Application of Annex 1 Principles to Biological Drug Substance Manufacturing.

GMP Information Seminar; 27th September 2012

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Biologics: Annex 1 Application

- Annex 2 status update
- Introduction: Annex 2 and Annex 1
- Examples of Annex 1 Application to Biological DS Manufacturing
• Annex 2 relates to the Manufacture of Biological Active Substances and Medicinal Products for Human Use

• Has been updated and published on the European Commission website on 6\textsuperscript{th} September 2012.

• Implementation date is 31\textsuperscript{st} January 2012.

• Previous Presentation on Major Changes
  • IMB Information Day 2010.
Before we start...

A quick question...

- From which point do you think Annex 1 is relevant to Biological DS manufacture?

1. Purification
2. Viral Inactivation & Removal
3. Entire Process
4. Production BioRx
Assumptions of this Presentation:

• Biological DS process is low bioburden
In the revised Annex 2:

- Premises and Equipment
  - Paragraph 6

- Prevention of extraneous contamination
• Where processes are not closed...control measures should be put in place, including engineering and environmental controls on the basis of QRM principles

• These QRM principles should take into account the principles and guidance in the appropriate sections of Annex 1...when selecting environmental classification cascades and associated controls.
Looking at Annex 1:

- Title: “Manufacture of Sterile Medicinal Products”
  - Title does not reflect the Annex’ entire contents
  - Only EU GMP guidance on all classified rooms (Grades A to D)
Some good and some not so good news!

The good news:

- It is not intended to apply Annex 1 in its entirety
- No new expectations to manufacture in a sterile environment beyond that required by the Clinical Trial Authorisation or Marketing Authorisation
• The not so good news:

  ▪ Justification for the level of Annex 1 application is required

  ▪ Reference to this presentation is not considered justification!

  ▪ Documented Risk Assessment
Biological DS: Controls

- Contamination Control
  - Engineering solutions to provide primary containment (closed systems)
  - Equipment Cleaning and Sanitisation
- Area Classification
- Aseptic Technique
- Training & Garbing
- Environmental Monitoring
Biological DS: Annex 1 Example

• Inoculation/Cell culture passage:
  • Occurs in a Biological Safety Cabinet (BSC)
  • Typically Grade C background with Grade A supply BSC is considered acceptable.

• Appropriate Garb for Grade C area
  ▪ Consideration for appropriate garb within the BSC critical zone
    ▪ e.g. Gauntlets/gloves
• Environmental Monitoring:
  • BSC is Grade A supply
  • Continuous non viable monitoring of BSC is not necessarily expected on a per batch basis.
  • Other forms of batch specific EM are expected
    ▪ Settle plates
    ▪ Personnel monitoring.

• Approach must be justified.
Aseptic Technique should be applied to both set up and manipulations.

Aseptic practice takes on greater importance.

Robust training and ongoing assessment of Operators should include:
  - Training (theoretical and practical)
  - Assessment
  - Disqualification
  - Periodic Requalification
Process Simulation

- Process Simulation of BSC inoculation / passaging steps can be a useful aid in assessment of Operators asepsis

- It is not generally expected that process simulation for the entire production process is performed unless required by the CTA or MA
• Other areas to consider?
  • Risk Assess manufacturing process for potential contamination points
    ▪ E.g. Areas of aseptic or clean as possible connection.

• Risk Assessment is a living document
  ▪ maintained
  ▪ re-evaluated at least annually
  ▪ consider EM program effectiveness
In Summary

• Should take into account the principles and guidance in the appropriate sections of Annex 1 when selecting environmental classification cascades and associated controls.

• No new expectations to manufacture in a sterile environment beyond that required by the CTA or MA.

• Sites are expected to have documented justification of their approach.
Questions
Thank You for Listening

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