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Current Practices in the Validation of Aseptic Processing—2001

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Introduction

The validation of aseptic processing continues to be a major area of interest within the pharmaceutical industry. Five years have passed since the last PDA survey on this subject. While there have been no new broadly applicable regulations or regulatory guidance since that time, there has been continued controversy over the details of aseptic processing and process simulation practice. Industry practices largely adhere to current regulations and guidelines on aseptic processing by the European Union (1), ISO (2), and FDA (3). The impact of PDA's TR #22 on "Process Simulation Testing for Aseptically Filled Products" (4) is also apparent.

Overtime, industry methods, practices, and limits have been modified to adapt to the changing circumstances. The Pharmaceutical Manufacturers Association (now PhRMA) in 1979 (5) and PDA in 1986 (6), 1992 (7), and 1996 (8) conducted surveys on this subject that have provided a clearer understanding of contemporary industry practice. This survey addresses the continuing need to track industry practices in the validation of aseptic processing as it evolves.

Questionnaires were sent to eighty-eight (88) firms that specifically agreed to participate with PDA in this effort. Forty-three (43) responses were received representing both US and overseas locations. The results were tabulated to provide both raw numerical and percentage of total respondents. Where the respondents provided comments (whether solicited or given voluntarily), these comments are provided after the question. Where more than one respondent provided essentially the same response selection and comment, they have been consolidated and a number appears next to the response indicating the number of comments of that type. The nature and extent of the comments received were extensive, and for this reason, the authors have chosen to combine similar responses. One of the major benefits of surveying on a regular basis is the opportunity to follow the evolution of concepts and practices overtime. To that end, this survey instrument used many questions that were nearly identical to those asked in 1992 and 1996.

PDA 2001 Aseptic Processing Survey

1. In what country, or state, is your Aseptic Processing Area (APA) located?

   United States - 28 - California, Florida, Illinois, North Carolina, Pennsylvania, Texas (2), Indiana, Kansas, New Jersey, New York (3), US (4)

   International - 31 - Australia, Canada, Italy, Spain, Sweden (2), England, France, Germany, Hungary, Indonesia, Ireland, Korea (3)

   No answer - 2

2. What types of sterile products do you manufacture at this site? Please mark all that apply.

a.	Large volume parenterals	10	23.3%
b.	Small volume parenterals	36	83.7%
	Solutions	16	37.2%
	Suspensions	5	11.6%
	Lyophilized	11	25.6%
	Powders	9	20.9%
c.	Ophthalmic and/orotic solutions	11	25.6%
d.	Inhalation solutions	8	18.6%
e.	Ointments	3	7.0%
f.	Biologicals	14	32.5%
g.	Products for veterinary use	5	11.6%
h.	Medical devices - liquid based products	6	13.9%
i.	Medical devices - non-liquid products	4	9.3%
j.	Other - please describe	2	4.6%

Comments

j. Drugs containing implants, control release devices

j. Clinical supplies

3. How many different sterile product presentations (all strengths and ill sizes of all products) do you manu- facture at this site?

a.	0 – 5	8	19.0%
b.	6 – 49	14	33.3%
c.	50 – 99	6	14.3%
d.	100 – 149	6	14.3%
e.	>150	9	21.4%

4. What percentage of your sterile products is manufactured using aseptic processing?

a.	Less than 25%	2	4.6%
b.	25% to 50%	5	11.6%
c.	51% to 75%	3	7.0%
d.	More than 75%	33	76.7%

5. Is this percentage an increase or a decrease from ive years ago?

a.	Increase	7	16.3%
b.	Decrease	5	11.6%
c.	Same	31	72.1%

Comments

a. No production ive years ago.

6. At your site, is aseptic processing used for products that could be terminally sterilized? (For the purposes of this response, consider "could be terminally sterilized" to mean a product and container/closure/delivery system that could withstand moist heat sterilization processes with a total accumulated F_0 of 8 or more minutes.)

a.	Yes	14	32.6%
b.	No	29	67.4%

If yes, what percentage of the aseptically produced products does this represent?

2% (2), 5%, 10% (2), 20% (2), 30%, 35%, 47%, 60%, 75%, 85%

Comments

a. We are manufacturing clinical supplies only, so information is not available at this time.

7. What percentage of your aseptically illed products contains an anti-microbial preservative that complies with pharmacopoeial anti-microbial effectiveness testing requirements?

a.	None	14	33.3%
b.	Less than 25%	11	26.2%
c.	25% to 50%	5	11.9%
d.	51% to 75%	4	9.5%
e.	More than 75%	10	23.8%

Comments

b. The same product may be manufactured with or without preservative; depends upon whether they are for multi-dose markets, i.e., US states a multi-dose product will have a preser- vative. Single dose of same product -- no preservative.

d. All our products comply with USP but not with A criteria from European Pharmacopoeia; 60% comply with B criteria from European Phar- macopoeia.

d. Liquid >75%; Powder, none.

