Draft Annex 1 – The Good, The Bad, The Ugly

Presented by Ashley Isbel, 6 August 2018

Hosted by PharmOut

GMP, Engineering & Cannabis Forum 2018

PharmOut

Refresher – Why was Annex 1 Revised?

Concept Paper (Jan 2015)

1. Alignment with ICH Q9 (Quality Risk Management)
2. Alignment with ICH Q10 (Pharmaceutical Quality System)
3. Advances in sterile manufacturing technology since the previous revision
4. Historical ambiguity and inaccuracies in the 2007 version that need correction or clarification
5. Acknowledgement that Annex 1 has use beyond sterile manufacturing and that the scope and/or title require modification to reflect this.

Revision justifications – how did they go?

Reason	Comment	Grade
ICH Q9	There are *a lot* of references (107) to QRM and risk, and many are helpful. Some are not so helpful, and other opportunities to encourage QRM are missed	B
ICH Q10	A new section of PQS is added. Not easy to see the added value, nor are the concepts "embedded" in the Annex.	C-
Advances in technology	Several key advances are addressed and often in a useful way. Others may be mentioned without provision of useful guidance. Yet others are overlooked.	B
Ambiguity & Errors	Most of the ambiguity and errors arising from 2007 Annex 1 are addressed. But a whole lot more have been created.	C
Use outside of steriles	A small reference in the principle provides vague guidance for a small sub-set of non-sterile production. In my opinion, of virtually no value.	D

So, what was Good?

- Restructure of the document
- Contamination Control Strategy
- Expansion and clarification of training requirements
- Expansion and clarification of visual inspection requirements
- Expansion and clarification of environmental monitoring requirements

Document Restructure

Guide to GMP Part I	Annex 1 Draft Revision
	1. Scope
	2. Principle
1. Pharmaceutical Quality System	3. Pharmaceutical Quality System
2. Personnel	4. Personnel
3. Premises and Equipment	5. Premises 6. Equipment 7. Utilities
4. Documentation	
5. Production	8. Production and specific technologies 9. Viable and non-viable environmental and process monitoring
6. Quality Control	10. Quality Control
	11. Glossary
7. Outsourced Activities	
8. Complaints and Product Recall	
9. Self Inspection	

Contamination Control Strategy

A multi-element, formally documented strategy, which is implemented site-wide.

The Annex requires organisations to understand the sources and control mechanisms for contaminants, which are defined as microbiological and cellular debris, as well as particulate matter.

- The key purpose of a CCS is allow assessment of the strategies implemented.
  - Not just collation of risk assessments, validations, procedures and other information
  - Requires ongoing effectiveness evaluation and correction.

Training & operator qualification requirements

Enhanced information on:	Definition of who needs to be trained and qualified in sterile areas (4.3)
	What the training should entail (4.3)
	What operator gowning qualification entails (4.4)
	Considerations for other operator qualifications (process related) (4.3)
	Disqualification of personnel (4.5)
	How to manage untrained personnel (4.6)

b) Personnel must have appropriate skills, training and attitudes with a specific focus on the principles involved in the protection of sterile product during the manufacturing, packaging and distribution processes.

Visual inspection requirements

Significantly greater detail, including:

- Greater alignment with USP790 and USP1790
- Use of QRM to determine both defect types and their criticality (8.26)
- How to qualify manual inspection processes and operators (8.27)
- The basic principles to be met for automated inspection (8.28)
- Trending requirements (8.26 & 8.29)

Environmental monitoring requirements

More detailed and specific information	Generally much greater detail (49 vs 22 clauses)
	High degree of emphasis of use of QRM principles to establish and maintain programs for both viable and airborne particulate counts
	Alignment (generally) with ISO14644:2015 for classification
More information on aspects of EM programs	What to look for when trending viable data
	The purpose and expectations of alert and action limits

What was bad?

- Important non-clarifications
- Some weird inclusions
- New ambiguities

Non-clarifications

Airlock Grading

- The ambiguous statement "*final stage of the airlock should, in the at-rest state, be the same grade as the area into which it leads*" remains

Bioburden limits

- The misleading statement "*There should be working limits on contamination immediately before sterilization, which are related to the efficiency of the method to be used*" remains.

Grade A conditions

- The differences between "Grade A air supply" and "Grade A" are still not adequately explained, and are further confused by the myriad of terms used in conjunction with Grade A (Grade A conditions, area, zone, environment, air shower).

