Annex 1: 2017

What we know and what we can guess

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PharmOut

This Session

- A quick background on the update
- Sources of this information
- The headlines
- The fine print
- Annex 1 and the TGA

Annex 1 – The Concept Paper

The story to date:

- History of change – 1996, 2003, 2005, 2007 & 2009
- Proposal to review in 2012 and then again 2014
- Concept paper – in 2015Need for change listed in concept paper include:
  - Introduction of the principles of QRM
  - Need to keep up with new technology
  - Omissions – single use closed systems, disposable systems etc.

The Process

Following a *problem statement* a *concept paper* was presented to EMA & PICs and public consultation was held in February 2015 (deadline for *comments* was March 2015).

An inspectors working group was formed to take account of industry and regulatory concerns and to assess requirements for *revision*.

The Process

Joint EU GMP IWP and PIC/S working party established to make changes, including:

- EU – UK(lead), Poland, Germany, Ireland & France
- Rest of World – Australia, USA, Singapore, Canada & Japan

Guide broken up and put to various sub groups who worked on the different sections under lead rapporteur guidance (Andrew Hopkins Expert Inspector MHRA).

The Process

This joint working group has convened regularly over the last 2 years. And significant and robust debate has occurred on a number of issues

The final text has been *adopted by the IWG* and passed to the EC where legal aspects of the changes are being checked and the final document will be *published* with an implementation time period.

So, after 2.5 years, what do we know?

Frustratingly very little

- Some new sections
- Indications of some specific additions
- Indications of some specific clarifications
- Alignment with other standards and GMP guidance
  - ISO 14644
  - Ch. 1, 3 & 5 and Annex 15
- This is a major rewrite … the devil may yet be in the detail

Sources

- Andrew Hopkins presentations
- TGA presentations (e.g. last week's PDA dinner)
- PDA conferences in Germany and USA
  - Presentations
  - 'Off the record' discussions with attendees and members of PDA working groups
- PharmOut connections with EU regulators (AH again)
- Online sources
- PDA & ISPE publications

Annex 1 Proposed Structure

1	Scope	6	Equipment
2	Principle	7	Utilities
3	Pharmaceutical Quality System (PQS)	8	Production & specific technologies
4	Personnel	9	Non-viable & viable process & environmental monitoring
5	Premises	10	Quality control

Apparently the number of clauses has more than doubled

Headlines - Scope

What we think the new version will say	What the current version says	Certainty
Will acknowledge the benefit of the guidance for non-sterile production where microbial/particulate control is important	Nothing - new section	**High**

Headlines - Principle

What we think the new version will say	What the current version says	Certainty
You must document a site/facility contamination control strategy!	Successful sterile manufacture depends on good people and effective QA	**High**

Headlines - PQS

What we think the new version will say	What the current version says	Certainty
No known show-stoppers! But check the fine print …	New section	**Medium**

Headlines - Personnel

What we think the new version will say	What the current version says	Certainty
Gowning requirements updated for A/B • No facial skin exposed – masks/goggles to completely cover skin • Sterile footwear – disinfection and re-use not allowed	Section 43	**High**

Headlines - Premises

What we think the new version will say	What the current version says	Certainty
HEPA filtration required for all classified areas?	Section 1 – filters of appropriate efficiency	Medium
Stronger wording for separate entry and exit change locks?	Section 51 – sometimes desirable	Low
QRM to determine isolator background – D is a minimum standard based on very low risks	Section 23 – inferred that D is appropriate background	Medium
Qualification of cleanrooms should include microbiological aspects	Silent	Medium

Headlines - Equipment

What we think the new version will say	What the current version says	Certainty
No known show-stoppers! But check the fine print …	Nothing to compare	Medium

Headlines - Utilities

What we think the new version will say	What the current version says	Certainty
Data trending from critical utilities - (pure steam? WFI? PW? Compressed gases?)	New section	Medium
Significant guidance on WFI, including information on generation methods and lifecycle requirements	Section 59 – WFI distribution should prevent micro growth	High

Headlines – Production & Specific Tech

What we think the new version will say	What the current version says	Certainty
Significantly more detail around aseptic practice	Section 31-35	Medium
Visual inspection – visual defects to be trended by type. Visual inspection in general far more prescriptive	Nothing equivalent	Medium
PUPSIT largely unchanged, possibly with some concession for smaller manufacturers	Section 113	High