Release/Quarantine Practices

8. If a process simulation* action level is exceeded on a validated production line, what action do you take with regard to products manufactured on the line prior to the media ill failure?

a.	Release	3	7.0%
b.	Release after investigation	6	13.9%
c.	Release only after an investigation indicates good process control and one or more successful additional media ills are conducted	33	76.7%
d.	Other action - please describe	4	9.3%

Comments

c. Plus double sterility test.

d. Release only after investigation could assure SAL of products.

d. No formal procedure. Never occurred, there- fore, no test case.

d. Normally, release after investigation; however, would depend upon number of contaminated units and types of organisms. Worst case: recall product.

*Note: In this survey, the terms process simulation test, media fill, and media fill test are used interchangeably.

9. If a process simulation action level is exceeded on a line, what action do you take with regard to products manufactured on the line subsequent to the media ill failure?

a.	Release	0	0.0%
b.	Release after investigation	1	2.3%
c.	Release only after an investigation indicates good process control and one or more successful additional media ills are conducted	39	90.7%
d.	Other action - please describe	4	9.3%

Comments

c. Plus double sterility and stop production.

d. Release only after investigation could assureSAL of products.

d. Lots rejected unless assignable cause can be determined that was not present during the processing of the product batches.

d. Normally, release after investigation; however, would depend upon number of contaminated units and types of organisms. Worst case: recall product.

10. Is positive action taken against a certain number of lots or over a certain time period in the event of a media ill failure?

a.	Yes - please specify number of lots involved before and after the failure.	7	17.5%
b.	Yes - please specify time period involved before and after the failure.	15	37.5%
c.	No - please describe your practice	7	17.5%
d.	Other	11	27.5%

Comments

a. All.

a. Any product manufactured between illing trials and the date of the failure and subsequent batches must beheld in quarantine until the investigation is complete. Aseptic product manufactured on the illing line, and still in company control, should be quarantined until investigation is complete.

a. All unreleased lots before and after the failures are held until three successive media ills are per- formed and found to meet acceptance criteria.

a. Three lots before and after.

a. All lots after the failure.

b. Investigation will be conducted on all batches of the last successful media ill; refer to QC for further action.

b. All before the last media ill and all post.

b. Before: Back to previous acceptable media ill. After: Lots illed after action limit and prior to obtaining satisfactory results for repeat media.

b. Six months (2)

b. Since the last successful media ill on the affected line (3)

b. From previous media ill to the next media ill (3).

b. Three months before failure and all lots after media ill are kept in QA.

b. Depends upon the outcome of the investigation! Worst case scenario: all lots produced since the last approved media ill.

c. No practice is in place due to manufacturing under development.

c. Lots illed prior and post the failure will be dis- positioned depending upon the outcome of the investigation. Lots illed post media ill are quar- antined until investigation results are known.

c. Hold lots for investigation and draft an action memo for released lots.

c. Once investigation is concluded and corrective action taken, we return to normal production. Never occurred, therefore, no test case.

c. Action would be taken on individual batches as far back and forward as necessary to fence in the issue, based upon the individual investigation. This could go all the way back to the previous media ill.

d. Release only after an investigation indicates good process control and one or more successful additional media ills is conducted.

d. Dependent upon outcome of investigation (2)

d. No policy in place for this scenario; no history of failure.

d. We stop the line until there are three successful media ills.

d. Investigation reveals the source of failure and depending upon the type of source, the number of lots or time period are considered. If it is needed, recall for certain lots should be performed.

d. Everything not yet released since the last successful process simulation testis placed on hold until the investigation is complete and a successful process simulation testis completed. (3)

11. Is positive action taken on production during a set period of time before and after a media ill failure?

a.	Yes - please specify time period involved before and after failure	18	45.0%
b.	No - please describe your practice	9	22.5%
c.	Other	13	32.5%

Comments

a. All periods involved.

a. All before the last media ill and all post.

a. Production is on hold pending investigation.

a. Between current and previous media fill results (2).

a. Aseptic production ceases on the affected machine until investigation is completed and satisfactory repeat illing trial has been completed. Repeat trial in triplicate on the container size implicated.

a. Before: Back to previous acceptable media ill. After: Lots illed after action limit and prior to obtaining satisfactory results for repeat media.

a. Six months.

a. Going back to the last successful media ill. (3)

a. Depends upon the outcome of the investigation!

Worst case scenario: all lots produced since the last approved media ill.

b. Depends upon investigation results. (2)

b. Implement corrective actions based upon the outcome of investigation.

b. No practice is in place due to manufacturing under development.

b. Lots illed prior and post the failure will be dispositioned depending upon the outcome of the investigation. Lots illed post media ill are quarantined until investigation results are known.

b. Once investigation is concluded and corrective action taken, we return to normal production. Never occurred, therefore no test case.

b. Action would betaken on individual batches as far back and forward as necessary to fence in the issue, based upon the individual investigation. This could go all the way back to the previous media ill.

b. After the failure only.

c. Dependent upon outcome of the investigation (3).

c. We stop the line until there are three successful media ills.

c. It is dificult to take action before since we do not know that we have a failure.

c. Hold lots for investigation and draft an action memo for released lots.

c. If further investigation inds that there is a possible impact from equipment, facility, and/or personnel, re-qualiication would be required.

c. Everything not yet released since the last success- ful process simulation testis placed on hold until the investigation is complete and a successful process simulation testis completed. (3)

c. All lots manufactured during the prior six months would be investigated then an appropriate action could betaken by QC, normally.