Weird Inclusions

The whole utilities section

Some useful clauses, but arguably not enough to justify a stand alone section
The large majority feels like the regulators telling industry what we already know and do well.

ULPA filters

The mention of ULPA filters is unnecessary and unhelpful. ULPA filtration is not required (and would add unnecessary cost) for any grade of air currently specified for GMP.

VHP

VHP is one of many vapour disinfection or fumigation methods available. It is referenced twice, both times unnecessarily, and arguably produces an undesirably narrow mindset when considering best options for your facility.

New Ambiguities

HEPA filtration in Grade D?

400 5.11 A HEPA or ULPA filtered air supply should maintain a positive pressure and an
401 air flow relative to surrounding areas of a lower grade under all operational conditions and

Grade B room interfaces

334 Grade B: For aseptic preparation and filling, this is the background environment for
335 the grade A zone. In general, only grade C cleanrooms should interface with the grade
336 B aseptic processing area.

Restart testing requirements for after WFI sanitation or media fills

691 7.13 To prevent the formation of biofilms, sterilization or disinfection or regeneration of
692 water systems should be carried out according to a predetermined schedule and also when
693 microbial counts exceed action and alert limits. Disinfection of a water system with
694 chemicals should be followed by a validated rinsing procedure. Water should be analyzed
695 after disinfection/regeneration; results should be approved before the start of use of the
696 water system.

1932 9.46 All products that have been manufactured on a line subsequent to the process simulation
1933 should be quarantined until a successful resolution of the process simulation has occurred.

The "intent of the annex"

46 evaluating and controlling potential risks to quality. Risk assessments should be used to
47 justify alternative approaches to those specified in this Annex only if these alternative
48 approaches meet or surpass the intent of this Annex.

17 The intent of the Annex is to provide guidance for sterile medicinal products.

PharmOut

What was ugly?

- Holding fast to positions that are difficult to justify
- Providing a document that was riddled with mistakes
- Heavy use of ‘weasel words’

Positions that are difficult to justify

PUPSIT (Pre-Use Post-Sterilisation Integrity Testing)

- Hotly debated
- European position is that filters may be falsely identified as integral post-use
- Not supported by published science
- FDA, filter manufacturers, industry do not agree

5 micron particle monitoring

- Removed from classification, consistent with ISO14644
- Remains as monitoring requirement
- European position is that it is an important early indicator of failure
- Not well supported by published science (especially for ISO 5)
- Not a position held by FDA

Mistakes

Spelling mistakes & typos

622 treatment, generation, storage and distribution systems should be subject to qualificion,

762 product actively supports microbial growth and/or must be held for a long periods before

771 exposed for more than a few seconds beforeclosing, or the product is held for extended periods

Clause in the wrong section (and redundant)

1728 9.27 Continuous monitoring in grade A and B areas should be undertaken for the full duration
1729 of critical processing, including equipment (aseptic set up) assembly and filling operations
1730 (i.e., an understanding of function and interactions of each clean area). The monitoring
1731 should be performed in such a way that all interventions, transient events and any system
1732 deterioration would be captured and any risk caused by interventions of the monitoring
1733 operations is avoided.

Poor grammar & readability

2187 Manual Filling –~~Where the product is transferred into the final container by systems~~ where
2188 operator intervention is required to complete the filling of each container e.g. pipetting
2189 liquids.

154 e) Processes associated with the finishing and transport of sterile products should not
155 compromise the finished sterile product in terms of container integrity or pose a risk
156 of contamination and ensure that medicinal products are stored and maintained in
157 accordance with registered storage conditions.

How about "A filling process ..."

This document took 3 years to publish … they didn't think to pass it to a proof reader?

PharmOut

Weasel Words

The ugliest words

Appropriate (75), suitable (20), sufficient (12)

Slightly less ugly, but still weaselly

General (17) , typical (15), recommend (14), normal (12)

175 176	4.1 The manufacturer should ensure that there are sufficient appropriate personnel, suitably qualified and experienced in the manufacture and testing of sterile medicines and any of the

Final Thoughts

A lot of effort has gone into producing a new Annex, and there is a great deal of useful and appropriate guidance in the draft.

You can't make everybody happy, but you can fix the easy things. There is no excuse for the magnitude of errors in the draft.

We have had to put up with a poorly written, ambiguous Annex for too long. We are entitled to a well written text, with minimal variance of interpretation.

It is hoped that the huge amount of feedback will help accentuate the positive (and eliminate? the negative)

Questions?

Ashley Isbel
Validation Services Manager/Lead Consultant

Ashley.isbel@pharmout.net