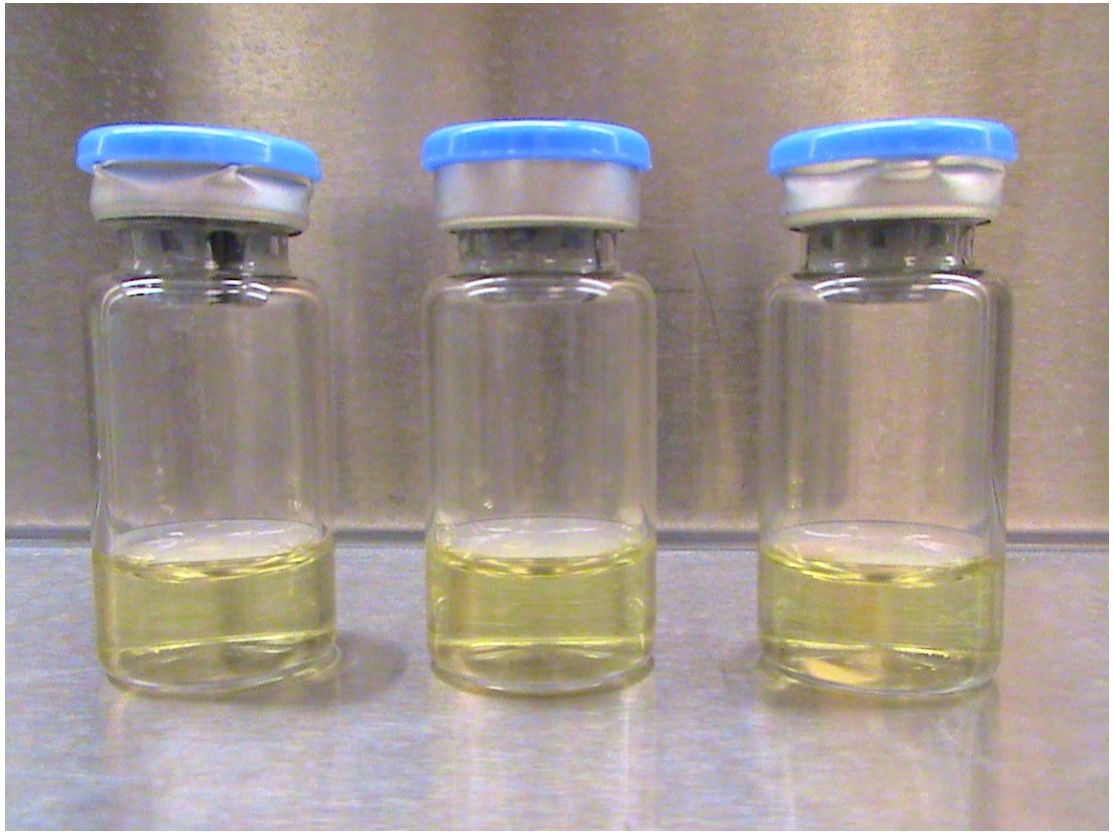
- **Major Defects: Defect in cap**



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- **Defects**
  - Minor
    - Defects not related to integrity
    - Cosmetic glass defects
    - Units that fall on the floor after container closure is secure and intact
    - Segregated and incubated as part of the fill

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- **Minor Defect: Defect in glass**

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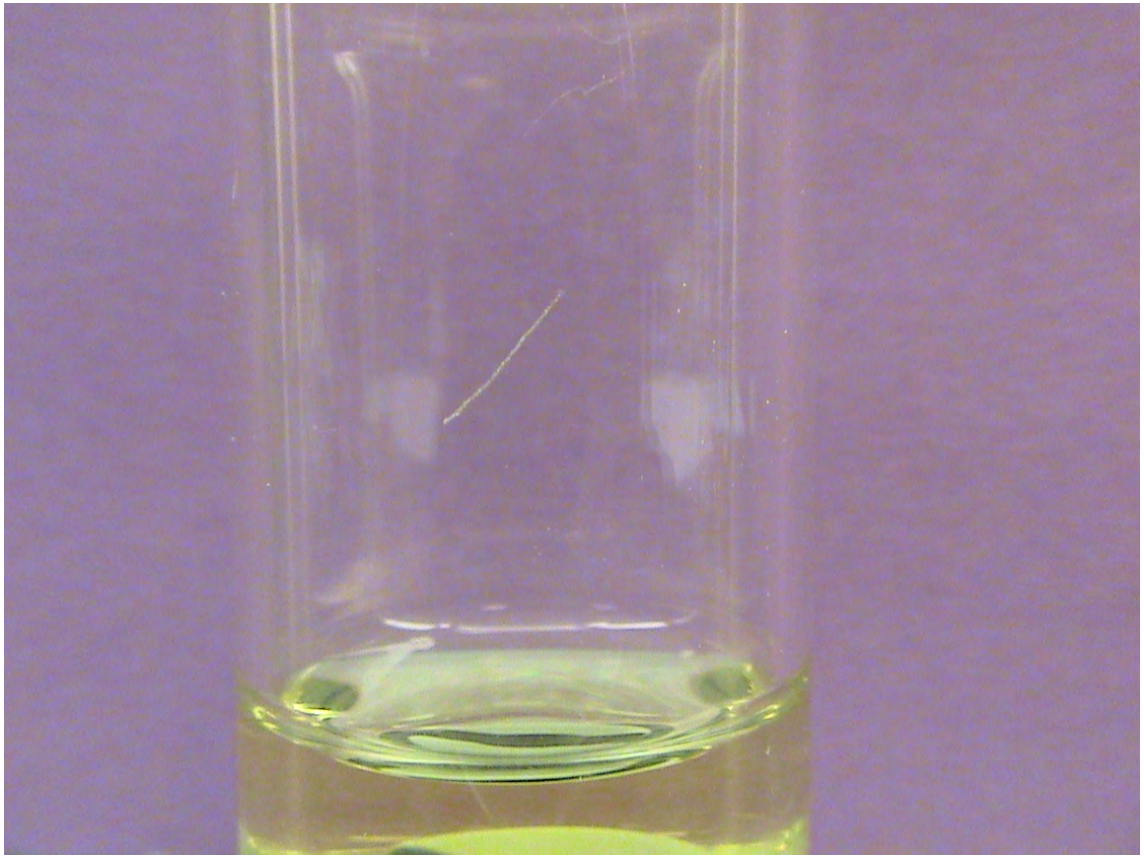
- **Minor Defect: Scratch in glass**



