Aseptic Processing

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Agenda

- Other GMPs that could impact A1? (5 mins)
- PDA Information and mini-survey (5 mins)
- Quick workshop Topics (10 mins)
- Workshop Feedback (10 mins)

Thank you to Mike Morris and PDA Ireland Chapter for information from event in Dublin.

Thank you to Richard Johnson, PDA President for information from Cuba 2017.

Other GMP Updates impacting Annex 1?

Other GMP Updates impacting A1?

- **ISO 14644**
- **WFI by RO**
- **EudraLex Vol 4 Part I Chapter 5: Production**
  - Section on "**Prevention of cross-contamination in production**"
  - 5.20: discusses a QRM process… control the cross-contamination risks presented by the products manufactured. Factors including; facility/equipment design and use, personnel and material flow, **microbiological controls**,…

Other GMP Updates impacting A1?

- 5.21: QRM process should be the basis for determining the extent of **technical and organisational measures** required to control risks for cross-contamination.
- Use of “closed systems”, physical barrier systems, including isolators, as containment measures, disposable technologies, airlocks,
- 5.22 Measures to prevent cross-contamination and their effectiveness should be **reviewed periodically** according to **set procedures**.”

Other GMP Updates impacting A1?

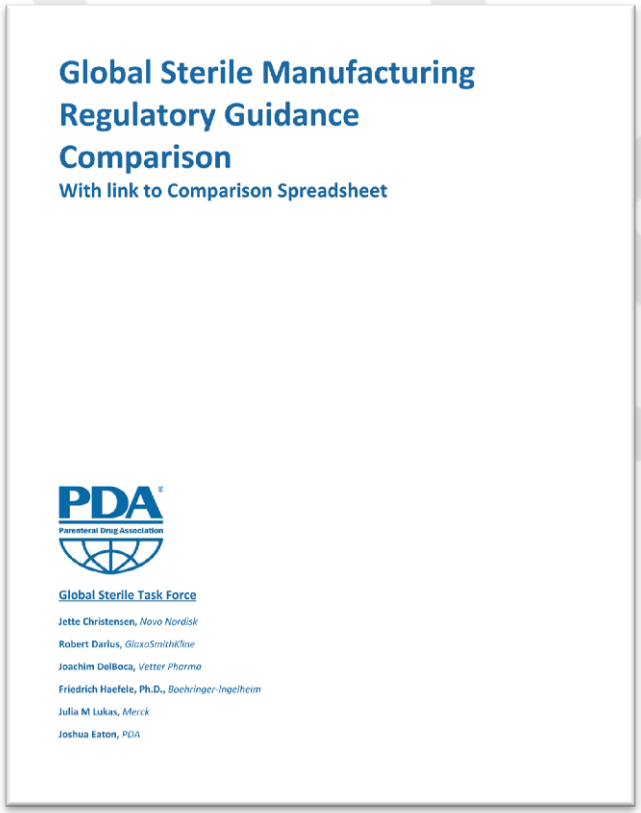
Annex 15 Qualification & Validation (Oct 2015)

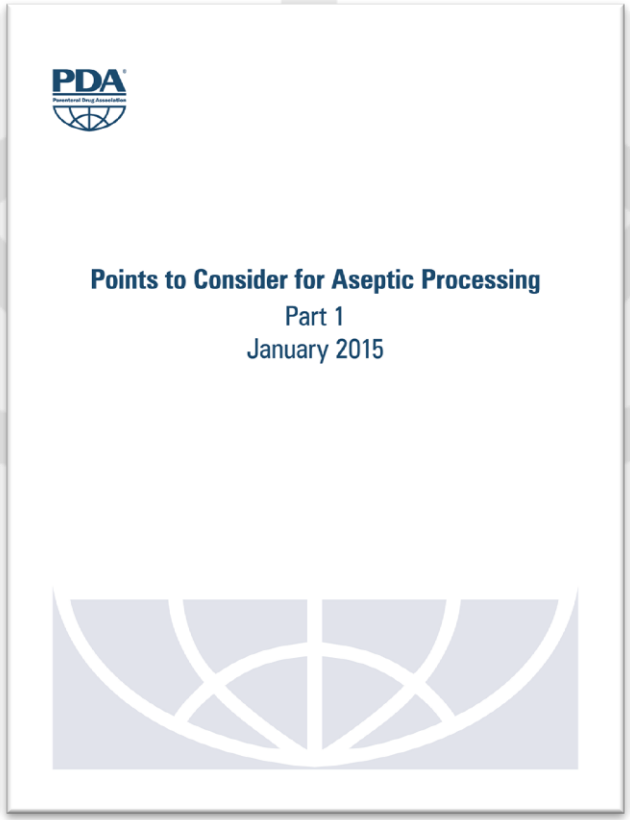
9.1: Where microbial testing of product is carried out, the **method should be validated** to confirm that the product **does not influence the recovery of microorganisms**.

