

Grade A Capping What's the Story?

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Content

Grade A Capping

- Regulatory Perspective & Position
 - EU & FDA
- Company experiences
- The Future?

Dealing with the Requirements



EU GMP Guide, Annex 1

(30 May 2003)

General Requirements

1. Manufacture in clean areas
2. Entry through airlocks for personnel, equipment & materials
3. Various operations of component preparation, product preparation and filling in separate areas within the clean area
4. Clean areas are classified by the required characteristics of the environment



EU GMP Guide, Annex 1

(30 May 2003)

5. Clean areas are designed to meet specified air-cleanliness levels when “at rest”
 - “...the installation is installed and operating, complete with production equipment but with no operating personnel present”
6. Clean areas must meet “in operation” conditions
 - “...the installation is functioning in the defined operating mode with the specified number of personnel working.”



EU GMP Guide, Annex 1

(30 May 2003)

7. Four grades of area

- **Grade A** = local zone for high risk operations
“...e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections.”
- **Grade B** = background environment for grade A zone for aseptic preparation & filling
- **Grades C & D** = for less critical stages in manufacture of sterile products

8. Appropriate number of air changes & air system must have appropriate terminal filters (e.g. HEPA) suited to the area classification (A, B or C)



Annex 1: Airborne Particulate Classification

The airborne particulate classification for these grades is given in the following table.

Grade	at rest (b)		in operation (b)	
	maximum permitted number of particles/m ³ equal to or above (a)			
	0.5 µm (d)	5 µm	0.5 µm (d)	5 µm
A	3 500	1 (e)	3 500	1 (e)
B (c)	3 500	1 (e)	350 000	2 000
C (c)	350 000	2 000	3 500 000	20 000
D (c)	3 500 000	20 000	not defined (f)	not defined (f)



Annex 1: Particulate Measurement

- Should be continuous in Grade A zones during operation
- Continuous monitoring is also recommended in the Grade B zones
- For routine testing, the total samples volume should be not less than 1 m³ for Grade A & B areas and preferably also for Grade C areas
 - How are these samples to be taken?
 - Are numerous ft³ samples acceptable?



Annex 1: Particulate Measurement

- Grade A conditions required immediately surrounding the product whenever the product or open container is exposed to the environment
- May not be possible at the point of fill when filling is in progress, due to generation of particles or droplets from the product itself
- Grade A & B areas expected to be completely free from particles $\geq 5\mu\text{m}$ in size
- Appropriate alert & action limits are required. If exceeded, CAPAs should be defined



Annex 1:

Microbiological Contamination

- “Frequent” monitoring is required where aseptic operations are performed
 - Settle plates, volumetric air & surface sampling (e.g. swabs & contact plates)
 - Sampling methods should not interfere with zone protection
- Recommended limits may be exceeded on occasion
 - Documented review &
 - Trend analysis



Annex 1: Microbiological Contamination

Recommended limits for microbiological monitoring of clean areas during operation.

Recommended limits for microbial contamination (a)				
Grade	air sample cfu/m ³	settle plates (diam. 90 mm), cfu/4 hours (b)	contact plates (diam. 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	-



Proposed Revision to Annex 1 (EMEA 21 Sept. 2005)

Clarifications re

- environmental clean room classification
- clean air device classification
 - Clean rooms & clean air devices to be classified as per EN ISO 14644-1
- particulate classification table and requirements
 - Max permitted number of particles at $\geq 5.0\mu\text{m}$ is $1/\text{m}^3$, but a limit of $20/\text{m}^3$ “could be considered”
 - Sampling rate of particle counter of $1 \text{ ft}^3/\text{min}$ ($28.3 \text{ l}/\text{min}$) requires a sampling time of approx 35 mins at each location
 - Requirements relating to length of tubing used with portable particle counters



Proposed Revision to Annex 1 (EMEA 21 Sept. 2005)

- Clarifications re particulate classification table and requirements
 - Requirements relating to validation of the radii of any bends in tubing
 - Locations for monitoring clean rooms should be based on formal risk analysis & results from the initial qualification
 - A continuous or frequent sampling particle monitoring system should be used for Grade A zones
 - Similar system for Grade B but sampling frequency may be decreased
- Sample size for monitoring purposes does not have to be the same as that used for formal classification
 - Function of the sampling rate of the system



