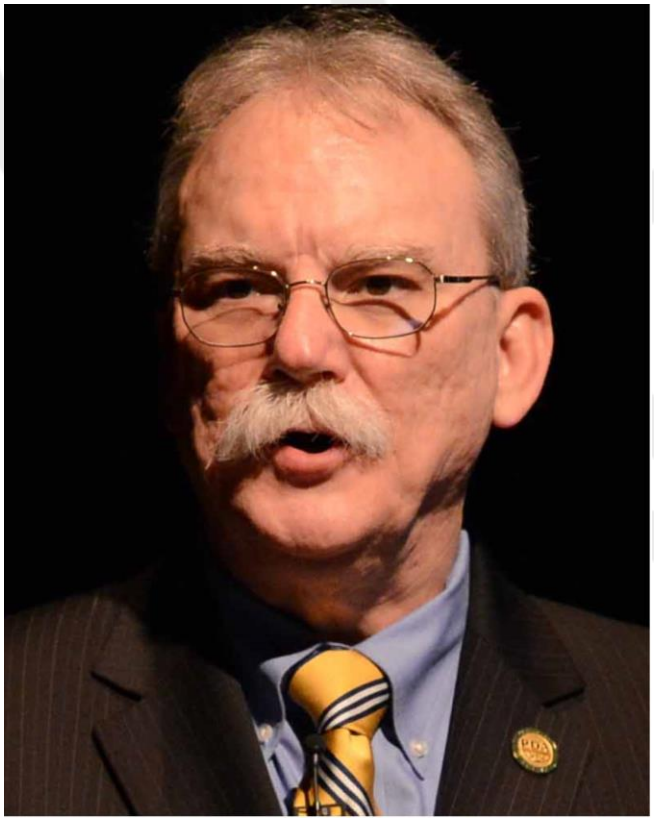
Aseptic Processing – Current Issues & Trends