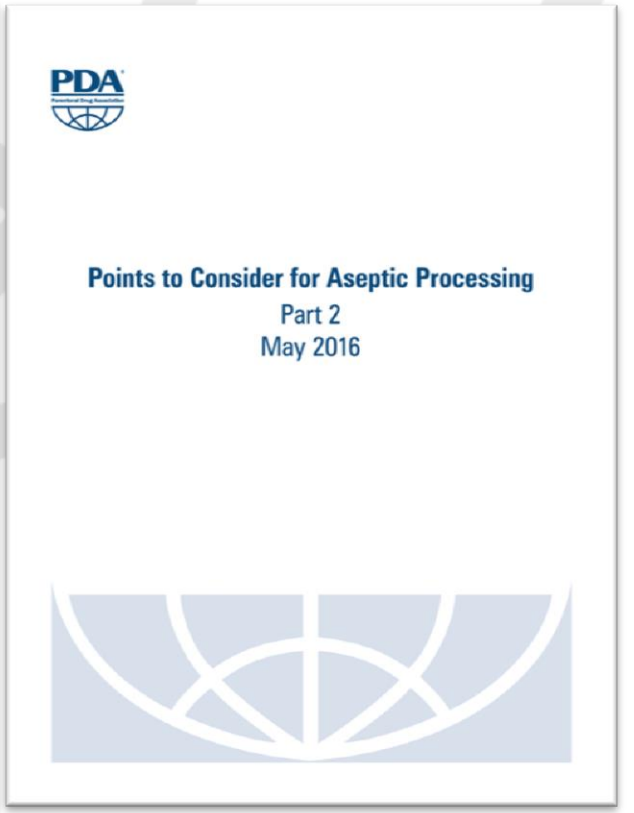
9.2: Where microbial testing of surfaces in clean rooms is carried out, validation should be performed on the test method to confirm that **sanitising agents do not influence the recovery of microorganisms**.

PDA Information

Available at the PDA on-line Bookstore







Examples of Hot Topics

- Airflow Velocity Measurements
- HEPA Filter Patching
- 5µm Total (non-viable) particulate monitoring
- Incubation temperatures for EM
- Identification of Environmental Isolates
- PUPSIT
- Supervision in the Aseptic Processing Area
- Interventions – Type & Frequency
- Duration of Process simulations
- Incubation temperatures for media fills
- Process simulation acceptance criteria

2016 Aseptic Mini-Survey

2016 Aseptic Mini-Survey

- **19 questions** that were hotly debated during the development of the PDA Points to Consider for Aseptic Processing.
- Results were tabulated from all 4 workshops.
  - San Diego
  - Berlin
  - Dublin
  - Washington, DC

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

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

2016 Aseptic Mini-Survey

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

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

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

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

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

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

2016 Aseptic Mini-Survey

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

2016 Aseptic Mini-Survey

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

More from PDA?

- A more extensive survey has just come out from PDA.
- Over 170 multiple choice questions.
- Closes on 31st of July
- **Please contribute**.

Quick Workshop

Quick Workshop Topic 1

EM Excursions:

What do you do if there are EM excursions in Grade A filling area – and why?

Would the excursion trigger automatic batch rejection? If so, then what is the reason for rejection?

Or would there be an investigation to determine batch disposition,? If so, then what would be the criteria for batch acceptance?

Quick Workshop Topic 2

EM of non-viable particulates:

What is the objective of monitoring EM of 5.0 µm or greater particulate?

What are the challenges to doing so?

What is the result of this type of EM indicate?

Are there other ways to meet the same objective?

Quick Workshop Topic 3

PUPSIT (Pre-Use, Post Sterilization Integrity Test):

Should you perform a PUPSIT?

What are the benefits?

What are the risks?

What are the elements of a risk assessment to be considered?

Quick Workshop Topic 4

Incubation:

What incubation temperatures are scientifically appropriate for environmental monitoring samples?

Should one temperature range be used?

Two temperatures? If so, which sequence?

What is the scientific rationale?

Thank you

Thank you for your participation.

We hope that you enjoy your dinner.

Safe journey home.