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- **No Defects**
  - Integral Units
    - Vials with no visible defects
    - Container closure is integral

Understanding the Basic Aseptic Process Simulations

- **Integral Unit**

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- **Incubation**
  - Incubator must be on a system to continuously record the temperature
  - Documentation required
    - The time into and out of the incubator
    - Starting and ending temperature
    - Person who placed the vials into the incubator

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- **Incubation**
  - Temperature must be suitable for recovering personnel and environmental isolates
  - Must not be outside the range of 20-35^{o}C after placing the vials into the incubator.
  - Incubation temperature should be maintained within +2.5^{o}C of the target temperature.

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- **Incubation at one of the following times and temperatures**
  - A day is considered 24 hours
  - 14 days @ 20-25 ºC
  - 14 days @ 30-35 ºC
  - 7 days @ 20-25 ºC & 7 days @ 30-35 ºC
  - Recommend starting with the lower temperature first unless validated differently

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- **Accountability**
  - All units must be accounted for through final read
    - Missing units must be post incubation is considered a positive units
    - If a vial breaks before reading, it's considered a positive units
    - Additional units counted post incubation indicates cGMP documentation and compliance issues

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- **Reconciliation of Media Units**
  - Count all filled media units and integral rejects
    - A 100% reconciliation is required after each media fill inspection
    - Unresolved counts must be immediately reported and investigated

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Acceptance Criteria Guidance

- Fewer than 5000 units, no contaminated units should be detected
  - One contaminated unit is considered cause for revalidation, following an investigation.

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Acceptance Criteria Guidance

- From 5,000 to 10,000 units
  - One contaminated unit should result in an investigation, including consideration of a repeat media fill.
  - Two contaminated units are considered cause for revalidation, following investigation.

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Acceptance Criteria Guidance

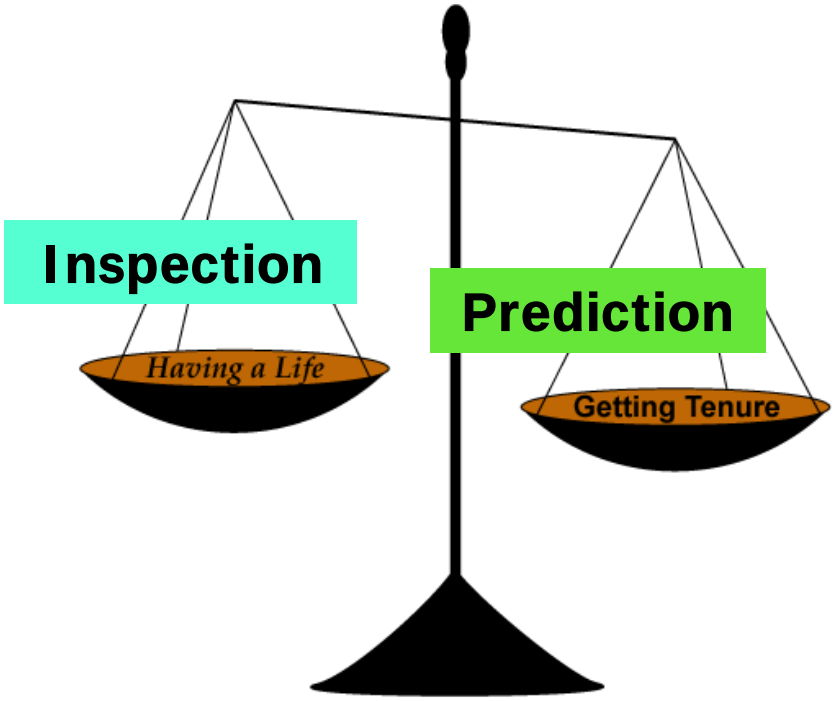
- More than 10,000 units
  - One contaminated unit should result in an investigation
  - Two contaminated units are considered cause for revalidation, following investigation

Understanding the Basic Aseptic Process Simulations

Assurance - To feel sure, to make certain, provide confidence, freedom from doubt

Proving assurance is a balance of approaches:

- Observation (Inspection)
- Prediction (Validation)



Validation is prediction of outcome based on observed conditions

Understanding the Basic Aseptic Process Simulations

- **Takeaway Message**
  - Are there any differences between media fill and routine product fills
  - Evaluate the corrective action
  - Is there a re-occurring trend
  - Does media fill properly bracket all size and shape configurations