PDA Points to Consider relating to EU GMP Annex 1 changes

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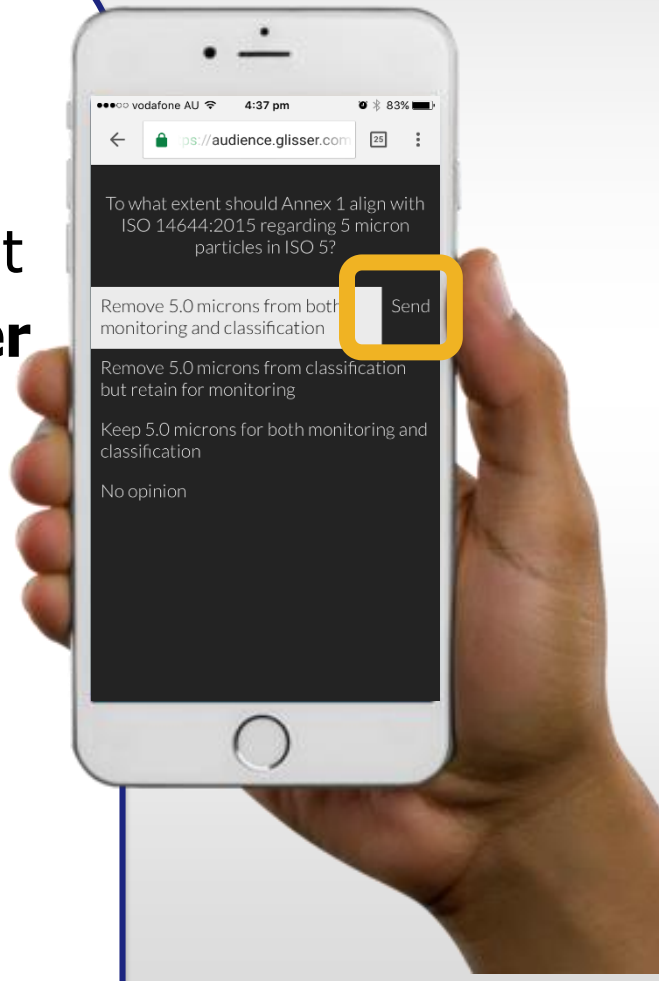
Regulatory Knowledge, Practically Applied.

Lets get interactive!

- On your smart device, open a browser app and go to the link provided
- **Click on the link**
- You can now view the slides as I present
- I will also ask you to **answer a number of questions** as we go
- When we get to the question, you will see a screen like the one on the right.
- Click on **your answer** and hit **Send**.
- I will then show you the results of the room!



What's this all about?

New Annex 1 is coming

- We still **don't know when**
- We have **some information** on what is changing
- But **not everything**

PDA developed two papers

- PDA "**Points to consider**" for aseptic processors
- Also hoping to **influence regulators** developing new Annex 1
- PDA **surveyed opinions** on the PtC documents around the world

Why change at all?

Where do I start?

So many issues with Annex 1 2008

- Instances of **lack of clarity** of wording and interpretation – **Clause 51 anyone**?
- Some requirements **arguably unscientific** (e.g. PUPSIT, 5.0 µm)
- Apparent **contradictions** (e.g. 34 vs 116)
- Apparent important **missing words**
- **Grammatical mistakes**
- Now **inconsistencies** with referenced standards (ISO 14644)

Some interesting issues (the interactive part!)

- 5.0 micron particles
- HEPA filter patching
- Incubation temperatures
- Media fill rejects
- Pre-Use, Post-Sterilisation Integrity Testing (PUPSIT)

0.5 and 5.0 micron particles

PDA PtC AP Part 1, Section I, Topic P

Annex 1, 2008: Classification and monitoring required at both ≥0.5µm and ≥5.0µm

"≥5.0 µm particle concentration count takes on a particular significance as it is an important diagnostic tool for early detection of failure"

0.5 and 5.0 micron particles

PDA PtC AP Part 1, Section I, Topic P

- On **what basis** is this statement made?
- ISO 14644 **removed ≥5.0µm counting** from the classification table for ISO 5 (Grade B at rest, basis for Grade A)
- **Is it a problem to keep counting ≥5.0µm?**

And **we have a discrepancy** between US FDA and Annex 1 requirements. Do we **need alignment** on this issue?