CAPPING STATION

- Whether a product is freeze dried or in liquid form it must be securely sealed.
- Vials are transferred to the capping station where they are fitted with an aluminium overseal



Capping station turret



Slide courtesy of
Genzyme, Ireland

Proposed Revision to Annex 1 (EMA 21 Sept. 2005)

Proposed addition to Paragraph 88 Finishing of Sterile Products

“Partially stoppered freeze drying vials should be maintained under Grade A conditions at all times, from the time of partial stoppering to capping. The container closure system for aseptically filled vials is not fully integral until the aluminium cap has been crimped into place. Vials should be maintained in Grade A environment until the cap has been crimped. As the equipment used to crimp vials can generate large quantities of non-viable particulates, the equipment should be located as a separate station equipped with adequate air extraction. The capping station may not be able to meet Grade A conditions for non-viable particles in the “in operation” condition but should meet the microbiological requirements.”



Differences with FDA

- Air classifications differ
- Facility qualification studies are required “in operation” only; “at rest” not expected
- FDA does not require the classification of the final stage of robing to be the same as the room into which it leads
- Robing change requirements between Grade C and B are not defined by FDA
- Gowning requirements for Grade C are not defined by FDA
- Particulate monitoring at 5um is not required



Differences with FDA

- Sample volume is not specified
 - appropriate based on risk
- Different microbiological monitoring methods can be used as alternative rather than additional requirements to each other
 - In US, active air sampling & contact plates are typically used
 - EU expectation for settle plates additionally
- Recommended limits for micro contamination
 - EU Annex 1 – “average” value – interpretation of average?
 - FDA – “individual” value



Differences with FDA

- Background requirement of Grade B for stoppering of vials is not required by FDA
- FDA requirement is for unidirectional airflow in Grade A areas; EU Annex 1 requirement is for laminarity
 - Low turbulence unidirectional flow is sometimes accepted in EU
- Grade A air velocity is defined in EU Annex 1 (0.45 m/s +/- 20%)
 - Is this speed excessive?



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Company Experiences

- **Grade A environment for capping is now the norm**
- **Is a Grade B background required?**
 - Regulators differ
 - EU v FDA
 - Between Regulatory Agencies in EU
 - Lack of clarity for Industry
 - Current proposal for revision to Annex 1 does not provide clarification
 - Indication that final text will not define a standard requirement of a Grade B background
 - Potential for lack of clarity to continue?



Company Experiences

- **Cost of Compliance?**
 - Significant capital investment, often through U.S. parent companies
 - Challenge to justify & procure the investment
 - Corporate pushback
 - Cost of downtime
 - Construction, commissioning, qualification & validation
 - Stock piling
 - Cost of lost market share
 - Ongoing operational costs



Green field v upgrade project



Grade A/B Capping: Green Field

- Can plan design to best suit operations
- Can predict & project costs
- Can define operational costs

BUT

- What regulatory requirements should be met?