Headlines – Environmental Monitoring

What we think the new version will say	What the current version says	Certainty
5 micron particles ***not*** required for classification (for all classifications)	Section 4 – requires 5 micron for all zones	**High**
5 micron particles required for monitoring (all classifications)	Expected for all zones (singled out for A/B as important)	**High**
Organisms detected in Grade A and B to require identification. Recommended for lower grades	Silent (PI032 requires identification of Grade A isolates)	**Low**
Expectations around frequency of monitoring (especially particulate) for Grade C & D likely to result in increased monitoring events	Section 15 – risked based frequency, more than classification	**Low**
No more averaging statement for microbiological sample	You can average samples	**High**

Headlines – Quality Control

What we think the new version will say	What the current version says	Certainty
Extensive information on sterility test requirements	Section 125 & 127	**High**

Fine Print - Scope

What we think the new version will say	What the current version says	Certainty
Apart from the headline, this section has not been the subject of public discussions.	Nothing – Scope is not defined	**Low**

Fine Print - Principle

What we think the new version will say	What the current version says	Certainty
QRM should be embedded in decision making.	Successful sterile manufacture depends on good people and effective QA	High
More emphasis on good facilities		High
More detail on what constitutes good people		High

Fine Print - PQS

What we think the new version will say	What the current version says	Certainty
Will detail aspects of a PQS which require specific attention and/or attributes for sterile manufacturing	New section	Medium

Fine Print – Personnel

What we think the new version will say	What the current version says	Certainty
Significant increase in focus regarding operator gowning practices, qualification and monitoring	Section 41 – very brief	**High**
Sterile garments required to be changed every working session	Section 44 – similar, but wording slightly ambiguous	**High**
Increased focus on gowning inspection – during gowning? During processing?	Sections 41-45 – no mention of inspection	**Medium**

Fine Print - Premises

What we think the new version will say	What the current version says	Certainty
Clarification for requirements for pass-throughs crossing two grades. CNC to C ✓ D to B?	Section 1 – is silent. Other clauses have been used historically	Medium
Passive pass-throughs not acceptable	Section 1 – is silent	Low
Qualification of cleanrooms according to Annex 15 mandated	Sections 4-7– discuss classification rather than qualification	High
Disinfectant effectiveness to be demonstrated for facility	No equivalent	High
Changes in the description of Grade A and B	Section 3	Medium
Classification of Grade A/B zones may require additional sampling above ISO based on risk	Section 5 – comply with ISO 14644	Medium

Fine Print - Equipment

What we think the new version will say	What the current version says	Certainty
Require PQS based detailed descriptions of key equipment	No equivalent	**Low**

Fine Print - Utilities

What we think the new version will say	What the current version says	Certainty
Bring focus on quality aspects for non-contact utilities (e.g. heating/cooling fluids)	Silent on non-contact utilities	Medium

Fine Print – Production & Specific Tech

What we think the new version will say	What the current version says	Certainty
The use of technology – RABS/isolators, closed systems, automation encouraged to reduce contamination risks	Section 21	**High**
Aseptic operations subject to validated maximum time	No equivalent	**Low**
More detail on technology options, including: • BFS • Single use systems • Closed systems	Section 26 -27 covered BFS	**High**

Fine Print – Environmental Monitoring

What we think the new version will say	What the current version says	Certainty
Environmental monitoring program subject to formal regular review	No equivalent	Medium
Additional specific instructions around how to perform media fills	Section 66-71	Low
Requirements for EM media and testing detailed (growth promotion, stasis, etc)	No equivalent	Low
Change in Grade A cfu limit from <1 to 1	Section 19	High
Strong focus on data trending	Section 20	Low

Fine Print – Quality Control

What we think the new version will say	What the current version says	Certainty
Will allow rapid micro as QC if validated	No equivalent	Medium

Anything Else?

- Until we get the document, we won't know for sure
- If there really is 100+ more clauses, there's bound to be additional challenges
- Expect that rapporteur information has given fair warning on big issues
- Hopefully we can see a removal of clarity issues (but I'm not counting on it)

The TGA and Annex 1

The TGA Dilemma

Overdue adoption of new PE009. Late Annex 1.

- Do they adopt v13 now without Annex 1 (2017)
- If so, can they de facto adopt new Annex 1 through an interpretation, guidance or TGO?
- Will they push for an automatic adoption mechanism?
- If not, do they wait even longer for v14 (probably not until Q3 2018)

ANY QUESTIONS?