Richard Johnson, PDA

Introduction

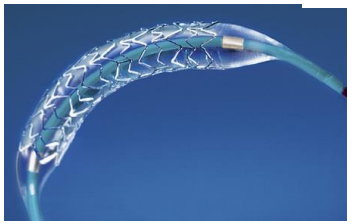


Richard M. Johnson
Member, PDA for 20+ years
President & CEO since 2009

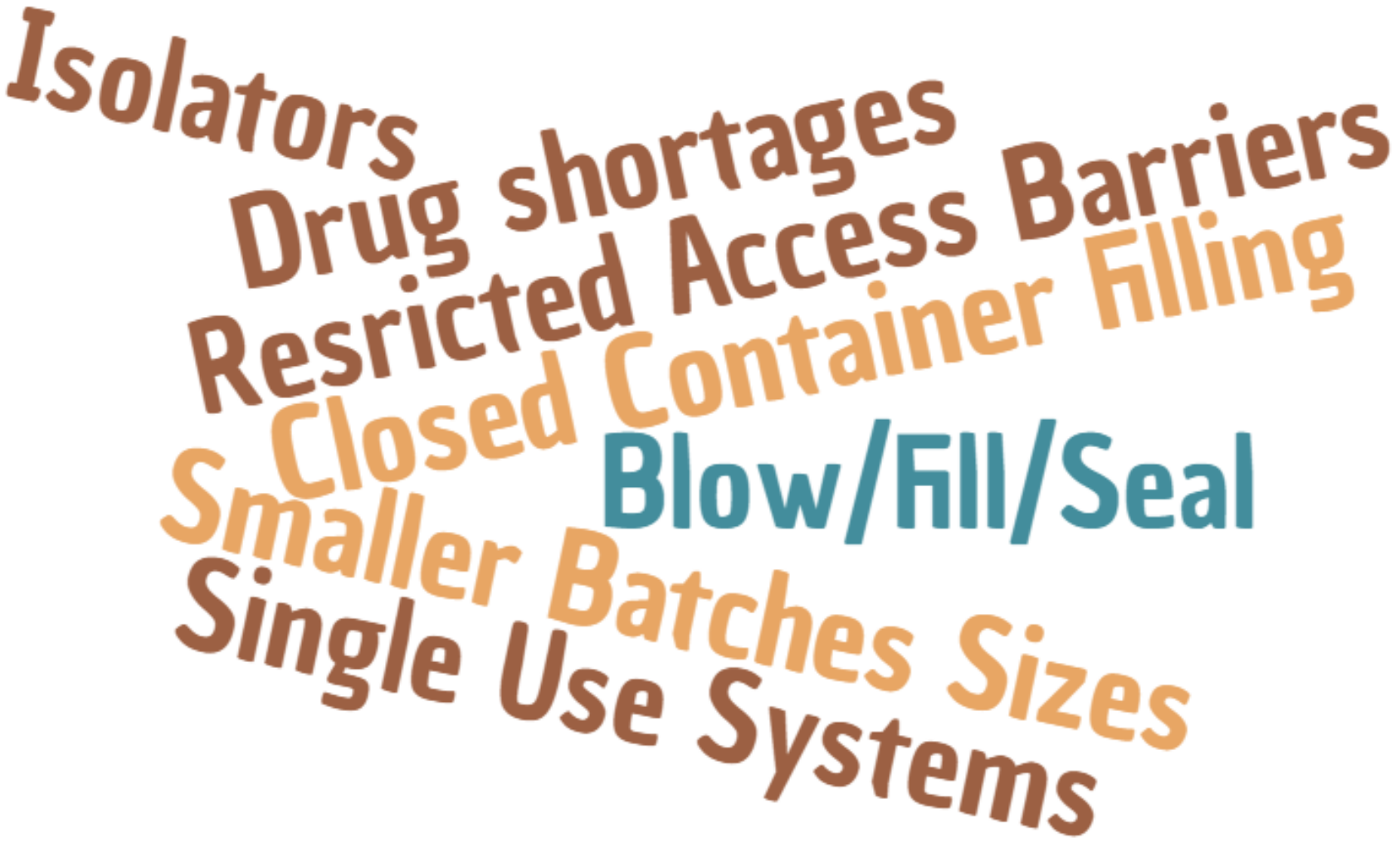
- **Ladies and Gentlemen, I am happy to be here with you.**
- **Senhoras e Senhores, estou feliz por estar aqui com vocês.**
- **Señoras y señores, estoy feliz de estar aquí con ustedes.**
- **Signore e Signori, io sono felice di essere qui con voi.**

Products using Aseptic Technology

- Powders
- Liquids
- Medical Devices
- Combination products
- Small Volume Parenterals
- Advanced Therapies/Personalized Medicine
- Biologics/biosimilars
- Compounded Drugs
- Ophthalmics
- Lyophilized Drugs