Retro-Fitting – The Real Challenge

Company Experiences

- Design & Construction
- Qualification & Requalification
- Routine Operation

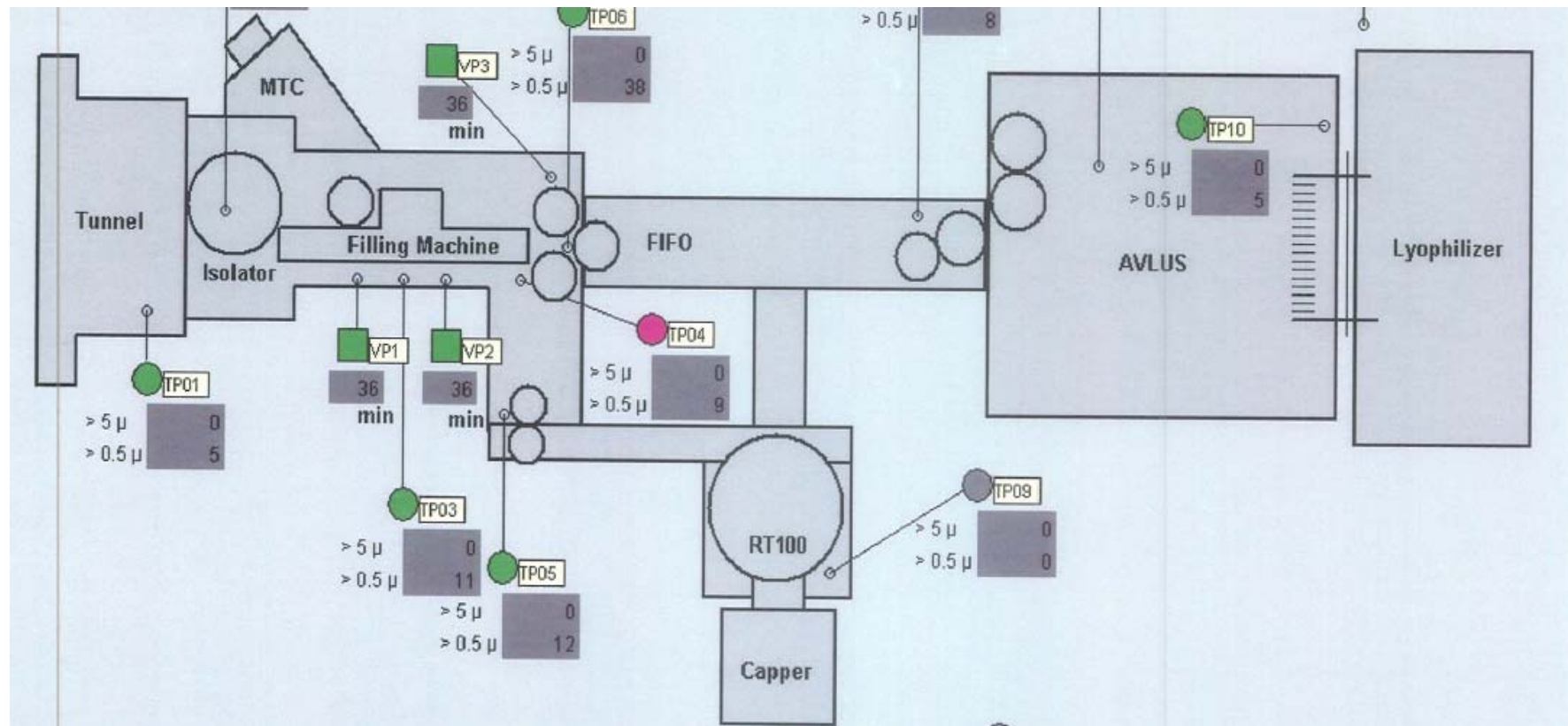


Retro-Fitting: Design & Construction

- Reconfiguration of rooms
 - Movement of vials from lyophiliser to capping station
 - Loading of seals
 - Fan filter unit (Grade A) required in Grade B room
 - Impact on pressure profiles etc
- Re-engineering of manufacturing line
 - Continual sterilisation of a belt moving between a Grade A or B area & an area of lower cleanliness
 - Flow of empty vials (e.g. capper set-up) and filled / lyophilised vials



Example of a Re-Engineered Manufacturing Line



Retro-Fitting : Design & Construction

- Upgrade of capping station to Grade A
- Upgrade of background to Grade B... more later
- Upgrade of change rooms
 - Final stage Grade B (for EU)
- Upgrade of air handling system(s)
 - Increase number of fan units?
 - Suitability of air flow ?
 - Laminar v unidirectional v non-turbulent unidirectional?