0.5 and 5.0 micron particles

PDA PtC AP Part 1, Section I, Topic P

Particle measurement equipment will measure **multiple particle sizes simultaneously**. ≥5.0 micron measurement requires no additional equipment

Some people think it's important – **maybe they're correct!**

0.5 and 5.0 micron particles

PDA PtC AP Part 1, Section I, Topic P

Accuracy of sensors mean that ≥5.0 micron counts in Grade A are of questionable value, both in absolute terms (are they real particles?) and statistical (are trends meaningful?)

Counter sampling rates mean that assessing ≥5.0 micron counts usually involves **extrapolation over time**

To what extent should Annex 1 align with ISO 14644:2015 regarding 5 micron particles in ISO 5?

- Remove 5.0 microns from both monitoring and classification
- Remove 5.0 microns from classification but retain for monitoring
- Keep 5.0 microns for both monitoring and classification
- No opinion

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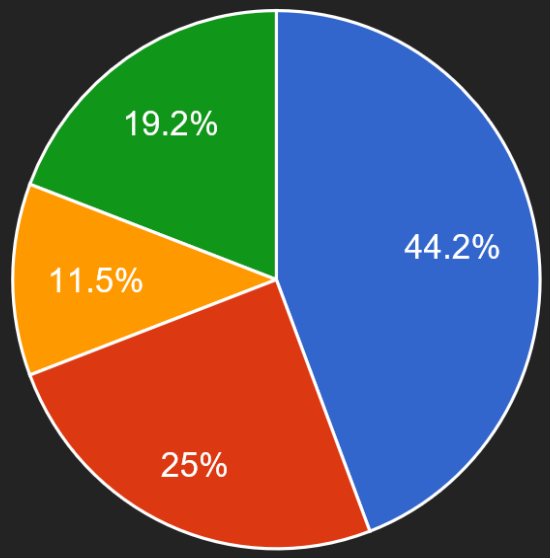

HEPA Filters, Testing & Patching

PDA PtC AP Part 1, Section I, Topic F

- **Annex 1, 2008:**
- "…" no reference to HEPA filters in Annex 1!

Clean area air should pass through *"filters of an appropriate efficiency"*

HEPA Filters, Testing & Patching

PDA PtC AP Part 1, Section I, Topic F

- **ISO 14644** parts 1 & 2 (2015) **do not mention HEPAs**
- **ISO 14644** part 3 – provides **HEPA leak test**.
  - Allows for patching **only agreement between customer and supplier**, and considering filter manufacturer instructions
- **AS 1807.6** requires that patching information be **recorded in report**, provides some information on patching limits
- **What should we be doing??**

At National GMP & Validation Forum in July, 53% of respondents didn't know what their company did

HEPA Filters, Testing & Patching

PDA PtC AP Part 1, Section I, Topic F

Problems

- **PIC/S** and **ISO** provide **no guidance** on limitations of patching – size, area, patching materials?
- Filter manufacturers **often discourage patching**

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HEPA Filters, Testing & Patching

PDA PtC AP Part 1, Section I, Topic F

There is help!

