Annex 1 Draft Revision – Focus on Facilities, Production & Environmental Monitoring

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PharmOut
Regulatory Knowledge, Practically Applied.

Chapter Focus

5 Premises

8 Production & specific technologies

9 Viable and non-viable environmental & process monitoring

Thoughts on ISPE vs PDA Responses

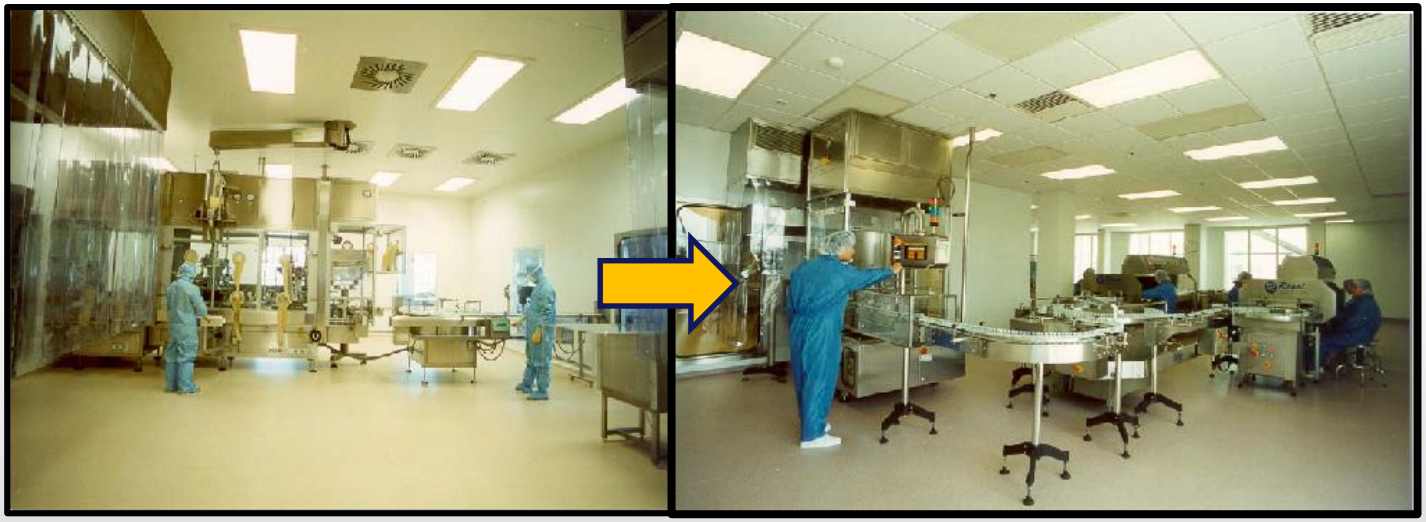
ISPE Response (ispe.org/sites/default/files/regulatory/ISPE-Commenting/CommentEMA2018-0320.pdf)	**PDA Response** (www.pda.org/docs/default-source/website-document-library/scientific-and-regulatory-affairs/regulatory-comments-resources/2018/pda-annex-1-comments-20march2018.pdf?sfvrsn=4)
60 pages!	28 pages
Very specific feedback on preference for wording and detail (hence length)	General feedback of area of concern and provides suggested replacement wording
Tone tends to be one of agree/disagree	Tone is more suggestive, but can tend to lobbying for pre-held perspectives
Most commonly expresses concern at the individual clause level	General concern for the lack of definition of intent (may, should, typically, encouraged, can, sufficient, appropriate, etc.)
Particularly concerned about contamination terminology	Particularly concerned about the requirement for perceived unnecessarily risky practice (PUPSIT, EM in Grade A)

Selected Interesting Tidbits!

ISPE Response	PDA Response
Believes the term contamination is largely incorrect, wants it replaced with ”microbes” and “particulates”. (e.g microbial and particulate control strategy)	Agrees that the term contamination is over-used, but takes the “further explanation route”
Wants newly expanded WFI and PS references in chapter 7 to reference monographs instead	Wants more emphasis on the limitations of APS
Sees RABS and isolators as equivalent, and wants differences to be noted in one section, then reference using a common term (e.g. barrier technology)	Wants to allow for stopper bowls and tracks to be decontaminated instead of sterilised
Wants to reduce definition of gowning requirements significantly, instead encourage selection based on QRM	Most significant proposed rewrites are around filter integrity testing and sterilization (not a fan of PUPSIT)
Advocates for some older technology – e.g. passive pass-throughs	Wants to align A/B/C/D with 5/6/7/8

Significant Change 1 – 5.3

Draft	2007	Subject
5.3	3	Definition and requirements for graded clean areas
Change		
Grade B definition has been changed to define "interface" rooms as Grade C only.		