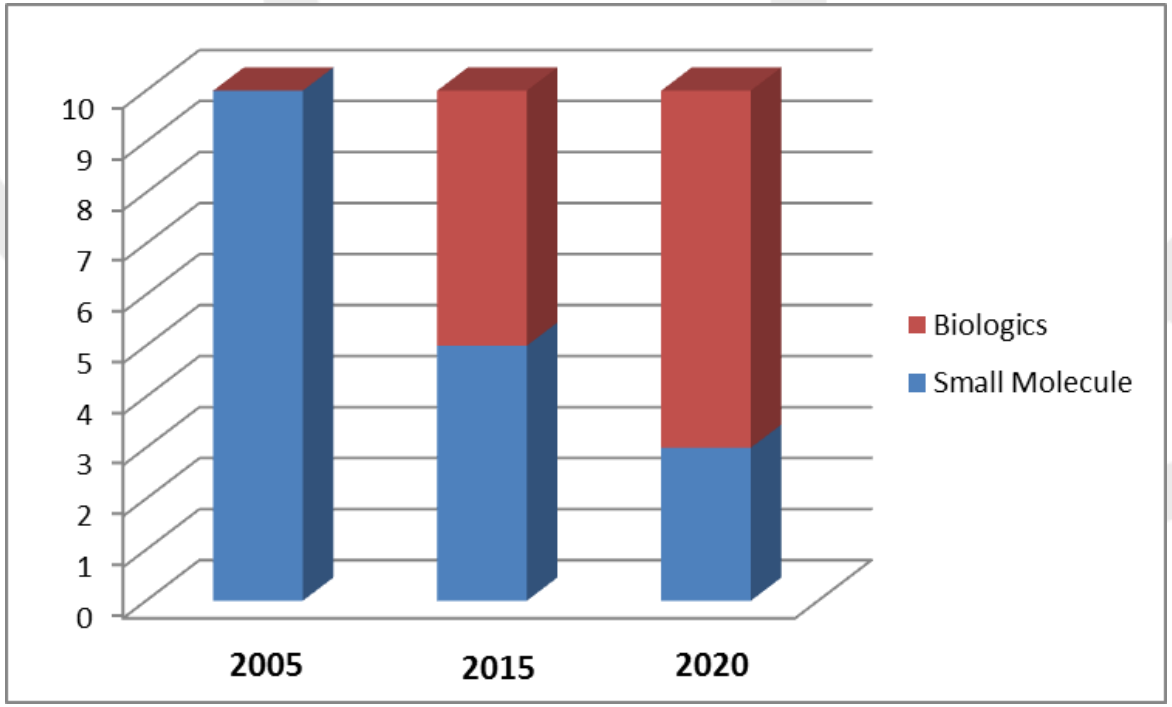


Hot Topics in Aseptic Manufacturing



Advent of Biologics

Top 10 Global Drug Products



As more Biologics are developed, they are becoming a bigger part of the dominant products.

Currently, all biologic drug products are produced by aseptic processing

Advent of Combination Products

Drivers for Combination Products

- Prefilled Syringes to reduce medication errors and risk of contamination in healthcare setting.
- An explosion of new therapies that are self administered – Drug or Biologic in an Auto injector.
- Development of drug/device combinations, e.g. drug eluting stents.

All of these involve aseptic processing

CURRENT ISSUES – ASEPTIC PROCESSING

EU and PIC/s GMP Annex 1

Concept paper (EMA/INS/GMP/735037/2014) recommending the revision of the current Annex 1 developed by EMA and PIC/S combined working group and released on 5 February 2015 – for public consultation (deadline for comments was 31 March 2015).

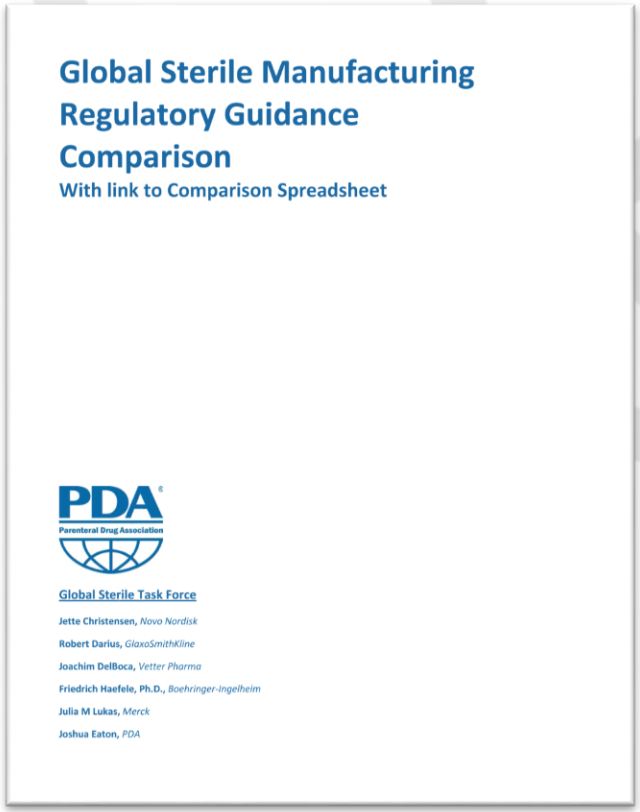
- Current Annex 1 is being reviewed to reflect changes in regulatory and manufacturing environments.
- New guideline should clarify how manufacturers can take advantage of new possibilities deriving from application of enhanced process understanding by using innovative tools as described in ICH Q9 and Q10.
- The revision of annex 1 should also take into account related changes in other GMP chapters and annexes as well as in other regulatory documents.
- The revised guideline will seek to remove ambiguity and inconsistencies and will take account of advances in technologies.