12. In the event of an unsuccessful* revalidation media ill test, how many consecutive satisfactory tests must be completed before the production line is considered re-qualiied for manufacturing operations?

a.	None	0	0.0%
b.	One	1	2.3%
c.	Two	1	2.3%
d.	Three	37	86.0%
e.	Other - please describe		13.9%

* The test fails to meet the acceptance criteria.

Comments

d. If notable to invalidate media ill.

e. One: In case of identiied failure cause after correction action. Two: In case of unidentiied cause.

e. Based upon investigation, 1-3 maybe performed.

e. If reason for failure is known, one. If reason for failure is not known, three. (2)

e. If cause of failure is known, one only. If cause of failure is unknown or uncertain, three. In all cases, an investigation is also conducted.

e. One repeat if able to invalidate media ill.

Frequency

13. Do you routinely conduct revalidation media ills on eachilling line or machine on a regularly scheduled basis?

a.	Yes	43	100.0%
b.	No - please describe your practice	0	0.0%

Comments

a. We do it quarterly, but the process used is not determined in order to cover all processes.

14. If yes, how often?

a.	Weekly	0	0.0%
b.	Monthly	0	0.0%
c.	Every other month	0	0.0%
d.	Quarterly	2	4.6%
e.	Semi-annually	36	83.7%
f.	Annually	4	9.3%
g.	Other - pleasedeine	1	2.3%

Comments

e. At minimum, each line typically has ive or six due to new product container closure systems.

e. At least two media trials per year. However, to validate/re-qualify operators, many lines are performing up to six trials per year.

g. Every fourth month.

15. If a sterility test failure occurs, does this failure initiate a media ill test on the line that manufactured the product that failed the sterility test?

a.	Yes	12	27.9%
b.	No - please describe your practice	7	16.3%
c.	Sometimes - please explain the decision factors that would lead yourirm to require are-validation media ill test to clear a sterility test failure	24	55.8%

Comments

b. Initiates investigation and exception reports. (2)

c. After investigation: lab failure = retest; no lab failure = batch rejected.

c. Depends upon results of investigation and if additional controls were positive.

c. Based upon investigation indings. (7)

c. If the investigation determined the root cause to be a failure in design or practice requiring signiicant change. (2)

c. Response to product test failure requires investigation covering sterility testing and production records/environments. Outcome of the manufactur- ing investigation indicating production environment/ procedure may result in a media trial. (2)

c. Investigate to exclude analytical error or if some obvious event has caused the failure.

c. Cross-functional team assembled to investigate. Findings would decide if additional media ill necessary.

c. If no assignable cause found.

c. QC management would assess the aseptic produc- tion area and determine a probably cause. If no assignable cause was found, a media ill would be requested.

c. EM monitoring data, sterile cleaning practice, sterilizing cycle, DOP, Royco of HVAC, LFs, education, new operators.

c. Decision to conduct a media ill is based upon the results of the sterility test failure investigation.

c. If no cause can be identiied from lab error or pro- cess error, a media ill test maybe carried out.

c. Investigation into failure conducted against ma- chine and batches taken if warranted.

c. May require that production be stopped on the line. Depends upon results of investigation of sterility test failure.

c. Norevalidation is performed if a lab error is the cause of the failure.

c. If aseptic processing.

c. If cause is assigned to line failure.

c. An investigation will be initiated. If the investi- gation doesn't show that the failure is due to a lab contamination, all steps in production will be checked. Depending upon the results, an evalua- tion will be done if a new media ill is necessary to verify that the process is under control. For example, an upward trend of microorganisms in the APA or a recently failed media ill could lead to arevalidation.

c. Would depend upon type of organism and if any other failures from same line, e.g., two sterility test failures with anaerobic organisms – have investigation and anaerobic media ill.

16. How are your media ill tests distributed among dif- ferent shifts?

a.	Equally distributed across shifts	32	74.4%
b.	Distributed according to production volumes	5	11.6%
c.	No - please explain	6	14.0%

Comments

c. There is only one shift. (5)

c. In some areas, media ills are performed which cover shift changeover. In other areas, because of their design and need for only one operator, we have a rationale that states shift changeover has no impact on integrity of process.

17. Are all aseptic ill and set-up personnel included in the process simulation program?

a.	Yes - on an annual basis	34	79.1%
b.	Yes - please specify frequency	7	16.3%
c.	Other - please describe your practice	1	2.3%

Comments

a. Vial size on rotating basis.

b. Semi-annually. (6)

c. Frequency depends upon type of intervention.