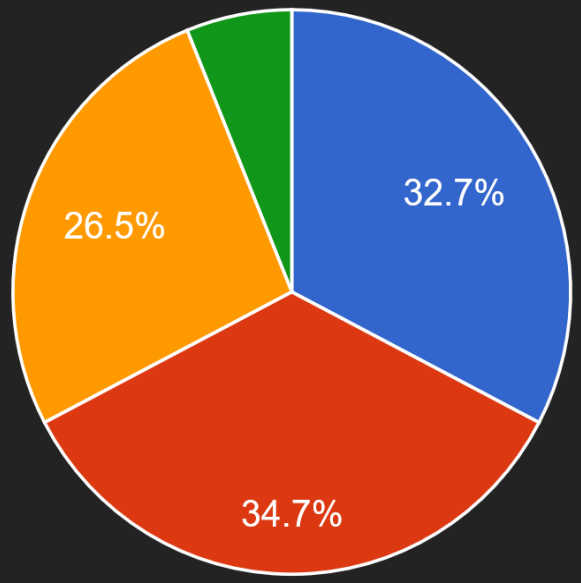
- AS1807.6, BS EN 1822.4 & IEST RP-CC034.4 give **guidance on limitations of size/area**
- Some manufacturers (eg. Camfill Farr) provide **recommendations on patching material** (hot melt silicone such as RTV 162, RTV 108, Dow 732) same as or similar to pleat separator

Should HEPA filters be patched?

- Yes, any HEPA should be repairable in accordance with company procedures and QRM principles. Decision to repair or replace should be justified and documented
- Yes, HEPAs outside Grade A should be repairable according to company procedures and QRM principles. Grade A HEPA filters must be replaced when non-integral
- No, all HEPAs in classified areas should be replaced when non-integral
- No opinion

Should HEPA filters be patched?

- Yes, any HEPA should be repairable in accordance with company procedures and QRM principles. Decision to…
- Yes, HEPAs outside Grade A should be repairable according to company procedures and…
- No, all HEPAs in classified areas should be replaced when non-integral
- No opinion



Incubation of media fill units (and EM)

PDA PtC AP Part 2, Section III, Topic C

Annex 1, 2008:

"…" no reference to incubation requirements for EM or process simulation units

- **20-25°C** followed by **30-35°C** common practice
- Some **reverse the order**
- Some do **different temperatures**
- Some do **one temperature**

Incubation of media fill units (and EM)

PDA PtC AP Part 2, Section III, Topic C

Annex 1, 2008:

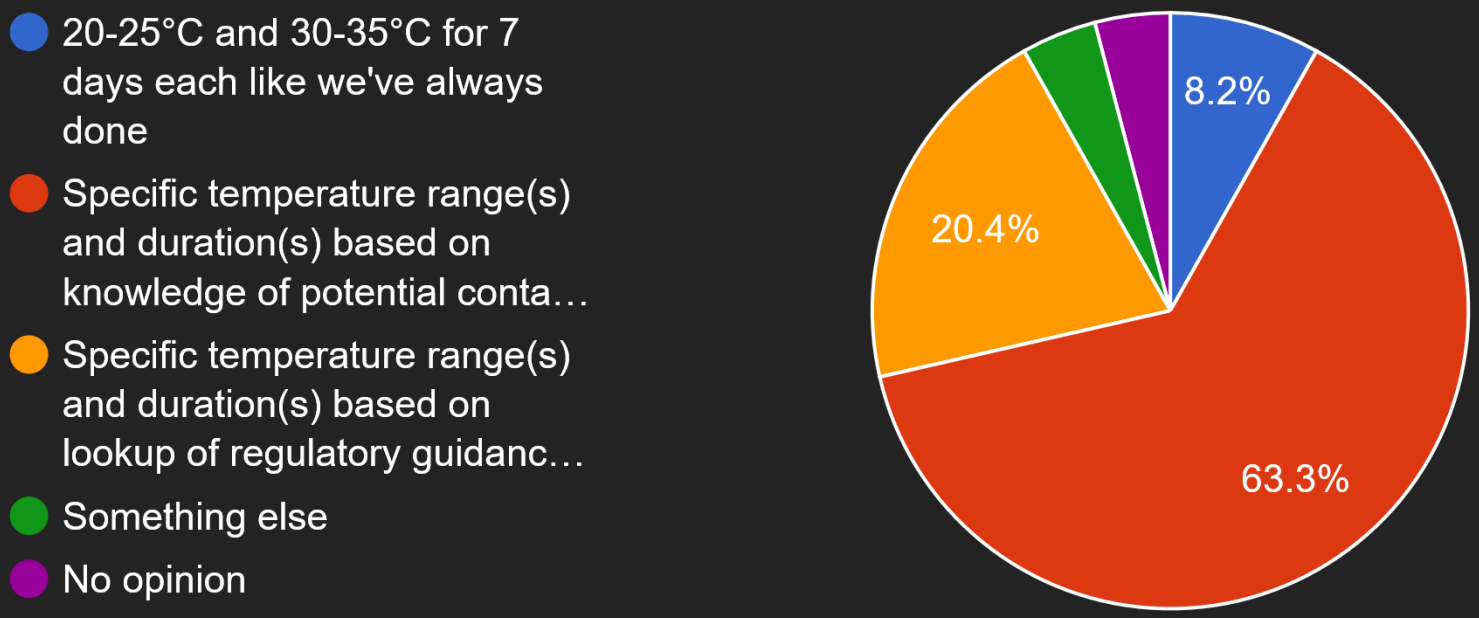
- USP historically supported **two temperatures**. Not specific anymore
- **Different flora** may have **different optimal growing conditions** (e.g. moulds typically prefer lower temperatures
- **Mesophilic organisms** by definition are rarely growth inhibited between 20-35°C