Fill/Stopper Area – Grade A/B

Capping Area – Grade D

Significant Change 1 – 5.3

ISPE Thoughts

Wants to add *"Access to grade B should normally be directly from grade C. Grade D and CNC may serve as entry to Grade B via separative devices such as washers, autoclaves and pass-thru boxes, as justified by quality risk management. Materials and personnel may exit Grade B directly to Grade D and CNC" with appropriate cascade pressure airlock"*

PDA Thoughts

Wants to add *"or when mouse holes are used to transfer filled, closed products to a lower grade, and this is confirmed through air flow visualization studies and monitored through the differential pressure."*

My Thoughts

In both cases, the responses are in context of what the PDA and ISPE representatives understand, but in each case the examples are limiting. At least we all agree that the clause as stated is potentially too restrictive.

Significant Change 2 – 5.9

Draft	2007	Subject
5.9	51	Personnel and material airlocks

Change

This clause is significantly expanded, especially with regard to material movement, and now includes new expectations:

- personnel movement should "typically" be through separate areas CNC → D → C → B
- separate entry and exit changing rooms imperative has changed from "sometimes desirable" to "generally desirable"
- pass-throughs should be actively ventilated, with exceptions risk assessed and mitigated
- materials entering Grade A/B shall have been qualified and listed as authorized. Unauthorized material should enter only by a documented exception procedure
- Movement of material from unclassified to Grade C (without transition through Grade D) should be risk assessed and mitigated

Significant Change 2 – 5.9

ISPE Thoughts

5.9 – wants significantly greater clarity for "final stage" "at-rest" statements
(a) Wants CNC→D→C→B cascade restricted to entry
(b) (i) Advocates passive pass-throughs on QRM principles
(b) (ii) Doesn't see the point of specifying detail on transfer lists to Grade A
(b) (iii) Thinks all grade skipping for materials transfer should be based on QRM principles, not restricted to CNC→C only

PDA Thoughts

5.9 – no comment
(a) Wants a clarification for outbound traffic
(b) (i) no comment
(b) (ii) no comment
(b) (iii) wants to removed CNC terminology

My Thoughts

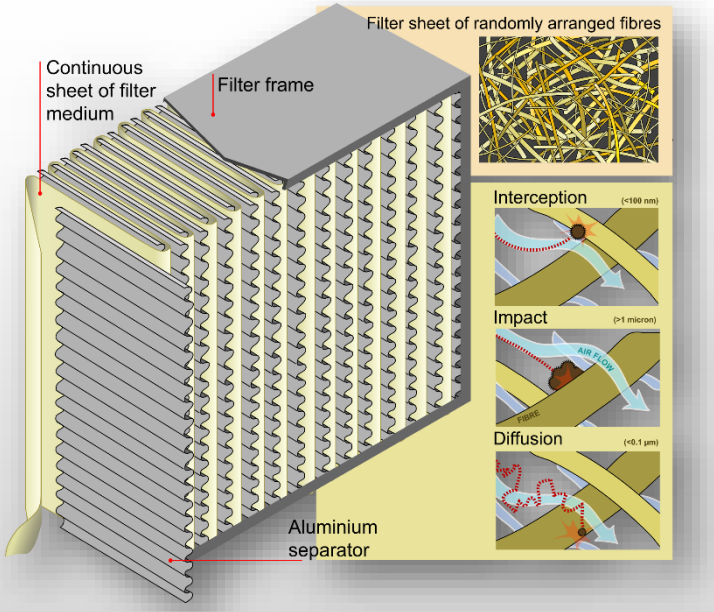
We see a difference in the approach of the organisations (engineers vs scientists?). Generally agree with ISPE positions, except perhaps (b) (ii), where their argument is weak for limiting equipment lists to "type" rather than detail.