18. Are personnel, including new hires, qualiiedtooperate in the APA through participation in a media ill test?

a.	Yes - using participation in an actual process simulation	31	72.1%
b.	No - please describe your practice	12	27.9%

Comments

c. They are qualified performing the job, but a media fill is not scheduled to complete their qualification. They will participate in the next scheduled media fill if a media fill is not scheduled at completion of their qualification.

c. Operator certification program for aseptic technique and gowning, as well as GMP training. Due to media fill frequency operators generally participate in media fills within about six weeks of employment.

c. No practice setup yet. Intention to make them qualified with media fill as one part of the qualification.

c. Using a “hand fill” simulation.

c. New hires are trained to work in aseptic processing areas via SOPs and on-the-job-training. They are cycled into media program after initial training has been completed.

c. We perform a specific training program and final validation in accordance with the SOP.

c. Qualification of an operator is based upon training for gowning and aseptic practices. The operator can then operate in the aseptic processing area and participate in the next media fill.

c. New operators are scheduled for the first avail- able media fill.

c. Prior to entering the APA, employees must pass a “broth test” in a lab environment demonstrating

good aseptic technique, then successfully partici- pate in a process simulation study.

c. Process uses barrier technology, therefore, person- nel participate in the media ills, but they are not qualiied.

c. Gowning certiication only.

c. Gown qualiication, personnel monitoring, media ill within six months.

19. How many media ill tests must a new hire participate in to be considered qualiied to work on a speciic validated process?

a.	None	13	30.9%
b.	One	28	66.7%
c.	Two	0	0.0%
d.	Three	2	4.8%
e.	Four or more	0	0.0%

Comments

b. All training related to aseptic behavior. b. But must perform all critical activities.

b. Plus micro training, aseptic training, and repetitive (3x) gowning assessment.

20. If different illing set-ups and/or closure systems are utilizedonailling line, will your process simulation program address all combinations?

a.	Yes	30	71.4%
b.	No - please explain your rationale	12	28.6%

Comments

a. On a rotating basis according to product.

b. Initial qualiication would be yes, but routine re-qualiication would be about largest and smallest.

b. Worst case conditions will be investigated.

b. One simulation trial tooneilling line.

b. Bracket the largest/smallest vial/closure combina- tions. (2)

b. Different lines have different combinations to bracket all.

b. Because we are in research, it is changing all the time.

b. We only do the minimum and maximum ill, based uponline speed.

b. All formats are covered; not all stoppers.

b. Worst case, large vial openings – most dificult ill set-up.

21. Does yourirm employ a minimum time duration for media ill tests?

a.	Yes - not less than 1 hour	4	9.3%
b.	Yes - not less than 2 hours	1	2.3%
c.	Yes - not less than 3 hours	2	4.6%
d.	Yes - four hours or more	1	2.3%
e.	Yes - duration of ill process	16	37.2%
f.	Yes - minimum number ofilled containers		55.8%
g.	No - please describe your practice		13.9%

Comments

d. Typically, 8-16 hours.

e. Including all worst cases.

e. "Start-Stop" Approach: Actual minimal ill time is not more than three hours.

f. 6,800 units

f. Would normally ill for length of typical production shift. ≤ 6,300 units processed to cover all production intrusions.

g. Both: minimum number of units to ill and the whole duration of the process.

NLT to 60% ofilling process duration.
Duration of the longestilling time.

g. Simulate 1-1/2 hours of empty running during some of the challenge.

g. Plus necessary time for simulations.

g.

Methods

22. Is the ill volume of media employed the same as that utilized in production?

a.	Yes	18	45.0%
b.	No - container size is too large	2	5.0%
c.	No	20	50.0%

Comments

c. Half volume of a vial. (4)

c. Volume of media is greater than product fill (2).

c. Vial volume suficient to promote growth.

c. Suficient media is added to ensure one-half of the vertical surface of container is covered. Units inverted during incubation.

23. Do you utilize the same illing line speed for process simulations as that utilized in production for that container?

a.	Yes	20	46.5%
b.	No - speed equal to slowest normal ill speed on that line	15	34.9%
c.	No - speed equal to the highest normal speed on that line	2	4.6%
d.	No - other speed - please explain	9	20.9%

Comments

b. Re-qualiications.

b. Majority of cases slowest (longest dwell time).

c. On certain high-speed illers, >300/minute (high- est) is deemed worst case; units fall over and there are more interventions.

d. The line speed is lower than the standard speed due to the necessary equipment to dose the media and represent worst case.

d. Process simulations require at least 25% of ill at minimum speed, 25% normal/routine speed, 25% maximum speed.

d. Currently, slower than normal production speed is used. In the future, this process and normal production speed will be used.

d. Initial Performance Qualiication utilizes minimum speed and approximate production speed.

d. Slowestilling speed and at the end of test, highest speed.

d. Combination of B and C.

d. Slowest speed for largest container and fastest speed for smallest container.

d. Slower and faster speeds are used during the challenge.

d. The speed that is considered as worst case for each container size.

