Update on revision of Annex 1

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11th July 2016

National GMP & Validation Forum

Hosted by PharmOut

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Overview

Why change Annex 1 and how these changes may impact you?

Annex 1 in the context of EU regulations

Related EU Regulatory documents & process of EU GMP updates

The concept paper

- History of changes to Annex 1
- What changes can we work out?
- What are we being told about the changes?

When can we expect the first draft of changes for comment?

Why change Annex 1

- Revision is overdue – last revised 2009
- There are questions about logic of flow and ambiguities in current version
- Updates to take account of scientific & technical developments
- Changes to other (non GMP) regulations
- Manufacture of Sterile products generates a lot of inspection deficiencies i.e. additional guidance needed

- Significance – this is an EU GMP update and a PIC/S update

EU Regulatory Changes

Annex 1 is just one of a range of changes to EU GMP others include:

- Chapters 3 & 5 and
- Annex 15, 16, and 17

The new Annex changes will need to be fully integrated into the Guide

It should be noted that there are other on-going (non GMP) changes that link to EU GMP Annex 1 that also need to be considered:

- Changes to dossiers in line with Annex 1 changes
- EDQM changes – Ph. Eur. changes
- Changes to ISO standards
- Changes to Q & As

Recent draft guidance on Sterilization of Drug Products, APIs and Excipients

Guideline on the sterilisation of the medicinal product,
active substance, excipient and primary container

Out for public consultation until October 2016

Provides guidance on the selection of appropriate methods of sterilisation for sterile products & documentation expected in the MAH / Variation (quality dossier). It states that terminal sterilisation is the method of choice (whenever possible) & provides information on when other processes could be accepted

Some interesting points:

"The use of the reference condition of Ph.Eur (>121 / 15min)"…"validation data of the sterilisation cycle is not required."

This of course is written from the point of view of the dossier.

The phrasing of the document will need to be carefully considered.

Recent changes related to Water for Injection (WFI)

The Ph. Eur. Commission revised monograph on Water for Injections

Until now the Ph.Eur. Monograph for WFI has been limited to distillation only.

A revised monograph will be published in Ph.Eur 9.1 effective April 2017.

Revision allows for production of WFI by a purification process equivalent to distillation (such as reverse osmosis) coupled with "appropriate techniques".

- Equivalence does not simply mean compliance with specification but also considers the robustness of the manufacturing process
- The use of a non-distillation approach requires notice to be given to the supervisory authority before implementation

Changes to ISO 14644 standard

Some Changes:

- Removal of 5 micron sample level
- Increase in the number of sampling points
- ISO 21501-4 compliant particle monitors

Most importantly changes impacting the clean room classification take place from Jan 2016 and the new Annex 1 will not be available for some time.

Q: Should a cleanroom certified to the current Annex 1 reference the 1999 version of ISO14644-1 or be replaced with the sample point selection from the revised 2015 version? The sample volume for certification is defined in Annex 1 and is current – at least until reviewed.

A:IWG are going to publish Q and A along the lines that both approaches will be accepted for a 12 month period to allow the re-issuance of the Annex 1

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 2015 (Note "cohesion" EU and PIC/S)
- Need 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.
- A lot of suggestions were made as to what needed changing by those who commented on draft concept paper… a lot of inspectorate work...

How the process of revision of EU Guide works

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*.

This joint working group has commenced work on revision and will present a *draft for public consultation* in Q3 2016. Comments will then be *reviewed and text revised* in line with the comments.

The final text will then be *adopted by the IWG* and passed to the EC where legal aspects of the changes will be checked and the final document will be *publish* with an implementation time period.

Who is making the changes and methodology

Joint EU GMP IWP and PIC/S working party established to make changes – most of the Agency players are known:

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

Methodology – guide broken up and put out to various sub groups who have been working on the different sections. Now coming together under lead rapporteur guidance (Andrew Hopkins Expert Inspector MHRA).

Acknowledgement; Much of the information in these slides is taken from a presentation at the MHRA Symposium in 2015. Thanks to Andrew Hopkins Expert Inspector MHRA for his kind permission to use this content.

What is going to change – what do we know today – GMP aspects

Common sense dictates that the new Annex must be integrated into the rest of EU GMP e.g.

- Chapter 5, a QRM process for micro controls with technical and organizational measures to control risk of cross contamination with associated periodic review
- Annex 15, validated micro methods and confirmation that recovery of organisms not influenced by test method

- Also will need to take account of deficiencies (particularly quality system) seen by inspectors in sterile manufacture inspections – refer to published deficiencies

What is going to change ? – what we know today – non GMP updates

As per earlier the new Annex must take account of non GMP changes:

- ISO 14644 (Clean Room Qualification) changes such as classification nomenclature, increased sample number (same size) & guidance on sample locations etc. Question about 5 micron ?
- WFI Monograph – preparation other than by Distillation to be allowed under certain circumstances – new monograph 2017
- GMP ATMPs (EC Document) – to be produced in 2016/17 but consultation on-going now.

