



31 March, 2015

European Medicines Agency
GMP/GDP Inspectors Working Group (GMP/GDP IWG)
30 Churchill Place
Canary Wharf
London E14 5EU United Kingdom

Subject: MA/INS/GMP/735037/2014
Annex 1 of the GMP Guidelines on Good Manufacturing Practice - Manufacture of Sterile
Medicinal Products

Dear Sir or Madam,

Thank you for the opportunity to comment on Annex 1 of the GMP Guidelines on Good Manufacturing Practice - Manufacture of Sterile Medicinal Products. Both A3P and ISPE are in favor of a complete revision of Annex 1 in order to remove inaccuracies and ambiguity, and to clarify GMP expectations and interpretations. There is an expectation by both associations that as part of this revision the opportunity would be taken to introduce new technologies for the production and control of pharmaceutical products.

Please find attached general comments from A3P and ISPE related to Annex 1. The attached specific comments reflect the commentary of ISPE only; additional specific comments will be submitted by A3P separately.

The International Society for Pharmaceutical Engineering (ISPE) is an individual membership Society of more than 20,000 professionals involved in the manufacture of pharmaceuticals and related products. All scientific and technical areas of the pharmaceutical manufacturing industry are represented among the ISPE membership. ISPE is committed to creating a forum for uniting the world's pharmaceutical manufacturing community and regulators.

We thank you for the opportunity to provide our feedback, and please accept our highest considerations.

Yours sincerely,

John Bournas
President/CEO, ISPE

cc: Roland Guinet, PhD, A3P



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 March, 2015

Submission of comments on annex 1 of the guidelines on good manufacturing practice – manufacture of sterile medicinal products

Comments from:

A3P

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Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).



1. General comments

| Stakeholder number | General comment (if any) | Outcome (if applicable) |
|--|---|--|
| <i>(To be completed by the Agency)</i> | New aseptic filling technologies become available, bringing specificities that are not addressed by the current version of the annex 1, what leads to some uncertainty. | <i>(To be completed by the Agency)</i> |
| | <p>A3P and ISPE are in favour of a comprehensive and complete revision of annex 1 in order, to correct inaccuracies, to remove ambiguity by giving clearer interpretations of GMP expectations and to introduce new technologies for the production and control of pharmaceutical products.</p> <p>- The current title could be retained or modified as appropriate e.g. “Manufacture of Pharmaceutical Products in Controlled Environments ” is a potential suggested title.</p> | |
| | <p>A3P and ISPE propose:</p> <ul style="list-style-type: none"> Annex 1 should be reorganized under the following headings: following any general introduction Each point of the revised Annex 1 should be followed by a section rationale to clarify regulatory expectations and to avoid misunderstandings | |
| | <p>Proposed Summary for the future Annex 1</p> <p>Principle</p> <p>1 Quality Management System</p> <p>2 Personnel</p> <p>3 Premises and equipment</p> <p>3.1 Premises</p> | |

| Stakeholder number <i>(To be completed by the Agency)</i> | General comment (if any) New aseptic filling technologies become available, bringing specificities that are not addressed by the current version of the annex 1, what leads to some uncertainty. | Outcome (if applicable) <i>(To be completed by the Agency)</i> |
|--|---|---|
| | <p>Cleanroom classification</p> <p>Cleanroom monitoring</p> <p>Conventional cleanrooms</p> <p><i>Product sterilized in their final containers</i></p> <p><i>Aseptic processing</i></p> <p>Blow-Fill-Seal technologies</p> <p>Closed systems (Barrier technologies)</p> <p><i>RABS</i></p> <p><i>Isolators</i></p> <p>Airlocks and changing rooms</p> <p>Processing areas</p> <p>Dedicated areas</p> <p>Technical areas</p> <p>3.2 Equipment</p> <p>Qualification</p> <p>Metrology</p> <p>Maintenance</p> | |

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|--|--|---|
| | <p>Manufacturing equipment</p> <p>Sterilization equipment</p> <p>Filling equipment</p> <p>Transferring equipment</p> <p>Water and steam</p> <p>Others fluids</p> <p>3.3 Sanitation</p> <p>4 Documentation</p> <p>5 Production</p> <p>Raw materials</p> <p>Packaging materials</p> <p>Bulk products</p> <p>Sterilization</p> <p><i>Heat sterilization</i></p> <p><i>Moist heat sterilization</i></p> <p><i>Dry heat sterilization</i></p> <p><i>Sterilization by radiation</i></p> | |

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|--|--|---|
| | <p><i>Sterilization with ethylene oxide</i></p> <p><i>Others sterilization gases</i></p> <p><i>Filtration</i></p> <p>Filling</p> <p>Lyophilisation</p> <p>Validation</p> <p>Finishing of sterile products</p> <p>6 Quality Control</p> <p>Sampling and reserve samples</p> <p>Microbiological methods</p> <p>Sterility testing</p> <p>OOS results</p> <p>7 Contracting and outsourcing</p> <p>8 Complaints handling and recalls</p> <p>9 Self-inspection</p> | |
| | A3P and ISPE propose: that there is a statement at the start of the new | |