24. Do your process simulation trials include inert gassing if used in production?

a.	Yes - using Fluid Thioglycollate medium and nitrogen	3	7.0%
b.	Yes - using Soybean Casein Digest medium and nitrogen	4	9.3%
c.	Yes - other method - please explain	15	34.9%
d.	No - please explain	23	53.5%

Comments

c. Using Soybean Casein Digest medium and compressed air. (3)

c. Using compressed air in place of N_2 with SCDM.

c. Compressed air. (4)

c. Sterile iltered air as part of production process.

c. Soybean Casein and oxygen.

c. Soybean Casein Digest medium and nitrogen.

c. TSP medium and nitrogen.

c. SCDBand compressed air to simulate inert gas. (3)

c. Inert gas is exchanged with air.

d. Not used. (3)

d. Soybean Casein Digest medium without nitrogen.

d. Is considered worst case using air.

d. Compressed iltered air.

d. Inert gas is not used.

d. SCD broth.

d. Purge needles, tubing, etc., installed; no gas used.

d. Inert gassing is not used in production.

d. During media ills that simulate processes utilizing nitrogen, sterile iltered air is utilized due to inhibitory microbial nature of nitrogen.

d. Inert gas replaced with air for duration of media ill(s).

d. Pressurized air is used instead of nitrogen, as our production lines apply both techniques (air and nitrogen).

d. No gassing.

d. Replace N_2 with compressed air to increase the challenge for growth.

d. Inert gases are not used to prevent product degradation or exposure in our process.

d. Sterile iltered pressurized air instead of nitrogen.

d. Use SCD and compressed air.

25. Will the number of samples used in a process simulation vary from line to line?

a.	Yes - please explain	15	34.9%
b.	No	28	65.1%

Comments

a. >6,300 units

a. Only one line. (3)

a. NLT 6,000 vials.

a. Depends upon batch size.

a. One of four linesills at a faster speed.

a. Depending upon the speed of the machine.

a. Depending upon challenge time and production complexity.

a. Conventional: NLT 10,000; high speed: NLT 30,000; FFS: NLT 15,000.

a. In order to respect the minimum one-hour ill, high- speed line tends to have more samples illed.

a. Minimum of one-hour illing and 3,000 units, whichever is greater for each shift.

a. Depends upon commercial batch size.

a. Actual number attained is dependent upon line speed with a minimum yield targeted.

a. Higher speed lines are challenged with higher numbers of units.

a. If aseptic ill is validated for two days, the amount is doubled.

b. Normally >6,300; exception is high-speed ampoulem/c – 10,000 units.

26. Which media do you utilize for process simulation trials on a regular basis?

a.	Soybean Casein Digest	39	90.7%
b.	Fluid Thioglycollate	3	7.0%
c.	Other - please specify	1	2.3%

Comments

c. SCD with HEC or HPMC for ointment or gel lines

27. Do you use exactly the same compounding and iltration equipment in conducting a media ill test that you use in actual production?

a.	Yes	33	76.7%
b.	No	6	14.0%
c.	Other - please describe	4	9.3%

Comments

c. Additional pre-ilters are used.

d. The same ill line equipment used, however, additional equipment is necessary for the media ill dosing.

d. Same compounding equipment and ilter housings, but noilters.

d. Filtration is the same; compounding as close as possible.

d. The same illing equipment is used, but not the solution preparation equipment. (2)

28. When performing process simulation trials, do you retain sterile media in sterile holding vessels to simulate standard manufacturing holding times prior to filling?

a.	Yes	30	69.8%
b.	No	13	30.2%

Comments

a. Annually.

a. Overnight approach.

b. Yes, during the initial qualification of new product.

b. Separate ventilation.

b. No sterile vessels.

29. Do you inspect the illed containers prior to the end of the full incubation period (14 days)?

a.	Yes - once after seven days of incubation	25	58.1%
b.	Yes - once, please specify number of days of incubation	1	2.5%
c.	Yes - twice, please specify number of days of incubation	3	7.5%
d.	Yes - three times, please specify number of days of incubation	6	15.0%
e.	No	8	20.0%

Comments

a. Eye drops.

b. 14 days

c. 7 days and 14 days (2)

c. 3 days and 7 days

d. 1, 4, 7, 10, 14 on aroutine basis.

d. 2 or 3, 6 or 7, 14 (2)

d. 3, 7, 14 (2)

d. 3, 5, 14

e. If containers are opaque.

e. Ophthalmic ointments.

e. Only in cases of special problems, an additional inspection after seven days is performed.

e. Inspected prior to incubation and after 14 days.

30. Does your process simulation program include the following routine interventions?

a. Weight/ill volume adjustment

Yes	38	88.4%
No	4	9.3%
N/A	0	0.0%

b. Component replenishment

Yes	34	79.1%
No	4	9.3%
N/A	0	0.0%

c. Filter change

Yes	21	48.8%
No	16	37.2%
N/A	4	9.3%

d. Filling needle change

Yes	30	69.8%
No	7	16.3%
N/A	3	7.0%

e. Operator breaks

Yes	40	93.0%
No	2	4.6%
N/A	0	0.0%

f. Change in illing vessel

Yes	21	48.8%
No	19	44.2%
N/A	2	4.6%

g. Component change

Yes	20	46.5%
No	16	37.2%
N/A	3	7.0%

h. Powder can changes

Yes	12	27.9%
No	16	37.2%
N/A	12	27.9%

i. Dosing wheel, dosing disc changes

Yes	13	30.2%
No	18	41.9%
N/A	10	23.2%

j. Powder hopper changes

Yes	6	13.9%
No	21	48.8%
N/A	12	27.9%

k. Operator change

Yes	40	93.0%
No	1	2.3%

l. Other - please specify

Yes	17	39.5%
No	5	11.6%

Comments

f. Only one vessel.