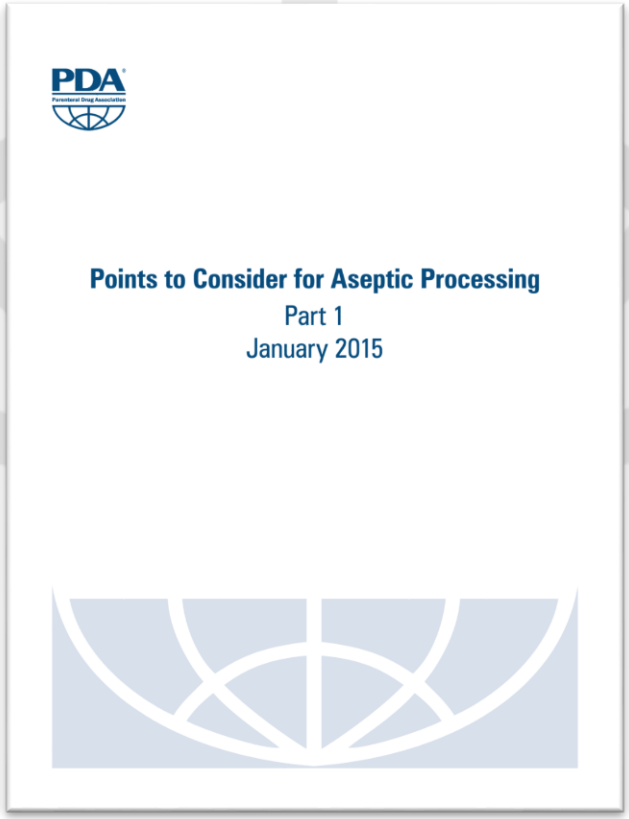
EU and PIC/s GMP Annex 1 (cont.)

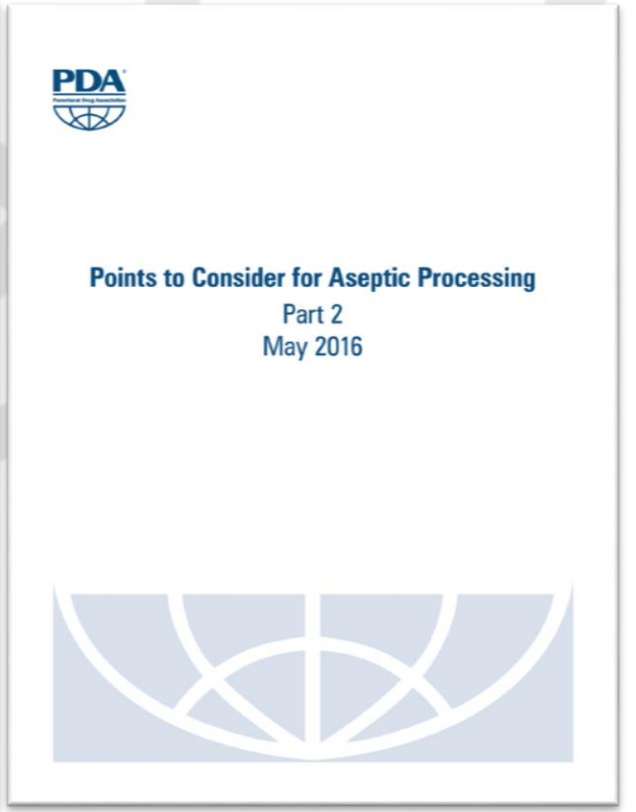
EMA -PIC/S Proposed timetable:

- Preparation of draft concept paper - September 2014
- Approval of draft concept paper - October 2014
- Released for consultation – February 2015
- Deadline for comments – March 2015
- Discussion in PIC/S Committee – May 2015
- Discussion in GMDP IWG - June 2015
- Discussion with other Working Parties - June 2015 – September 2015
- **Proposed date for release of draft guideline – Q 2 2017???**
- Deadline for comments - 3 months after publication
- Re-discussion in GMDP IWG – Q3, 4 2017
- Re-discussion in PIC/S Committee – Q3, 4 2017

Available now at the PDA on-line Bookstore







Examples of Hot Topics

- Airflow Velocity Measurements
- 5µM Total (non-viable) particulate monitoring
- Incubation temperatures for EM
- Incubation temperatures for media fills
- Duration of media fills
- Process simulation acceptance criteria
- PUPSIT

PDA PtC: Airflow Velocity Measurements

Problem Statement

Airflow velocity of 0.45 m/s ± 20% at the working surface in a critical filling zone?

Recommendation

- Airflow patterns should be sufficient to protect exposed product, product contact packaging components, and product contact surfaces
- Importance of unidirectional flow
- Linear air velocity of 0.45 meters/sec ± 20 % measured 15 – 30cm from the filter face commonly recommended range to establish unidirectional air flow,

NOTE: Current EU Annex 1 states 0.36-0.54 m/s as a guidance value, at the working position.