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| | annex which promotes the incorporation and use of Quality Risk management approaches to develop and implement control strategies and acceptance criteria which may affect the Sterility Assurance of sterile products. | |
| | A3P and ISPE propose: $\geq 5 \mu\text{m}$ particle limits should be maintained for classification purposes as well as for routine monitoring: regardless as to whether this size of particles is considered in revisions to ISO 14644-1 for ISO 5 and other guidelines such particles are well recognized as carriers of microorganisms and hence monitoring should be retained. | |
| | A3P & ISPE propose: the inclusion of additional recommendations for initial microbiological evaluation and routine monitoring of clean zones following ISO 14698-1. This guidance should include frequencies, timing, duration, and time limit between sampling and incubation. The importance of trend analyses should be reinforced in addition to class specification. | |
| | A3P & ISPE propose: a Barrier Technology chapter be developed in order to include Restricted Access Barrier System (RABS) together with isolators, and to encourage their use avoiding direct human interventions for aseptic process. If justified, Barrier Technology systems could have specific environmental monitoring programmes and aseptic process simulations. | |
| | A3P and ISPE propose: a routine point of use packaging integrity check for sterile components, containers and equipment not sterilised in the primary manufacturing site. | |
| | A3P & ISPE propose: new control technologies should be promoted in | |

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|--|---|---|
| | the revised annex. This to include: 100% Container Closure Integrity (CCI), Rapid Microbiological Methods (RMM) and Real Time Viable Particle Monitoring. | |
| | A3P & ISPE propose: aseptic process simulations should be performed for each aseptic production step. The target should always be zero growth. Any CAPA for one growth should be related to investigation results. | |
| | A3P & ISPE propose: for moist heat sterilization steam quality control checks should be robust and align with current standards. | |
| | A3P & ISPE propose: greater references to other aligned regulatory guidelines and state of the art publications e.g. WHO GMP and technical reports which give more guidance. | |
| | A3P & ISPE propose: that as far as possible the new annex avoids the use of expressions “as far as practicable”, “wherever possible”, “periodic”, “when appropriate” in order that guidance given is clear and unambiguous. | |
| | A3P & ISPE propose: The word “contamination” should be restricted and used only for the action. Alternative wording such as “contaminant agents” should be used. | |

2. Specific comments on text

| Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i> | Stakeholder number <i>(To be completed by the Agency)</i> | Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i> | Outcome <i>(To be completed by the Agency)</i> |
|--|--|---|---|
| After articles 26-27 about BFS | | <p>Comment: Proposal: to add a paragraph about the use of new closed vial technology as an alternative technique for aseptic filling; in a similar way BFS is addressed in annex 1.</p> <p>Proposed change: paragraph to be introduced after article 27: Introduction of new technology using pre-sterilized vials with a system to guarantee integrity closure under grade A air flow.</p> <p>Closed vial filling is based on purpose built machines that proceed with sterile closed vials; the stopper of these vials can be punctured without damage by the filling needle and immediately restored (resealed) using a laser beam. Closed vials are produced in ISO_5 cleanrooms and further sterilized by irradiation before being delivered to the pharmaceutical manufacturer. Such filling machines should be installed in at least a grade C environment, provided that a grade A environment covers and surrounds the filling station. The applicable environmental and gowning requirements are identical to those set for the BFS technology.</p> | |
| §3, Grade B | | <p>Comment: That "... this is the background environment for the grade A zone" should be more clearly described particularly in relation to the location of isolators and RABS.</p> | |

| Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i> | Stakeholder number <i>(To be completed by the Agency)</i> | Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i> | Outcome <i>(To be completed by the Agency)</i> |
|--|--|--|---|
| | | <p>Proposed change: this is the background environment for the grade A zone without restricted access barrier technology, see also §21 Isolator technology.</p> | |
| §3 | | <p>Comment: Additional guidance should be provided in relation to the sentence: "In order to meet "in operation" conditions these areas should be designed to reach certain specified air-cleanliness levels in the "at rest" occupancy state."</p> <p>Proposed change: In order to meet "in operation" conditions these areas should be designed to reach certain specified air-cleanliness levels In the "at rest" occupancy state." " Aspects that need to be considered for the "at rest" occupancy state include but are not limited to: the number of personnel working in this area, activity and clothing (cleanroom garment) of personnel, necessary heat removal for personnel comfort, particle disposal of process and intended air-stream within this area caused by the positioning of supply-air grids and extract-air grids (e.g. extract-air grid in the ceiling near the supply-air-grid can cause short circuits of air-flow)."</p> | |
| §3 | | <p>Comment: Clarification and a better definition of what is considered the "at rest" and "in operation" states is required to be detailed in the new annex e.g. does "in operation" cover the maximum allowed people in the room and all furniture or the normal number of people and furniture in the room during normal production.</p> | |
| N° 21/26/28 | | <p>Comment: Clarification regarding minimum requirements for Isolator technology, Blow/fill/seal technology and terminally sterilized products is required in the new annex.</p> | |

| Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i> | Stakeholder number <i>(To be completed by the Agency)</i> | Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i> | Outcome <i>(To be completed by the Agency)</i> |
|--|--|--|---|
| N° 44 | | <p>Comment: §44 addresses clothing requirements from outside to graded area.</p> <p>Proposal: If this paragraph is incorporated into the beginning of 43 it could address all gowning change from street to clean areas</p> | |
| N° 116 - 120 | | <p>Comment: Clarification is required (in the preamble for finishing of sterile products) in the new annex regarding interpretation of air classification for closed vials existing from class A to class C area: under what circumstances does this actually constitute a problem (given these vials are closed and the core pressure is outwards).</p> | |

Please add more rows if needed.