j. Stopper.

l. Equipment change out; reboot computers, etc.

l. Stopper bowl change; pump changes.

l. Lyophilizer.

l. Speciic foreachilling line.

l. Too numerous to list here.

l. Container, stopper, cap jam, synchronization failure.

l. Not really detailed in our program; done on observation sheet.

l. Maintenance interventions. (2)

l. Line adjustments, equipment replacement, line jams. (3)

l. All interventions that occur during routine production.

l. Simulation of in-process compounding sampling.

l. Use of sterile clarifying ilters.

l. Tip/cap track adjustments.

l. Removal of jammed bodies.

l. Tube cap change out on ointment lines.

l. All filling lines have individual intrusion rationales. These define all allowable intrusions in production (validated in media fill). Will also include electrical/ engineering adjustments.

31. Do you routinely videotape process simulation operations?

a. Yes	13	30.2%
b. If yes, do you retain the tapes?	10	23.2%
How long? (see comments)		69.8%
c. No		

Comments

a. All routine action concerning production.

a. Until end of incubation/reporting of trial.

Video is used to formally assess production operator technique.

b. Tapes are discarded if media fill is success- ful. If investigation is required, tapes are retained to assist in investigation.

b. Not yet determined. (2)

b. Until batch is released.

b. Until successful results are confirmed. If a failure occurs, the tape is iled with the inves- tigation report.

b. Until results are approved. (2)

b. Two years.

b. Next media ill.

d. But have Quality Assurance observe aseptic handling.

Growth Promotion Studies

32. When are growth promotion studies conducted on each medium? Please mark all that apply.

a.	Before illing	9	20.9%
b.	After illing	7	16.3%
c.	After incubation	36	83.7%
d.	Other - please explain	1	2.3%

Comments

a. Bulk sample from reactor.

d. Before illing and after incubation.

33. In conducting growth promotion studies do you use only pharmaceutical test organisms (e.g., those recommended in USP <71> Sterility Testing)?

a.	Yes – use only USP <71> organisms	12	27.9%
b.	No – explain	30	69.8%

Comments

Use organisms recommended by European Pharmacopoeia. (3)

Suitability test organisms for the TGA, SUP, EP, and BP. Sterility testing is included.

Environmental isolates and USP organisms. (21)
We use the European Ph organisms, plus two more frequently isolated from aseptic area.

Range of organisms – B. subtilis, C. albcans

USP and facility isolates and S.aureus, ATCC 6538.

The strains have been chosen with respect to other growth promotion tests – ive different strains are used.

Use organisms found during environmental monitoring of the media run and USP organisms.

Incubation of Process Simulation Samples

34. If you answered No to Question 33, how many species isolated from the aseptic processing environment do you include in the growth promotion test?

a.	One	12	44.4%
b.	Two	8	29.6%
c.	Three	2	7.4%
d.	Four	2	7.4%
e.	More than four	4	14.8%

Comments

e. Depends upon how many found during environmental monitoring.

e. It depends upon what is recovered.

e. It may also be from sterility test failure, if that is the reason for media ill, and from any positives from previous media ill.

35. What temperatures do you use to incubate process simulation samples? If more than one temperature is utilized, please mark all that apply and explain your practice.

a.	20 - 25ºC	38	88.4%
b.	26 - 29ºC	0	0.0%
c.	30 - 35ºC	40	93.0%
d.	36 - 39ºC	0	0.0%
e.	40 - 49ºC	0	0.0%

Comments

a. First seven days. (8)

a. For fungi.

a. Days 8-14. (2)

a. Yeast and molds. (2)

c. This temperature is used when performing the media ill for the AddVantage line.

c. Second seven days. (8)

c. For bacteria.

c. Days 1-7. (2)

c. All other process simulation studies. (2)

36. How long do you incubate process simulation containers?

a.	Less than 7 days	0	0.0%
b.	7 days	0	0.0%
c.	8 - 13 days	0	0.0%
d.	14 days	42	97.7%

e.	15 to 20 days	0	0.0%
f.	21 days	0	0.0%
g.	More than 21 days	0	0.0%
h.	Other - please describe		2.3%

Comments

d. At least 14 days. Incubator rooms are thermally mapped. Some large vial sizes take longer to reach incubation temperature and will receive extra day of incubation.

h. NLT 7 days at 20-25°C or 30-35°C.

