IRISH MEDICINES BOARD

Application of Annex 1 Principles to Biological Drug Substance Manufacturing.

GMP Information Seminar; 27th September 2012

Paul Moody,
Inspector

Biologics: Annex 1 Application

- Annex 2 status update
- Introduction: Annex 2 and Annex1
- Examples of Annex 1 Application to Biological DS Manufacturing

IRISH MEDICINES BOARD

Biologics: Annex 2 Status

- 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 6th September 2012.
- Implementation date is 31st January 2012.
- Previous Presentation on Major Changes
  - IMB Information Day 2010.

IRISH MEDICINES BOARD

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

IRISH MEDICINES BOARD

Biologicals: Annex 2 and Annex 1

Assumptions of this Presentation:

- Biological DS process is low bioburden

IRISH MEDICINES BOARD

Biological DS: Annex 1 reference

- In the revised Annex 2:
  - Premises and Equipment
    - Paragraph 6
  - Prevention of extraneous contamination

IRISH MEDICINES BOARD

Biological DS: Annex 2 Text

- 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.

IRISH MEDICINES BOARD

Biological DS: Annex 1 Relevance

- 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)

IRISH MEDICINES BOARD

Biological DS: Annex 1 Relevance

- 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

IRISH MEDICINES BOARD

Biological DS: Annex 1 Relevance

- 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

IRISH MEDICINES BOARD

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

IRISH MEDICINES BOARD

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

IRISH MEDICINES BOARD

Biological DS: Annex 1 Examples

- 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.

IRISH MEDICINES BOARD

Biological DS: Asepsis

- 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

IRISH MEDICINES BOARD

Biological DS: Annex 1 Example

- 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

IRISH MEDICINES BOARD

Biological DS: Annex 1 Example

- 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

IRISH MEDICINES BOARD

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.

IRISH MEDICINES BOARD

Link to the Revised Annex 2

http://ec.europa.eu/health/files/eudralex/vol-4/vol4-an2_2012-06_en.pdf

IRISH MEDICINES BOARD

Link to Presentation on Major Changes

http://www.imb.ie/images/uploaded/documents/GMP info day presentations/8 Annex 2 Update Paul Moody.pdf

IRISH MEDICINES BOARD

Questions

IRISH MEDICINES BOARD

Thank You for Listening

Paul.Moody@imb.ie
Compliance@imb.ie
+353 (0)1 676 4971

IRISH MEDICINES BOARD