Significant Change 3 – 5.11

Draft	2007	Subject
5.11	53	Air supply requirements to graded areas

Change

The new clause is almost an exact copy of the 2007 clause, but the change is significant. The words "a filtered air supply .." have been replaced with "a HEPA or ULPA filtered air supply …" when referring to the air supplied to graded areas.



Significant Change 3 – 5.11

ISPE Thoughts

Concerned that HEPA or ULPA is implied for ISO 8, when not required. Prefers removal of ULPA reference altogether. Wants HEPA mandated for A and B, optional for C and F9 for D

PDA Thoughts

No comment

My Thoughts

Agree that ULPA adds nothing. HEPA should be mandated for C and based on QRM for D. Recirculated systems with F9 filters have significantly poorer recovery rates.

Significant Change 4 - 5.21

Draft	2007	Subject
5.21	25	Isolator glove testing
Change		
The requirements for integrity testing of gloves has changed from "frequent" to "… at a minimum of the beginning and end of each batch, and following any intervention that may affect the integrity of the unit"		

Significant Change 4 – 5.21

ISPE Thoughts

Wants further clarification on the frequency and requirements for each different integrity method (visual, mechanical, physical)

PDA Thoughts

Wants instruction for use of non-invasive (e.g. visual) integrity testing during production (i.e. after interventions)

My Thoughts

A combination of both comments would greatly enhance this requirement and make it easier to understand and implement.

Significant Change 5 – 8.60

Draft	2007	Subject
8.60	95	Steam sterilizing load considerations
Change		
Adds requirement to confirm load dryness as part of sterilization process acceptance		

Significant Change 5 – 8.60

ISPE Thoughts

No comment

PDA Thoughts

Wants clarification that load dryness applies to porous hard goods (items) only

My Thoughts

The load dryness requirement has raised eyebrows with manufacturers – exactly what is intended needs to be clarified, both in terms of sterilised items and in terms of acceptance criteria

Terminology : non-viable monitoring

Why did they call it "Non-viable monitoring"? … We have spent the last several years conditioning people to understand particle monitoring to be just that - the monitoring of particles which may be either viable or non-viable.

The industry adopted terminology is "airborne particulate monitoring". It feels a bit like "laminar" vs "uni-directional" all over again.

PDA agrees (although suggests "total particulate monitoring"). ISPE didn't pick this up

Significant Change 6 – 9.17

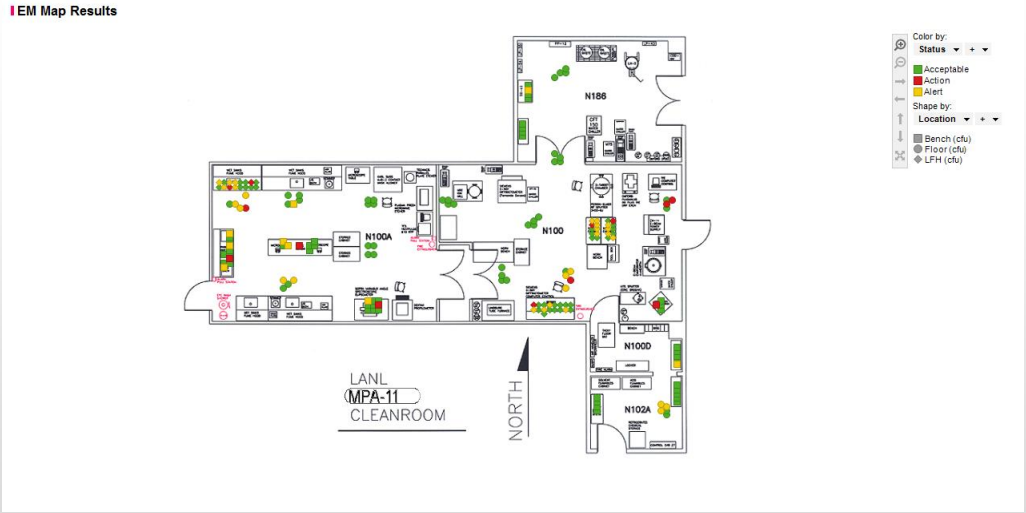
Draft	2007	Subject
9.17	15	Determination of monitoring requirements in Grade C & D

Change

The basis for determination has expanded from QRM to QRM + enough data for effective trend analysis.

