GMP Training Course
20-21 October 2009

EU GMP Requirements

Sterile medicinal product
Dr. Martin Melzer
Pharmacist / GMP Inspector

Tel.: + 49 (0) 511 9096 450

martin.melzer@gaa-h.niedersachsen.de
Agenda

- Relevant and legally binding documents
  - EU GMP annex 1
  - European Pharmacopoeia
  - PIC/ S

- Other helpful documents
  - EN ISO 14644-1, -2
  - ISPE
  - FDA Aseptic Processing guide
EU GMP Annex 1

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels, 15 February 2008

EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines to
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

Annex 1
Manufacture of Sterile Medicinal Products

Coming into operation: 1.3.2009
Coming into operation (capping of freeze-dried vials): 1.3.2010
EU GMP Annex 1

- Why is sterile manufacturing regulated in a separate annex?
  - Annex 1 contains guidance to minimize the risk of contamination
    - Microbes
    - Particles
    - Pyrogen

- What is the not the goal of Annex 1?
  - it must not be followed just by law
  - others approached should not be forbidden by the CA
EU GMP Annex 1 - Basic Elements

- Clean room classification
- Monitoring
- Technologies
- Personnel
- Premises
- Equipment
- Sanitation
- Processing
- Sterilisation Methods
- Aseptical Filling
- Finishing
EU GMP Annex 1- Basic Elements

- Clean room classification
- Monitoring
- Technologies
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- Premises
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- Sterilisation Methods
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- Finishing
Clean room classification A, B, C,
- Particle limits at rest/ in operation
- Microbiological limits in operation

Classification
- Only particle contamination is used for classification purposes
- Classification ≠ Monitoring
- In accordance with EN ISO 14644 (Methodology)
- During normal production, media fills (worst case scenario)
**EU GMP Annex 1- Basic Elements**

**Clean Room Classification**

<table>
<thead>
<tr>
<th>Grade</th>
<th>At rest</th>
<th>In operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 μm</td>
<td>5.0μm</td>
</tr>
<tr>
<td>A</td>
<td>3 520</td>
<td>20</td>
</tr>
<tr>
<td>B</td>
<td>3 520</td>
<td>29</td>
</tr>
<tr>
<td>C</td>
<td>352 000</td>
<td>2 900</td>
</tr>
<tr>
<td>D</td>
<td>3 520 000</td>
<td>29 000</td>
</tr>
</tbody>
</table>

**Recommended limits for microbial contamination (a)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>air sample cfu/m³</th>
<th>settle plates (diameter 90 mm) cfu/4 hours (b)</th>
<th>contact plates (diameter 55 mm) cfu/plate</th>
<th>glove print 5 fingers cfu/glove</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>B</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>C</td>
<td>100</td>
<td>50</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>D</td>
<td>200</td>
<td>100</td>
<td>50</td>
<td>-</td>
</tr>
</tbody>
</table>
EU GMP Annex 1- Basic Elements
Clean Room Classification

- **US-FDA Requirements ≠ EU GMP Requirements!**

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<td>2 900</td>
</tr>
<tr>
<td>D</td>
<td>3 520 000</td>
<td>29 000</td>
</tr>
</tbody>
</table>

**TABLE 1 - Air Classifications**

<table>
<thead>
<tr>
<th>Clean Area Classification (0.5 μm particles/ft²)</th>
<th>ISO Designation</th>
<th>≥ 0.5 μm particles/m³</th>
<th>Microbiological Active Air Action Levels (cfu/m³)</th>
<th>Microbiological Settling Plates Action Levels (diam. 90mm; cfu/4 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>5</td>
<td>3,520</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1000</td>
<td>6</td>
<td>35,200</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>10,000</td>
<td>7</td>
<td>352,000</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>100,000</td>
<td>8</td>
<td>3,520,000</td>
<td>100</td>
<td>50</td>
</tr>
</tbody>
</table>

FDA Aseptic Processing Guide

cGMP

Niedersachsen

20.10.2009
Dr. Martin Melzer
EU GMP Annex 1 - Basic Elements

- Clean room classification
- Monitoring
- Technologies
- Personnel
- Premises
- Equipment
- Sanitation
- Processing
- Sterilisation Methods
- Aseptical Filling
- Finishing
EU GMP Annex 1- Basic Elements
Monitoring