Does your organisation have justification for the temperatures/times used?

What should be the basis of incubation temperatures for media fills/process simulations?

- 20-25°C and 30-35°C for 7 days each like we've always done
- Specific temperature range(s) and duration(s) based on knowledge of potential contaminants
- Specific temperature range(s) and duration(s) based on lookup of regulatory guidance (e.g. USP)
- Something else
- No opinion

What should be the basis of incubation temperatures for media fills/process simulations?



Inclusion of units for Media Fills

PDA PtC AP Part 2, Section III, Topic D

Annex 1, 2008:

"…" no guidance on determining incubation set

- **PI 007-6** provides some **very limited (and arguably questionable) advice**:

> "damaged containers should not be included as failures (positives) when evaluating results"

- **No regulatory advice** on whether to **include rejects** for incubation and/or evaluation of media fill disposition

Inclusion of units for Media Fills

PDA PtC AP Part 2, Section III, Topic D

Annex 1, 2008:

"…" no guidance on determining incubation set

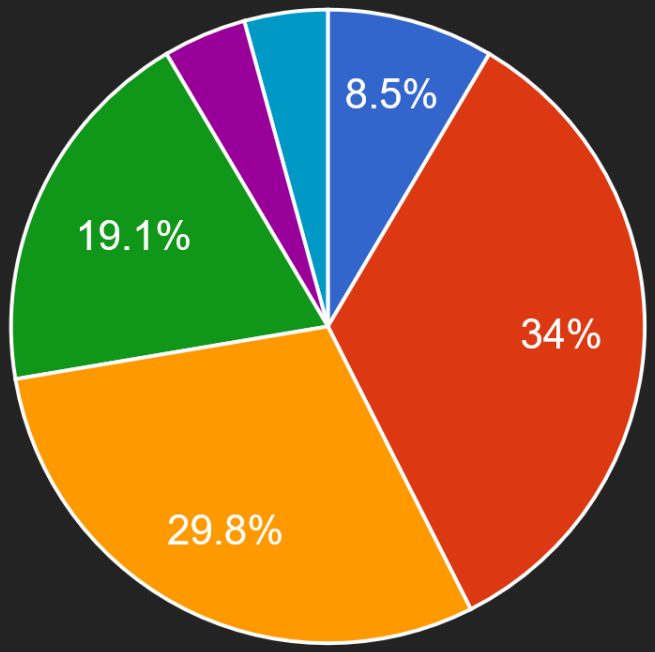
- Should we incubate high/low volume?
- Cosmetic defects?
- Particulate defects?
- Non-integral containers (closure problems, cracks, leakers)?
- If we incubate, how should we evaluate results from defects?

