



Staatliches Gewerbeaufsichtsamt Hannover

GMP Training Course

20-21 October 2009

EU GMP Requirements

Sterile medicinal product



Niedersachsen



Dr. Martin Melzer



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

Coming into operation

Coming into operation: 1.3.2009

Coming into operation (capping of freeze-dried vials): 1.3.2010



EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels, 14 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





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
- Personnel
- Premises
- Equipment
- Sanitation
- Processing
- Sterilisation Methods
- Aseptical Filling
- Finishing





EU GMP Annex 1- Basic Elements Clean Room Classification

- **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 $\neq$ 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

Particles

	Maximum permitted number of particles per m ³ equal to or greater than the tabulated size			
	At rest		In operation	
Grade	0.5 µm	5.0µm	0.5 µm	5.0µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

Microbes/ cfu

	Recommended limits for microbial contamination (a)			
Grade	air sample cfu/m ³	settle plates (diameter 90 mm) cfu/4 hours (b)	contact plates (diameter 55 mm) cfu/plate	glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-





EU GMP Annex 1- Basic Elements Clean Room Classification

■ US-FDA Requirements ≠ EU GMP Requirements !

EU GMP Annex 1

Grade	Maximum permitted number of particles per m ³ equal to or greater than the tabulated size			
	At rest		In operation	
	0.5 µm	5.0µm	0.5 µm	5.0µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

FDA Aseptic
Processing Guide
cGMP

TABLE 1- Air Classifications^a

Clean Area Classification (0.5 µm particles/ft ³)	ISO Designation ^b	≥ 0.5 µm particles/m ³	Microbiological Active Air Action Levels ^c (cfu/m ³)	Microbiological Settling Plates Action Levels ^{c,d} (diam. 90mm; cfu/4 hours)
100	5	3,520	1 ^e	1 ^e
1000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50





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
- Monitoring
- **Technologies**
- Personnel
- Premises
- Equipment
- Sanitation
- Processing
- Sterilisation Methods
- Aseptical Filling
- Finishing





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
- Monitoring
- Technologies
- **Personnel**
- Premises
- Equipment
- Sanitation
- Processing
- Sterilisation Methods
- Aseptical Filling
- Finishing





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
- Monitoring
- Technologies
- Personnel
- **Premises**
- Equipment
- Sanitation
- Processing
- Sterilisation Methods
- Aseptical Filling
- Finishing





EU GMP Annex 1- Basic Elements Premises

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





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 Equipment

- Various regulations





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 Sanitation

- **Desinfectants/ Detergents**
- **Fumigation**





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 Processing

■ Media Fill

- Details
- Acceptance Table

*Harmonized with
US FDA
and
PIC/S
requirements*

- 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.





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 Sterilisation Methods

- **Principles ((moist) heat/ radiation/ ethylene oxide)**
 - Validation
 - Biological Indicators for routine production





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 Aseptical filling

- Filter 0.22 μm
- Filter integrity test before & after use



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 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)

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf>