Annex 1 Proposed Structure

1. Scope
2. Principles
3. General
4. Pharmaceutical Quality System (PQS)
5. Personnel
6. Premises
7. Equipment & Utilities
8. Production & Specific Technologies
9. Non Viable and Viable Environmental & process monitoring
10. Quality Control

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Title, Scope and Principles

Title – No change

Scope – Much wider than previous (e.g. will cover ointments and creams and biologicals) but still classed as revision not rewrite

Principles – Existing requirements of GMP will be detailed (EU Directive 2003/94 article 5 and EU Directive 2001/83 article 23) and a reference to chapters 3 and 5 of EU GMP and need to keep up with current technology to be re -enforced

General, Pharmaceutical Quality System (PQS) & Personnel

PQS – Greater emphasis to be placed on elements of Chapter One of EU Guide i.e. change control, investigations and CAPA. The need for risk management process (QRM), root cause analysis processes and product impact assessment to be re-enforced.

Personnel – Right people to be available, they must be appropriately knowledgeable and properly trained. There will be a greater focus on keeping the operator away from the product/process and keeping up with new technologies e.g. need for operator goggles

Premises and Equipment

- As indicated there will be a greater focus on keeping the operator away from the product hence inclusion of single use /disposables closed systems and aseptic connectors and how these are integrated into the QRM system will feature.
- New technology to be included – LABS, RABs and Isolators
- Clean Room Qualification is to be looked at:
  - ISO 14644
  - 5.0 micron size – to be kept (just for monitoring not qualification!)

Utilities

- This paragraph will be considerably expanded – it could be that it will move to a new separate section of the Guide (still under discussion).
- As a minimum it will cover:
  - General services e.g. compressed gases
  - Production of WFI (by distillation and by other means)
  - Biofilms

Production & Specific Technologies

Any omissions and discussion points from earlier editions to be clarified and Technology updates will be included e.g. revision will include sections on:

- Pre-Use/Post Sterilisation Integrity Testing
- Blow Fill Seal
- Form Fill Seal
- Disposables

Non Viable and Viable Environmental and Process Monitoring

- All monitoring to be in one place in the revised text – this to give improved logic of flow
- Process Simulations and all viable & non viable monitoring (except sterility test) to be included. Rapid Microbial Methods to be included
- Monitoring is to be part of QRM process with risk elements re-enforced i.e. facility and process should be fully known and understood by operators and monitoring appropriately designed e.g. interventions to be based on process knowledge & associated QRM
- Process simulation:
    - APIs – campaign or tail gate media fills to be included
    - Small scale manufacture – priority focus will be operators

Conclusions

- Although I have outlined what we can expect as far as we know today we will have to wait and see what materializes – dates a little like the proposals to review i.e. Q2 2016 now Q3 2016
- One aspect is clear – much like Annex 15 (Validation) there will be a need to ensure the Annex maintains its diversity i.e. caters for those with new technologies and those still using older systems whilst at the same time ensuring older systems not an excuse for poor GMP
- Given the interest it is also clear that the discussion about the actual changes which will go forward will generate a lot of comment on the draft revised text

Useful links

Title: Guideline on the sterilization of the medicinal product, active substance, excipient and primary container

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/04/WC500204724.pdf

Title: Ph. Eur. Commission adopts revised monograph on Water for Injections

https://www.edqm.eu/en/news/ph-eur-commission-adopts-revised-monograph-water-injections

https://www.edqm.eu/sites/default/files/edqm_webinar_slides_water_for_injections_22_april_2015.pdf

Title: MHRA GMP deficiencies

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/448609/Good_manufacturing_practice_inspection_deficiencies_2013.pdf

Title: EMA (EU GMP Guide)

http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

Glossary

EDQM – European Directorate of Quality of Medicines
IWP – Inspectors Working Party
Ph.Eur. – European Pharmacopoeia
QRM –Quality Risk Management
PQS – Pharmaceutical Quality System
BFS – Blow Fill Seal
FFS – Form Fill Seal
PUPSIT – Pre-use/post sterilization Integrity testing
NVP – Non viable particles
LABS – Limited Access Barrier Systems
RABS – Restricted Access Barrier Systems
WFI – Water for Injection
RO – Reverse Osmosis
ATMP – Advanced Therapy Medicinal Products

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Thank you for your time. Questions?

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