- **Principles**
  - Routinely monitored „in operation“:
    - Particles
    - Microbiological count
    - (+ temp + % rel. humidity)
  
- **Monitoring locations & frequency**
  - Based on formal risk analysis
  - Alert and action limits
EU GMP Annex 1- Basic Elements

- Clean room classification
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- **Technologies**
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EU GMP Annex 1- Basic Elements
Technologies

- The following Technologies are detailed:
  - Isolator
  - Blow/ Fill/ Seal
  - Terminally sterilized
  - Aseptic preparation

- With regard to…
  - Clean room classification / background
  - Monitoring
  - …
EU GMP Annex 1- Basic Elements

- Clean room classification
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- **Personnel**
- Premises
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EU GMP Annex 1- Basic Elements
Personnel

- Hygiene
- Training
- Clothing
  - Detailed for all clean room classes
EU GMP Annex 1- Basic Elements

- Clean room classification
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EU GMP Annex 1- Basic Elements

Premises

- Detailed for
  - General aspects
  - Sinks & drains
  - Changing rooms
  - Airlocks
  - Air supply
  - ...

Staatliches Gewerbeaufsichtsamt Hannover
EU GMP Annex 1- Basic Elements

- Clean room classification
- Monitoring
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EU GMP Annex 1- Basic Elements

- Various regulations
EU GMP Annex 1- Basic Elements

- Clean room classification
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EU GMP Annex 1 - Basic Elements
Sanitation

- Desinfectants/ Detergents
- Fumigation
EU GMP Annex 1- Basic Elements

- Clean room classification
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- Sanitation
- **Processing**
  - Sterilisation Methods
  - Aseptical Filling
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EU GMP Annex 1- Basic Elements

Processing

- Media Fill
  - Details
  - Acceptance Table

- When filling fewer than 5000 units, no contaminated units should be detected.
- When filling 5,000 to 10,000 units:
  a) One (1) contaminated unit should result in an investigation, including consideration of a repeat media fill;
  b) Two (2) contaminated units are considered cause for revalidation, following investigation.
- When filling more than 10,000 units:
  a) One (1) contaminated unit should result in an investigation;
  b) Two (2) contaminated units are considered cause for revalidation, following investigation.

Harmonized with US FDA and PIC/S requirements
EU GMP Annex 1- Basic Elements

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EU GMP Annex 1- Basic Elements
Sterilisation Methods

- Principles ((moist) heat/ radiation/ ethylene oxide)
  - Validation
  - Biological Indicators for routine production
EU GMP Annex 1- Basic Elements

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EU GMP Annex 1- Basic Elements
Aseptical filling

- Filter 0.22 µm
- Filter integrity test before & after use
EU GMP Annex 1- Basic Elements

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EU GMP Annex 1- Basic Elements
Finishing

- Final closing under class A
- Vial capping under class A (aseptic core) or class A conditions (whatever that means …)
- 100 % integrity testing (containers closed by fusion)
European Pharmacopoeia

- **2.6.1 Sterility**
  - Details of methods and sampling for sterility testing
- **5.1.1 Methods of preparation of sterile products**
  - Sterility assurance level: $10^{-6}$, achieved by
    - Overkill methods
    - $F_0$-Concept
- **5.1.2 Biological indicators**
- **5.1.5 Application of the $F_0$ Concept to steam sterilisation of aqueous solutions**
- **5.1.9 Guidance for using the test for sterility**
PIC/ S  
(Pharmaceutical Inspection Convention)

- Validation of aseptic processes (2009)
- Recommendation of Sterility testing (2007)
- Isolators used for aseptic processing and sterility testing (2007)
Other helpful documents

- EN ISO 14644-1, -2
- ISPE Guidelines
- US FDA Aseptic processing guide
Thank you!
Link to documents

The Rules Governing Medicinal Products in the European Union
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm

EU GMP
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4_en.htm

PIC/ S
http://www.picscheme.org/

FDA (Aseptic Processing guide)