How should rejects be handled in media fills?

- All rejects should be incubated and evaluated as part of media fill disposition
- All rejects should be incubated, but rejects categorised as a risk to sterility assurance should be "for information only".
- Rejects categorised as a risk to sterility assurance should not be incubated. All others should be included in evaluation of media fill.
- Rejects (all or some) should be incubated "for information only" and not included in evaluation of media fill
- Rejects should not be incubated
- No opinion

How should rejects be handled in media fills?

- All rejects should be incubated and evaluated as part of me…
- All rejects should be incubated, but rejects categ…
- Rejects categorised as a risk to sterility assurance should…
- Rejects (all or some) should be incubated for information…
- Rejects should not be incub…
- No opinion.



PUPSIT of Product Filters

PDA PtC AP Part 1, Section VI, Topic J

Annex 1, 2008:

" The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use …"

- Also confirmed in **PI 007-6**
- **Why pre-use, post-sterilisation? Who says this is required?**

  - Filter manufacturers?
  - Industry, based on knowledge of integrity failures?
  - Regulators, based on documented case studies?

PUPSIT of Product Filters

PDA PtC AP Part 1, Section VI, Topic J

Annex 1, 2008:

- *" The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use …"*

- Cases in EU where **major deficiencies** assigned to manufacturers based on failure to PUPSIT.
- **Anecdotal evidence** in Australia that PUPSIT expected of 'big pharma', but smaller manufacturers exempted

Another example of failure to align with US FDA.

PUPSIT of Product Filters

PDA PtC AP Part 1, Section VI, Topic J

Hint for what might be coming in Annex 1 - New draft EMA guidance on sterilisation provides exception:

- *"The integrity of the sterilised filter **should be verified before use** but after its sterilisation **unless specifically justified and validated**"*

- **ISO 13408-2** revision also allows for **risk-based decision** on PUPSIT.

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Should PUPSIT be a requirement of Annex 1?

- Yes, it is important to test pre and post sterilisation prior to use.
- Yes, post sterilisation is important, but pre sterilisation should be optional
- No, the regulations should give flexibility to allow sound scientific/risk based justification for not performing PUPSIT
- No, not performing PUPSIT is a business risk, not a quality risk as filter failure will always be picked up by post-use testing
- No opinion

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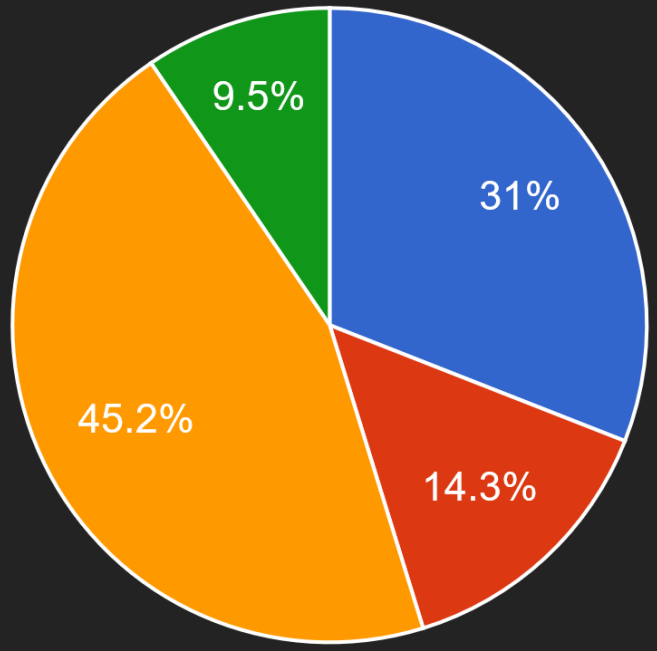


Just a snapshot

Highlighted just **5 issues** where Annex 1 currently does not provide clear guidance – but so many more (71) in PtC guides. For Example:

- Should **rotation of disinfectants** be mandatory or based on historical/scientific data?
- Is averaging of **environmental microbiological data** appropriate?