PDA PtC: Airflow Velocity Measurements

Rationale for Recommendation

- Unidirectional flow is intended to allow the air to flow smoothly past and around potential obstacles with minimal turbulence and no induction of potential contamination from outside the zone.
- Supply air velocity should be correlated to air flow visualization studies (i.e., “smoke studies”) and optimized to ensure airflow patterns that protect exposed product, product contact packaging components, and product contact surfaces from airborne contamination at the working level.
- This may be lower (or even higher) than the recommended accepted range.

PDA PtC: ≥0.5µm and ≥5µm Total Particle Monitoring

Problem Statement:

Should limits be applied for ≥5 µm particle monitoring for Grade A environments *?

Recommendation

- Limits should not be applied for ≥5 µm particle monitoring for Grade A environments**.
- Where companies separately count particles ≥5 µm, they should focus on the overall trend rather than individual numbers, based on the low accuracy of the measurement.

Notes:

*Quantification of ≥5 µm particle monitoring for Grade A in addition to ≥0.5 µm particles is currently required by some regulatory agencies, including in EU.

** The same recommendation should apply for Grade B environments in non-operational (as built/at rest) conditions (ISO Class 5).

PDA PtC: ≥0.5µm and ≥5µm Total Particle Monitoring

Rationale for Recommendation

- Draft International Standard ISO14644-1.2 (2014) Cleanrooms and Associated Controlled Environments: Part 1 - Classification of Air Cleanliness by Particle Concentration" concerning the Class 5, states that:

  "Sampling and statistical limitations for particles in low concentration make classification inappropriate." and …

  "Sample collection limitations for both particles in low concentration and particles greater than 1 micrometer make classification of this particle size inappropriate, due to potential particles losses in the sampling system."

- Monitoring of particles ≥0.5µm (which includes particles ≥5 µm) is adequate for Grade A environments.

Incubation temperatures for EM

Problem Statement:

- What incubation conditions are scientifically appropriate for environmental monitoring samples?

Recommendation

- Mesophilic incubation conditions (within 20°C to 35°C ± 2.5°C, 3-7 days) recover microorganisms from ambient-temperature environments
- Yeast and mold detection improved by the use of specialized recovery media, nonselective media (SCDA) usually suitable for total aerobic counts
- Assess media and incubation regimen to ensure sufficient for intended purpose
- Recovery of yeast and mold may be hampered by higher temperatures (above 30°C)

Incubation temperatures for EM

Rationale for Recommendation

- There is no universal set of incubation conditions for all EM isolates
- Defined conditions should permit microbial shifts occurring within the manufacturing environment
- Assessment of regimen assures adequacy to evaluate risk posed by any unique conditions

Incubation temperatures for media fills

Problem Statement:

What are suitable incubation temperatures for process simulations?

Recommendation

1. Incubation conditions should be suitable for recovery of all potential microbial contamination.
2. Generally, incubation conditions should be not less than 14 days at a temperature range between 20-35^{o}C.
3. Should provide scientific rationale for selection of incubation conditions including temperature. Literature, data or growth promotion tests of environmental isolates may be used to support temperature range.
4. Growth promoting tests should be performed to confirm the suitability of the incubation temperatures and conditions. This may involve multiple temperatures.
5. Where multiple temperatures are used, sequence and duration of temperature incubation should be justified.

Incubation temperatures for media fills

Rationale for Recommendation

- Temperature conditions should be selected based on the knowledge of the characteristics of potential contaminants and process conditions.
- Most mesophilic environmental contaminants will grow at any temperature within the range of 20-35°C over 14 days.
- Lack of definitive scientific data to support use of multiple temperatures.

Duration of media fills

Problem Statement:

What is the appropriate duration of an aseptic process simulation run?

How should process simulation address multiple shifts and campaign production runs?

Recommendation

1. Sufficient to challenge complete aseptic production process. Fill number of units to ensure activities/interventions are covered (perhaps even longer than normal production)
2. Assess highest risk events permitted during routine processing, simulate conditions which provide greater likelihood of uncovering contamination
3. Consider human variability in performance, level of automation and barrier technology
4. Address multiple personnel and shifts in risk assessment (RA)
5. Batches filled over days w/o intermediate sterilization (campaigns) evaluated in risk assessment

Duration of media fills

Recommendation (cont.)

