Introduction

The PHSS and collaboration partners wish to thank the EC/EMA for the opportunity to contribute as a commenting group on Annex 1 version 12 within the Targeted Consultation. The collaboration partners that joined in consolidating comments with the PHSS are: The Joint Pharmaceutical Analysis Group (JPAG) who are jointly sponsored by the Royal Pharmaceutical Society UK and the Royal Society of Chemistry, the Pharmaceutical Quality Group UK (PQG) and R3 Nordic. Collectively we have over 3000 members.

This covering letter is intended to provide an insight into the PHSS and partners commenting process and their comment submissions made via the official EC Commenting form; Excel format.

PHSS and partners recognise the difficulties and complexities involved in creating this Annex and considered version 12 of Annex 1 was a considerable improvement over the original version that received so many comments in the Stakeholder consultation. In particular we noted improvements around the clarity in requirements to follow QRM principles for the complete Annex 1 and the more specific requirement to prepare a Contamination Control Strategy (CCS) for a given product in manufacturing / processing.

It is understood how challenging it is to balance between regulatory requirements to follow principles and more prescriptive guidance. To achieve such balance it is essential clarity is provided.

PHSS and collaboration partners Annex 1 version 12 commenting

The PHSS commenting has focused around adding clarity where Annex 1 version 12 text is either open to interpretation, lacks content to ensure clarity, or has possible conflicts in current good practice.

To assist review of the Excel commenting form the PHSS have created Tab-pages for each specific topic / section and associated Annex 1 clauses.

There were two sections of Annex 1 that received significant comments in the PHSS review process where it was considered more substantial revision was required to add the necessary clarity. Other comments relate to adding clarity to existing clauses. In addition the PHSS have added Page Tabs that cover other significant comments. We stress that these are not a repeat of previous submissions, but have been identified as requiring revision to add clarity.

For easier review the PHSS include as attachments some word format working sheets for the Qualification and Barrier technology sections that aligns current text alongside suggested text together with supporting justifications for the proposed changes.

The use of examples can assist clarity but consideration is needed that examples are current and inclusive of new and alternative technologies. In PHSS commenting a case is made for inclusion of the new and proven technology of no-touch-transfer (NTT) for ready to use (RTU) product container entry into Grade A filling zones. There is a concern if only basic material transfer examples are provided these could be taken as the GMP expectation without consideration to new technologies if there is no reference in Annex 1. As a general principle examples should not be a limitation to new developments.
Pharmaceutical & Healthcare Sciences Society Covering letter for commenting in the EU GMP Annex 1 Targeted consultation

Two sections that the PHSS considered in need for most revision to add clarity

Qualification of Cleanrooms and Clean air equipment (including classification) was considered to require revision to better align with the ISO 14644 series of standards that has a focus on Classification by airborne particle concentration (Generic standards for all sectors) and full Pharmaceutical / Biopharmaceutical qualification requirements that includes microbiological control and associated monitoring of both surface and airborne contamination.

Industry practice typically takes a phased approach where Classification is performed in the lead up to full qualification to verify particle clearance performance related to particle generation at rest and in operation. The in-operation particle clearance studies for classification considers simulated occupancy (particle loading from maximum number of operators) and operating equipment that adds to the particle load [these studies are not considered a full APS].

The suggestion in Annex 1 version 12 that in operation classification studies can be completed as late as and combined with the aseptic process simulation (8.23) changes the complete context of the phased approach and is considered to put the APS at risk of both interference from parallel studies and the lack of assurance that particulate clearance is under control before entering subsequent phases of APS and Media fills.

Classification in Annex 1 considers compliance only to >0.5micron particle sizes although later routine monitoring requirements include 0.5micron and 5.0micron particle sizes. As this is the case it makes sense to monitor ‘for information’ 5.0micron particle sizes in Classification with guidance values to follow set out in Table 2.

Barrier Technology is such a significant contamination control attribute where Isolators and RABS are applied to separate the most contaminating source, people, from process / product it is essential there is clear differentiation of these Barrier Technologies. We consider Annex 1 Version 12 mixes requirements for Isolators and RABS without clear differentiation. In particular the difference in barrier separation defined as Open and Closed Barrier systems needs to be clear in the body of the text and not just in the glossary without connection to relevant clauses.

RABS and Isolators have a different approach to managing assurance of sterility of in-direct product contact parts and the expectations and requirements should be made clear. For RABS pre-sterilised in-direct product contact parts are installed into a Grade A environment (typically established using manual disinfection) where the assembly of parts has to assure that the Grade A environment and sterility of parts are not compromised. For Isolators the Grade A environment is typically established (via VHP) after installation of pre-sterilised in-direct product contact parts so bio-burden control and protection of sterilised parts from extraneous contamination becomes the priority. Two very different approaches.

Such fundamental differences in Barrier technologies and managing installation of sterilised in-direct product contacting parts would benefit being included in Annex 1 to provide clear guidance on application of these important technologies that support contamination control and subsequently the safety of patients.

Signed on behalf of the PHSS:

Jenni Tranter, PHSS Chair person

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