Retro-Fitting : Design & Construction

- Upgrade of air handling system(s) contd
 - Air speed?
 - Is 0.45 m/s +/- 20% for laminar flow excessive?
 - What speed if unidirectional?
 - Level of filtration
 - Air change rates
 - Control of particulate levels
- More sophisticated EM systems
 - Automated data collection & processing
 - Alarm functionality



Retro-Fitting – The Real Challenge

Company Experiences

- Design & Construction
- **Qualification & Requalification**
- Routine Operation



Retro-Fitting : (Re)Qualification

- Air Handling System(s)
 - To take account of re-engineering
- BMS
 - Air handling - change to alarm ranges
- Environmental classification
 - Particulate
 - Microbiological contamination
 - Design and qualify system for fogging of area?
- Particulate monitoring & data processing system



Retro-Fitting : (Re)Qualification

- Process (re)design and (re)qualification
 - Manufacturing process changes?
 - Media fill requirements
 - Sterilisation process changes?
 - New materials →
 - Design of new sterilisation processes →
 - Qualification & validation requirements
 - Requalification after shut-down
 - More extensive requalification requirements
 - Full gowning requirements even in shut-down



Retro-Fitting – The Real Challenge

Company Experiences

- Design & Construction
- Qualification & Requalification
- **Routine Operation**



Grade A/B Capping: Routine Operation

If Grade B background is required:

- Upgrade of type & extent of personnel robing
- Increased requirements for sterility of components / materials
 - Robing
 - Overseals/ caps
 - Change to materials of construction to withstand irradiation?



Grade A/B Capping: Routine Operation

- Procedural changes may be required
 - to deal with line configuration limitations
 - Sterilisation of parts for every batch v cleaning & sanitisation regime?
- EM programmes
 - Continuous particulate sampling for Grade A?
 - Definition of 'continuous'?
 - Continuous particulate monitoring for Grade B?
 - Sampling volumes?



Grade A/B Capping: Routine Operation

- EM programmes contd
 - Sampling locations and positioning of sensors?
 - Must represent Grade A (& B) conditions
 - Must be sufficiently close to key operations being conducted
 - Must not cause false alarms
e.g. operators hitting off the sensors during routine operations

“The capping station may not be able to meet Grade A conditions for non-viable particles in the “in operation” condition but should meet the microbiological requirements.” Annex 1



Grade A/B Capping: Routine Operation

- EM programmes contd
 - Which microbiological methods to use?
 - Frequency of microbiological monitoring?
- Excursion handling
 - What are appropriate limits, alert & action levels?
 - Greater potential for batch rejection
 - More conservative approach
 - More detailed investigations re determination of product impact
 - More time consuming



Grade A/B Capping: Routine Operation

- Sanitisation regimes
 - Change in disinfectant required?
 - Augmented sanitisation programme to achieve the micro classification
 - Introduction of fogging system & regime?
- Personnel
 - Increased number of operators required
 - Increased training of operators in aseptic procedures
 - Increased level & extent of personnel monitoring & qualification



Grade A/B Capping: Routine Operation

BOTTOM LINE

- ...Increased capital costs**
- ... Increased validation costs**
- ...Increased operational costs**
- ...Lost revenue costs**

**Patient
Benefit?**



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The Future?

- Complex area
- Requires analysis and interpretation by people
- Variability is inevitable
- Harmonisation & consistency of regulatory requirements would help significantly
 - What's the likelihood of this?
 - Timeframe?
- Industry must grow & prosper
- Industry must focus on
 - product quality in the best interest of the patient
 - ensuring compliance with the regulatory requirements



Dealing with the Requirements

- Know the regulatory requirements with reference to
 - Your manufacturing facility & process(es)
 - Principal markets e.g. USA v EU
 - Location of manufacturing facility e.g. USA v EU
 - Emerging standards & best practice
 - e.g. proposed revision to EU GMP Guide, Annex 1
- Define the critical requirements that must be met
 - Design & operate to meet them



Dealing with the Requirements

- Define key requirements around which there may be some flexibility
 - Use a Quality Risk Management approach (ICH Q9)
 - Focus on product quality & patient risk
 - Document the scientific rationale for what you propose to do & not to do
- Actively keep abreast of GMP developments
 - Membership of professional organisations
 - Continuous education
 - Participation in special interest groups
 - Knowledge management within your organisations



Dealing with the Requirements

- Communicate with other similar companies
 - Discuss approaches to achieving compliance
 - Keep abreast of developments in the industry
 - Share knowledge
- Build a relationship with your Regulatory Authorities
 - Don't be afraid to engage them in discussion on your proposals & practices BUT
 - Remember, they are not consultants and will not direct you or provide advice!



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Thank You



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Title