6. Determine rationale and approaches applicable to unique operations in documented RA
7. Simulate pre-determined interventions, consider filling platform (isolators, RABS, automation, manual), other characteristics of containers and closure systems
8. RA determines number and frequency of interventions and duration related conditions/activities
9. Where there are no risk-based duration-related effects, or where longer duration does not add scientific merit, it should not be necessary for a process simulation to equal or be longer than maximum production duration
10. Manual aseptic filling or closing processes are highly dependent on operator's individual performance as the process. Therefore it is recommended that full duration media fills be used to qualify these processes.

Duration of media fills

Rationale for Recommendation

- Contamination of an aseptic process is primarily a function of events rather than time.
- The maintenance of aseptic environmental conditions is best assessed through environmental system design and EM.
- Properly designed automation and barrier technology should reduce the frequency of, or risk associated with human interventions. These factors should be addressed in the risk assessment and process simulation design.
- Good process design including human factors assessment, adherence to first air principles, training, operations experience, monitoring, ergonomics, and the scheduling of breaks and rest periods are better tools for controlling the performance of clean room operators, operations, and the potential effects of human fatigue, than the passage of longer duration media fills.

Process simulation acceptance criteria

Problem Statement:

What are the acceptance criteria for aseptic process simulations (APS)?

Recommendation

- The objective of the aseptic process simulation (APS) is to produce zero contaminated units, irrespective of run size. Therefore the target involving such simulations should be zero positive units.
- Upon discovery of any positive units, an investigation including a comprehensive risk assessment should be performed to assess any potential root causes, implementation of Corrective and Preventative Actions (CAPAs), and respective documentation.

Process simulation acceptance criteria

Recommendation (cont.)

- It is critical to verify the robustness[1] of the modified process. In addition to other qualification requirements, it may be advisable to include multiple process simulation runs to verify the robustness of the implemented corrective actions with consideration of the following:
  - (a) Potential for multiple root causes
  - (b) Introduction of CAPAs may inherently introduce unintended consequences which are otherwise not sufficiently challenged; or may represent a departure from the original qualified state.
- Investigations which determine a definitive and readily identifiable root cause, might provide grounds for a reduced number of repeat run(s). However, CAPAs should be put in place to avoid such issues and deviations to studies and processes from reoccurring.
- In all cases, the execution of additional run(s) without the undertaking of a comprehensive risk based investigation to identify and correct any potential root causes is not acceptable.

[1]Robustness in this case focused on the maintenance of sterility.

Process simulation acceptance criteria

Rationale for Recommendation

- Process simulation contamination rates resulting in zero positive units should be achievable in well designed and operated production lines.
- The aseptic process simulation provides additional but not absolute assurance of process control on a periodic basis. While part of the overall approach to process validation, process simulation is only one of the many tools or approaches designed to evaluate the processing steps for aseptic manufacture. The necessarily high degree of control and assurance for aseptic processes relies collectively on the qualification and validation of many systems including product, equipment and component sterilization, personnel training and aseptic behavior, environmental controls, and extends to facility design, inclusive of personnel, material and equipment flows. Since these processes are inextricably linked in the overall control and assurance of asepsis, the occurrence of even a single contaminated unit in an APS, may be indicative of an underlying issue in any one of these systems and should be viewed as a significant event.

Process simulation acceptance criteria

Rationale for Recommendation (cont.)

- In the event that a root cause cannot be established, the expectation is that all reasonable potential causal factors of the failure are considered and steps taken to improve any and all identified issues arising from the investigation including a comprehensive risk assessment. Any and all deficiencies identified in the investigation and risk assessment should be addressed.

  - Note: A comprehensive investigation may conclude that the discovery of a single contaminated unit is not indicative of a failed process, consistent with local regulatory requirements.
  - Recurring positive units in successive process simulations indicate a problem and should be investigated and resolved even when the acceptance criteria are met for each individual simulation.

PDA PtC: Pre-Use, Post Sterilization Integrity of Sterilizing Filters (PUPSIT)

Problem Statement:

Should a pre-use, post-sterilization integrity test of sterilizing filters be performed?

Recommendation

- Pre-Use, Post Sterilization Integrity Testing (PUPSIT) of sterilizing grade filters as means to ensure filter integrity throughout use and product sterility should be evaluated case by case by means of comprehensive risk assessment.
- Risk assessment should be executed by line and by product to include side by side comparison of conducting vs. not conducting PUPSIT.