37. How do you insure the interior surfaces of the con- tainer are contacted with media?

a.	Swirl and incubate top-side up	5	11.6%
b.	Invert one or more times, and incubate top-side up	22	51.2%
c.	Incubate all containers on their sides	2	4.6%
d.	Incubate upside down	6	14.0%
e.	No special measures taken (incubate randomly)	2	4.6%
f.	Other - please describe your practice	7	16.3%

Comments

d. Ointments.

f. Invert vials after reading each time, so every three days switch from topside up to upside down. (2)

f. Invert one or many times and incubate upside down.

f. Combination of C and D.

f. Swirl and incubate inverted.

f. Incubate upside down for theirst seven days and topside down the last seven days.

f. Swirl and incubate top side up for seven days. Inspect at seven days, swirl, and invert for further seven days.

38. If you have found contaminated media fill test units, what type of microorganism was most prevalent?

a.	Gram positive rod	7	20.0%
b.	Gram positive coccus	31	88.6%
c.	Gram negative rod	4	11.4%
d.	Microaerophillicor “anaerobic” organism	1	2.8%
e.	Molds		2.8%
f.	Yeasts		0.0%

Personnel Monitoring

39. Are all personnel involved in media runs tested for the presence of microbes on their gowns and/or gloves?

a.	Yes	39	90.7%
b.	No	4	9.3%

40. If yes, which of the following sites are sampled? Mark all that apply.

A. Fingers (ingerprintoringer dab)

a.	Upon entering the APA	7	17.9%
b.	During the media ill test	20	51.3%
c.	After the media ill test	30	76.9%
d.	Not tested	1	2.6%

B. Palm or back of hand

a.	Upon entering the APA	3	7.7%
b.	During the media ill test	5	12.8%
c.	After the media ill test	8	20.5%
d.	Not tested	25	64.1%

C. Arms

a.	Upon entering the APA	2	5.1%
b.	During the media ill test	8	20.5%
c.	After the media ill test	22	56.3%
d.	Not tested	11	28.2%

D. Face-masks

a.	Upon entering the APA	2	5.1%
b.	During the media ill test	4	10.2%
c.	After the media ill test	16	41.0%
d.	Not tested	20	51.3%

E. Chest

a.	Upon entering the APA	3	7.7%
b.	During the media ill test	9	23.1%
c.	After the media ill test	25	64.1%
d.	Not tested	7	17.9%

F. Other gown surfaces - please specify

a.	Upon entering the APA	1	2.6%
b.	During the media ill test	5	12.8%
c.	After the media ill test	17	43.6%
d.	Not tested	15	38.5%

Comments

Ab. And after interventions

Ba. After processing

Bd. During routine personnel evaluation

Ca. After processing

Cb. And after interventions

Cd. Only required weekly

Da. After processing

Ea. After processing

Ec. Rotate chest and shoulder sites

Ed. Only required weekly

Fb. Forehead

Fb. Hoods

Fb. Top of hood and back of gown

Fb. Back, shoe covers, hood

Fc. Goggles, wrist, neck

Fc. Waist, hood (2)

Fc. Shoulders

Fc. Hood, armpit

Fc. Head, both shoulders

Fc. Stomach

Environmental Monitoring, Aseptic Processing

41. What environmental sampling methods do you use in the filling room environment? If more than one method is utilized, please mark all that apply.

A.	Microbiological Sampling Methods		
a.	Swabs	23	53.5%
b.	RODAC or another form of surface sampling plates	42	97.7%
c.	Settling plates	32	74.4%
d.	STA sampler	11	25.6%
e.	Electrostatic air sampler	2	4.6%
f.	Centrifugal sampler	20	46.5%
g.	Sieve-type sampler	8	18.6%
h.	Gelatin ilter	4	9.3%
i.	Other - please describe	7	16.3%
B.	Total Particulate Air Monitoring Methods		
a.	Continuous	14	32.5%
b.	Intermittent	28	65.1%

Comments

Af. Only during revalidation

Ai. SMA (4)

Ai. SAS (3)

Ai. MAS air sampler

Bb. Continuous in ill room for media ills; intermittent in production

Bb. None

Bb. Limited monitoring during every shift. Continuous for full day 1x week. Continues during media ill (one-day trial).

42. How frequently do you sample your APA for the presence of anaerobic organisms?

a.	Daily	2	4.6%
b.	Weekly	4	9.3%
c.	Monthly	6	14.0%
d.	Quarterly	5	11.6%
e.	Semi-annually	5	11.6%
f.	Annually	4	9.3%
g.	Not at all	20	46.5%

Comments

d. Swabs to FTM.

e. And daily when illingon one line.

f. RODAC.

g. Performed only in conjunction with media ills.

g. Historical data justiied discontinuance on initial validation.

43. If you test your APA environment for the presence of anaerobes, is this a result of potentially anaerobic process conditions?

a.	Yes	10	31.2%
b.	No	22	68.8%

44. How frequently do you sample your APA for the presence of molds and yeasts?

a.	Daily	20	47.6%
b.	Weekly	5	11.9%
c.	Monthly	5	11.9%
d.	Quarterly	4	9.5%
e.	Semi-annually	2	4.8%
f.	Annually	4	9.5%
g.	Not at all	2	4.8%

Comments

a. Our media (TSIS) is able to detect both fungi and bacteria.

