TECH TALK: WHAT IS LIKELY TO BE IN THE NEW ANNEX 1?

by John Johnson

At the time of going to press, there are no certainties on what will be in the revision of Annex 1 of EudraLex Volume IV but our research has focused on:

- What the headlines are in terms of
  - Clarification
  - Corrections
  - New expectations
  - Areas that required or will require further discussion
- What effect this will have on the pharma industry
  - For steriles manufacturing companies
  - For other dosage form manufacturers

As covered in Journal 37's Summary of Anticipated Changes to Annex 1 article, the draft concept paper was issued by MHRA to the EMA Inspection Working Group (EMA IWG) in September 2014 and was worked on by an EMA team (rapporteur: Andy Hopkins MHRA) leading to submission of a full draft to EMA IWG in mid-2016. A paper will be published in April or May 2017 (during publication of this edition of the Journal).

These are likely to be the key revisions:

Section	Notes
1. Scope	Provides better linkage to other related parts of GMP such as 2003/94 Article 5, 2001/83 Article 23, Chapter 3: Premises and Equipment and Chapter 5.10 on protection from microbial and other contamination
2. Principles	Reinforces existing GMP requirements and removes ambiguity
3. General	Corrects some existing contradictions
4. Pharmaceutical Quality System	Major re-emphasis on the need for proactive and thorough implementation of quality risk management (with reference to ICH Q9), availability of documented evidence of compliance to ICH Q9 and adoption of the key risk management tools across the sterile production process Underscores the need for a demonstrably timely, thorough and scientifically derived failure investigation process that includes a credible and justifiable product impact assessment Key message: Risk assessment cannot be used to justify bad practice, especially in the aseptic core

5. Personnel	Mandatory requirement for goggles in the critical zones Need to assess, train and enforce the right staff behaviors through initial and continued education programs Need to define, train, assess, enforce and continually verify the correct aseptic technique
6. Premises	Implementation of ISO 14644; definition of cleanrooms and their environment Reinforces the need for real-time trending, definition of out-of-trend and timely response to alarms Clarifies the need for monitoring 5 µm particles in cleanrooms
7. Equipment	Guidance on the need for separation of process from operators and other sources of contamination; special requirements for restricted access barriers (RABs) and isolators
8. Utilities	Adoption of common controls and monitors for compressed air and water systems Special considerations for the prevention and removal of biofilms in water systems Generation of WFI will align with the European Pharmacopoeia (the use of reverse osmosis to produce WFI is permitted)
9. Production	Two areas required a lot of discussion (see below) Special considerations for small batch production, ATMPs, 'specials' and other technologies such as blow-fill-seal
10. Monitoring	Adoption and reference to rapid microbial identification technology Clarification on the design and interpretation of process simulation trials Clarification of what continuous monitoring of cleanrooms means, both for viable and non-viable monitoring methods Need for a documented risk assessment when deriving an environmental monitoring program
11. Quality Control	No significant changes expected
12. Glossary	Now included

The key areas requiring a lot of discussion were:

Section 9. Production – Pre-Use Post-Sterilization Integrity Testing (PUPSIT)

Industry had long argued that PUPSIT has a theoretical or exceptional risk of damaging filters immediately before use or could contaminate the filter media, and that the act of sterilization of the filters has been proven not to affect the log reduction value that filters are expected to exhibit. As such, in some quarters, PUPSIT had been eliminated from the process with supplier certification and/or pre-use, pre-sterilization integrity testing being relied on. In other

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quarters, the opposite had been argued with no accepted justification for removing this critical filter integrity test (performed immediately before use). It is expected that PUPSIT will prevail and scientific justifications for alternatives may be challenged at regulatory inspection.

Section 9. Production – Integrity Testing of the Final Drug Product

As technology has improved, 100 percent container closure integrity has become a compelling method for improving product quality, but the technology doesn't work reliably for all container/closure types yet. Offline sampling and testing (for example dye bath testing) or 100 percent inspection for gross container defects is still prevalent (with many companies also using bacterial challenge tests or leak rate testing during initial and periodic validation studies). However, regulators and industry want to see technology developed that would make 100 percent online container integrity testing possible and economically viable. Until there is a breakthrough in the technology that sees all container types capable of being tested online, it looks like offline, periodic testing for container closure integrity is here to stay.

SO, WHAT HAPPENS NEXT?

> Adoption of the new annex is expected by end of 2017 and will be enforceable at some stage afterwards

> Keep up-to-date with the changes via our webinars; view our 2017 schedule at **www.nsf.org/info/pharma-webinars** or watch our pre-recorded webinars in our pharma biotech resource library at **www.nsf.org/info/pblibrary**

ABOUT THE AUTHOR

John Johnson is passionate about helping organizations foresee and overcome the barriers to sustainable long-term growth. He brings 28 years' experience across a range of companies in the pharmaceutical and healthcare industry. He has worked in small, medium and large pharma biotech companies across the product lifecycle for a wide range of dosage forms, holding senior operational and corporate-level experience in operations and quality assurance and leading multinational companies in many strategic projects.

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