NOTE: The current requirement in EU is to perform a pre-use, post-sterilization integrity test.

Recommendation (cont.)

The risk assessment should include risk related elements, such as:

- An assessment of the effect of a filter failure should one occur, including the potential introduction of non-sterile product into the aseptic area
- An assessment of the risk of contamination due to additional manipulations on pre-sterilized filters (e.g.: Ready to Use)
- Ability to detect a potential breach
- Likelihood of microbial ingress to the downstream side of the filter (when PUPSIT is performed)
- Potential for blocking the sterilizing filters due to processing stream (particulate or bioburden)
- Determine if the existing production lines can be modified to add ability to perform a PUPSIT and assess the potential risk to the product or sterile boundary by implementing such modifications
- Determine if there is a control strategy in place for the steam sterilization process (SIP) to prevent filter damage during SIP
- Impact of wetting fluid on product dilution and product attributes
- Impact of the additional time required on time-sensitive processes

Recommendation (cont.)

- If outcome of risk assessment indicates PUPSIT procedure reduces product quality (or business) risk, and PUPSIT procedure does not increase the overall product quality risk, then PUPSIT may be implemented.
- However, if risk assessment indicates PUPSIT procedure results in additional risk to product quality, then PUPSIT procedure should be avoided.

Rationale for Recommendation

- PUPSIT may provide added insurance of a filter's integrity throughout processing and can reduce risk of product loss in case a re-filtration is not possible, and for preventing the risk to introduce contamination into aseptic area.
- However, implementation of such a test must be risk assessed for each process and manufacturing site as PUPSIT implementation may result in a higher risk to product contamination after sterilization due to increased downstream manipulations and/or addition of equipment into downstream process, which may not be detected afterwards.
- No scientific evidence (*we are aware of*) that non-integral filter pre-use will not be detected by a post-use integrity test.

CURRENT TRENDS
- ASEPTIC PROCESSING

2016 Aseptic Mini-Survey Results

1. Nineteen questions that were hotly debated during the development of the PDA Points to Consider for Aseptic Processing
2. Results were tabulated from all four of the 2016 PDA workshops
3. A more extensive survey will be coming out from PDA later this year.

Mini-Survey Results

1. Where are your operations located? (indicate all that apply)

	San Diego	Berlin	Dublin	WDC	Total
Europe	16	26	53	17	112
Japan	4	2	6	8	20
Latin America	7	2	9	9	27
North America	31	10	15	34	90
Other Asia	8	7	11	13	39

2. How many aseptic filling lines does your company operate?

	San Diego	Berlin	Dublin	WDC	Total
0-5	23	15	29	14	81
5-15	5	4	14	16	39
25-30	2	4	4	2	12
More than 30	3	4	6	3	16

2016 Aseptic Mini-Survey Results

3. What percentage of your filling lines utilizes RABS or Isolators?

	San Diego	Berlin	Dublin	WDC	Total
50 – 100%	13	17	38	10	78
25 – 50%	3	5	5	9	22
1 – 25%	7	3	4	7	21
None	9	2	5	9	25

4. If you plan to purchase a new filling unit in the next year, what type are you planning to use?

	San Diego	Berlin	Dublin	WDC	Total
Located in Isolator	17	16	18	13	64
Located in RABS	7	8	2	18	35
Robotic or full automation	4	3	0	1	8
Conventional	3	0	4	3	10
Blow Fill Seal or Form Fill Seal	1	1	4	0	6
Closed Vial Filling	0	0	0	0	0
Manual Filling	2	0	0	0	2
Other	1	0	3	4	8

2016 Aseptic Mini-Survey Results

5. In what environment are your cappers located?

	San Diego	Berlin	Dublin	WDC	Total
Grade A	17	12	31	20	80
Grade B	5	2	6	4	17
Grade C	5	4	6	6	21
Grade D with Unidirectional HEPA airflow	6	9	8	11	34

6. Do you monitor for Total Particulate in the following sizes?

	San Diego	Berlin	Dublin	WDC	Total
≥0.5 µm and ≥5.0 µm	30	24	50	33	137
≥0.5 µm only	2	1	0	3	6
It depends on whether product is manufactured for EU	2	2	0	0	4