Explanation of "Significant" Change Status

For many manufacturers, this is likely to prompt an increase the necessary frequency of sampling, and in some cases, increase it significantly.

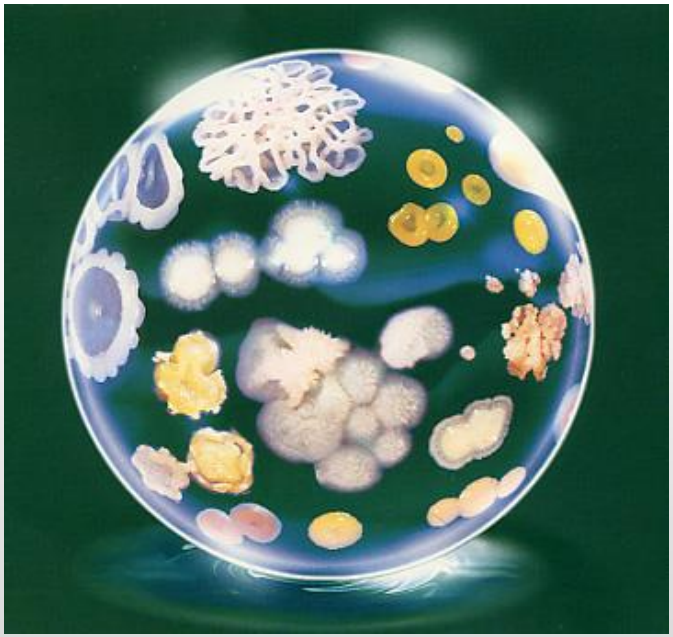


Significant Change 6 – 9.17

We all agree that this is a positive change (although no doubt will create additional work for some organisations)

Significant Change 7 – 9.33

Draft	2007	Subject
9.33	NA	Identification of isolates
Change		
Now mandates speciation of Grade B as well as Grade A isolates. Grade C & D identification should be considered		



Significant Change 7 – 9.33

ISPE Thoughts

Wants requirements for Grade B relaxed based on QRM determination of critical vs non-critical

PDA Thoughts

Wants the words "if possible" included to acknowledge that not all isolates can be identified using current techniques

My Thoughts

The PDA position is the likely outcome – many organisations already speciate in Grade B, and recent advances in identification technology (economics) make arguments against ID less justifiable

Proposed change where no change was made

Draft	2007	Subject
9.25 & 9.31	19	Viable methods and limits
Change		
Effectively no substantive change in limits or methods proposed, not withstanding separate references to rapid micro.		

Proposed change where no change was made

ISPE Thoughts

Wants substantially less emphasis on settle plates because of limitations of methods. Prefers volumetric samplIng

PDA Thoughts

Is concerned that emphasis on traditional methods may cause organisations to use these in preference to alternative modern methods -particularly where the traditional methods may pose additional riks (e.g. settle plates in Grade A)

My Thoughts

The regulations are not a place to champion new technology. They must allow for what is acceptable at a base level. There is already a number of references to advanced technologies and no hindrance to implementing these methods

General thoughts on APS

Draft	2007	Subject
9.34-9.49	66-71	Aseptic Process Simulation (APS)
Change		
Significantly greater depth of instruction and focus on the requirements of APS. Many clauses and concepts borrowed from PIC/S Guidance on Aseptic Processing (PI007-6) As a result, not too many contentious issues		

General Thoughts on APS

ISPE Thoughts

Concerned about 9 batches for three shifts
Wants clarity about what constitutes intervention (how they are identified) and the frequency of inclusion in APS
Prefers use of transparent vials over decanting from opaque vials

PDA Thoughts

Wants clarity about what constitutes interventions and how they are identified
Prefers use of transparent vials over decanting from opaque vials
Concerned that too much weight is placed on APS and the limitations should be defied

My Thoughts

I tend to agree with ISPE that 9 successful media fills across 3 shifts is excessive. With the exception that a note on QRM would be useful, I think the definitions and explanations on interventions and the holistic nature of sterility assurance are adequate

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Thank you for your time.
Questions?

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