Just a snapshot

Further examples:

- Do we need further clarification around conditions for **partially stoppered containers**?
- Should **media fills** be recorded and what should the archive requirements be?
- How should we test **Grade A environments** – where do we test velocity, how do we perform visualisations?

What will new Annex 1 say?

0.5 and 5.0 micron particles:

- Indications are that classification will be in accordance with ISO 14644 requirements, so **5.0µm will not be a classification requirement** for Grade B at-rest/Grade A
- But, likely that 5.0µm will be required for **continuous monitoring**
- Some hope that 5.0µm may be used as **indicative trending tool** rather than limit based requirement

What will new Annex 1 say?

Incubation & media fill clarity:

- There will be new section (9) on "**viable and non-viable environmental and in-process monitoring**".
- It is expected that there will be a strong emphasis on **science and risk based justification** for system implementation

What will new Annex 1 say?

HEPA Filters, Testing & Patching

- **No indication** if guidance on this will be introduced, **probably unlikely**. Consider application of **good practice** in any case

PUPSIT

- Will be **specifically addressed**. Reasonable prospect that a clause **at least as flexible** as that in EU sterilisation guidance **may** be included

Anything else of interest that we know?

Modifications to scope to highlight **relationship to other annexes and chapters**, as well as possible acknowledgement of use outside of sterile manufacturing

Strengthening of the principles of QRM, RCA and product impact assessment

Goggles for Grade A!

Anything else of interest that we know?

Emphasis on **segregation** of process from personnel (using technology where possible)

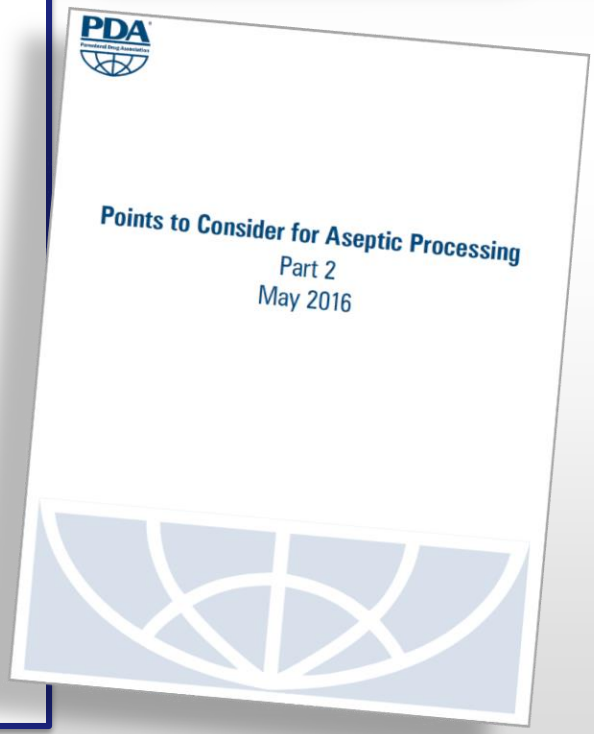
WFI production using RO and biofilm discussion

Training and knowledge management requirements in response to inspection findings

What to take home

We are getting a new Annex 1!

- **Change is necessary**
- Many, if not all of the issues raised here are **being considered** for further clarification in Annex 1
- As a result of these, and many other contentious issues, **it's taking a long time**
- In the mean time, industry should be looking at **compliant ways of taking the lead** …
- **PDA Points to Consider** is a great starting reference



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Thank you for your time.

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