2016 Aseptic Mini-Survey Results

7. What incubation conditions do you use for microbial Environmental Monitoring samples?

	San Diego	Berlin	Dublin	WDC	Total
One incubation temperature _____°C	13	2	8	7	30
All samples are incubated at two temperatures _____°C and _____°C	15	15	34	22	86
Some samples are incubated at _____°C and some at _____°C	2	8	8	4	22
Other	1	1	2	0	4

8. Who performs environmental monitoring in your operations?

	San Diego	Berlin	Dublin	WDC	Total
QC Microbiology	30	19	36	29	114
Production	14	13	31	8	66
QA	4	4	6	1	15
Other	3	1	1	2	7

2016 Aseptic Mini-Survey Results

9. What methods of production for WFI do you employ? (indicate all that apply)

	San Diego	Berlin	Dublin	WDC	Total
Distillation	19	25	39	29	112
Reverse Osmosis	18	7	22	15	62
Hot recirculation	16	7	15	13	51
Cold or room temp recirculation	2	0	4	3	9
Batch storage	2	1	2	2	7
Other	1	0	0	1	2

10. Does your company utilize Blow/fill/seal? If so, what environment is the BFS unit in?

	San Diego	Berlin	Dublin	WDC	Total
Do not use BFS	34	19	36	29	118
Grade A	0	3	5	0	8
Grade B	1	1	3	0	5
Grade C	1	2	3	3	9
Grade D	1	1	0	1	3
Uncontrolled	0	0	0	0	0

2016 Aseptic Mini-Survey Results

11. What cleanliness Grade do you use for manufacturing of terminally sterilized liquid products?

	San Diego	Berlin	Dublin	WDC	Total
We do not terminally sterilize	16	15	29	13	73
Grade A	15	7	15	10	47
Grade B	3	1	2	2	8
Grade C	7	7	6	12	32

12. What are your acceptance criteria for aseptic process simulations? (indicate all that apply)

	San Diego	Berlin	Dublin	WDC	Total
Less than 1 in 1,000 at 95% CL	3	2	8	2	15
FDA/EMA Criteria	20	15	24	23	82
Zero Positives	12	13	22	11	58
Other	0	0	1	1	2

2016 Aseptic Mini-Survey Results

13. What incubation temperatures do you use for process simulations?

	San Diego	Berlin	Dublin	WDC	Total
One incubation temperature _____oC	5	1	1	1	8
All samples are incubated at two temperatures _____ oC and _____ oC	14	22	45	29	110
Some samples are incubated at _____oC and some at _____ oC	0	1	2	0	3
Other	2	2	0	0	4

14. Do you incubate and evaluate non-integral media fill units and/or units which are otherwise procedurally deemed 'rejected' units (during routine operations) as part of the media fill study?

	San Diego	Berlin	Dublin	WDC	Total
Yes, startup units	1	3	3	3	10
Yes, all units	14	6	17	12	49
No	12	4	20	14	50
Yes, for some	2	14	12	4	32

15. Do you invert process simulation units prior to or during some or all of the incubation period?

	San Diego	Berlin	Dublin	WDC	Total
Do not invert	7	3	5	4	19
Inverts prior to media fill	12	9	9	12	42
Incubate inverted	10	10	20	6	46
Other	3	9	4	7	23

16. Do you perform anaerobic process simulation fills?

	San Diego	Berlin	Dublin	WDC	Total
Yes	1	X	4	3	8
No	21	X	38	24	83
Only in certain lines/situations	7	X	4	7	18

17. Do you have a disinfectant rotation program?

	San Diego	Berlin	Dublin	WDC	Total
Yes	28	X	44	29	101
No	6	X	7	6	19

18. Do you integrity test 0.2µm filters used for purposes other than sterilization (e.g., prefiltration, for bioload/bioburden reduction, et. al.)?

	San Diego	Berlin	Dublin	WDC	Total
YES	26	20	38	24	108
NO	6	6	8	9	29
Does Not Apply	3	0	3	3	9

19. How often do you verify sterilizing gas or vent filters for integrity?

	San Diego	Berlin	Dublin	WDC	Total
After each cycle/use	12	9	25	12	58
Monthly	2	5	4	3	14
Every 6 months	9	6	16	9	40
Some other frequency	7	4	5	6	22

Closing Thoughts

Closing Thoughts

- Aseptically produced products are becoming more important.
- The technology needs to advance, despite challenges:
  - Technical
  - Financial
  - Regulatory
- We need all stakeholders to work together

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