45. If your monitoring approach is different for media ill tests, how does it differ from routine or planned production monitoring?

a.	More locations than routine production	8	19.5%
b.	More samples at same sites than routine production	11	26.8% 56.1%
c.	Same as routine production	23	0.0%
d.	Fewer locations than routine production	0	0.0% 0.0%
e.	Fewer samples at same sites than routine production		
f.	Other - please describe		

Environmental Monitoring, Media Fills

46. Are the microbial results obtained from process simulations used to establish the alert and/or action levels used for environmental monitoring during routine production?

a.	Yes	6	13.9%
b.	No	30	69.8%
c.	In part - please explain	8	18.6%

Comments

a. Every lot.

b. Results are evaluated by intensive monitoring at the validation stage.

b. Limits attained from environmental monitoring validation.

b. Pharmacopoeial guideline limits are used.

c. Alert and/or action levels were internally based upon the results of the initial MFs. Subsequent levels are based upon the analysis of the annual EM data.

c. Process simulations are included to obtain alert/action levels.

c. Done in addition to routine EM sampling results (5).

c. Consider trend for non-viable.

47. To what extent are environmental isolates from process simulation runsidentiied?

a.	Morphology only	0	0.0%
b.	Gram stain	5	11.6%
c.	Genus	6	13.9%
d.	Species	37	86.0%

Comments

Do more.

b. Below alert/alarm levels.

b. If sample is above alert limit.

d. Plus species, if possible. (4)

d. Above alert/alarm levels.

d. Class 100 area and OOS samples are identiied.

d. If sample is above action limit.

d. All isolates from Class 100 areas identiied to species.

48. To what extent are isolates from contaminated units identiied?

a.	Morphology only	0	0.0%
b.	Gram stain	1	2.3%
c.	Genus	3	7.0%
d.	Species	41	95.3%

Comments

d. C and D whenever possible. (2)

49. Do you follow the same environmental monitoring strategy in prospective (PQ validation) media ill tests that you plan to use in conducting routine monitoring of your new or modiied facility?

a.	Yes	33	78.6%
b.	No	9	21.4%

Comments

b. More during validation, then reduce.

50. Do you follow the same environmental monitoring strategy for revalidation media fill tests that you use in conducting routine production environmental monitoring?

a.	Yes	39	90.7%
b.	No	6	13.9%

Comments

In the following section, please identify all of the aseptic processing technologies (see descriptions be- low) presently in use at your facility. The descriptions are meant to broadly define the filling environment. Please complete the table for those technologies that most resemble those within your facility. A separate page has been provided for each processing technol- ogy. Please indicate your response in the appropriate columns.

a. Manual Filling - Gowned personnel perform the majority of aseptic processing tasks, i.e., placing the container under the illing head, closing the container, sealing the container. Human intervention is continuous and very intensive. 4 9.3%

b. Semi-automated Filling - Containers are transferred from dry heat ovens by gowned personnel; illing, closing and sealing are performed by machines. Trays are manually loaded into lyophi- lizer. Continuous human intervention. 13 30.2%

c. Conventional Filling - Containers are conveyed from dry heat tunnel to machine illing; closing and sealing are performed by machines. Fill weights manually adjusted by gowned personnel. Human intervention is most intensive during set-up, but routine interventions for component charging, adjust- ments, minor maintenance, and weight checking occur. 16 37.2%

d. Advanced Conventional - Containers are conveyed from dry heat tunnel to machine illing; closing and sealing are performed by machines. Fill weights remotely adjusted. Human intervention is limited to minor adjustments and component charging. Fill machine equipped for CIP/SIP. Automated loading of lyophilizer. 7 16.3%

e. Form-Fill-Seal/Blow-Fill-Seal - Plastic containers formed/blow molded inline immediately prior toilling. Molds and product contact illing parts are subjected to CIP/SIP prior to start of the illing process. Human intervention rarely occurs, essentially an unmanned clean room process. 4 9.3%

f. Closed Isolator - Full processing in adecontaminated environment. Transfers in and out are accomplished using RTPs or specialized transfer systems that maintain the integrity of the illing environment. Generally restricted to low volume and/or lower speed illingor assembly operations. No human intervention except through isolator system gloves or half-suits. 2 4.6%

g. Open Isolator - Processing in a decontaminated environment, with discharge via a discharge port into an adjacent lower classiied environment. Filling and closure typically done using very highly automated equipment. Usually employed for high volume and/or high speed illing operations. No human intervention except through isolator system gloves or half-suits. 3 7.0%

Comments

b. EtO sterilizer.

c./d. All illing machines have some level of restricted access glove port protection. Only “major” interventions require door open intrusion.

g. Barrier with totally separate Class 100 system returns, etc. (800 air changes/hour) inside a Class 100 environment. Human intervention when needed (start-up and periodic issues – such as glass handling modiications). Media ills done with barrier doors open and human intervention. Normally, door totally closed during production. All CIP/SIP; stoppers supplied to line CIP/SIP only item requiring autoclave is stopper vibrating feed bowl.