PHARMACEUTICAL INSPECTION CONVENTION

PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 032-2
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RECOMMENDATION

GMP ANNEX 1 REVISION 2008, INTERPRETATION OF MOST IMPORTANT CHANGES FOR THE MANUFACTURE OF STERILE MEDICINAL PRODUCTS

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0. Document history

The present technical interpretation of Annex 1 to the PIC/S GMP Guide (PE 009) on the manufacture of sterile medicinal products (hereinafter referred to as GMP Annex 1) was initially drafted by Switzerland / Swissmedic and then commented by PIC/S Participating Authorities. It was agreed that the technical interpretation of GMP Annex 1 should be the same between the EU and PIC/S [1].

Adoption by Committee of PI 032-1	3 November 2009
Entry into force of PI 032-1	1 December 2009
Entry into force of PI 032-2	1 January 2010

1. Purpose and scope

In order to assure a harmonised conduct of inspections, with respect to the 2008 revision of GMP Annex 1 [2], this document summarises the interpretations which an inspector of the competent regulatory authority should adopt when performing an inspection of a manufacturer of sterile medicinal products.

This document reflects the most important changes and also addresses the feedback from industry concerning the GMP Annex 1 Revision. It is not meant to address all changes within the Revision.

[1] Annex 1 of the PIC/S GMP Guide is identical to Annex 1 of the EU GMP Guide (Eudralex Volume 4 GMP). Both Guides are equivalent in terms of GMP requirements.

[2] The revision of Annex 1 to PIC/S GMP Guide was adopted on 12 November 2008 by the PIC/S Committee and entered into force on 1 March 2009.

2. Basics

2.1 Legal requirements (binding)

- Refer to national legislation [3]

2.2 Regulatory guidance (to be justified if not applied)

- For EEA countries: Eudralex Volume 4 GMP, GMP Annex 1, revision of November 25th, 2008
- For non-EEA countries: PIC/S GMP Guide (PE 009), Annex 1 or equivalent

2.3 Relevant international norms (to be justified if not applied)

- EN ISO 14644-1
- EN ISO 14644-2
- EN ISO 14644-3
- EN ISO 14644-4
- EN ISO 14644-5
- EN ISO 14644-6

The relevant international norms used in the context of this paper were applicable at the time this document was drafted. Future revisions of these norms do not automatically apply to this document.

The GMP Annex 1 Revision came into effect on March 1st, 2009; the provisions for crimp capping for all vials will come into effect in March 1st, 2010. However, especially for new installations with respect to crimp capping, conformance with the revised GMP Annex 1 is to be encouraged already today.

3. Definitions and abbreviations

Room Classification	Room classification is part of the initial qualification of a facility and is also normally performed during routine re-qualification. Both, classification activities and the final / to be achieved classification status for clean rooms / clean air devices are meant. This Annex directly links to clean room / clean air device classification according to ISO 14644. For qualification and validation and re-qualification see also PIC/S GMP Guide Annex 15.
RABS	Restricted Access Barrier Systems

[3] E.g. for Switzerland: Federal Law on Medicinal Products and Medical Devices (Law on Therapeutic Products - LTP), SR 812.21 and Ordinance on Establishment Licenses (ELO), SR 812.212.1.

4. New texts and their interpretation

4.1 Clean room / clean air device classification

General interpretation: The GMP Annex 1 Revision distinguishes very clearly between clean room / clean air device classification which is described in sections 4 to 7, and clean room monitoring, which is described in sections 8 to 20.

Section 3 defines at rest and in operation states, which is not new. However, it should be noted that the company needs SOPs to define at rest and in operation states, which might be specifically required per production room. These SOPs should include a definition of equipment to be installed and running, number of operators to be present.

In general, clean room / clean air device classification is required to be performed according to EN ISO 14644-1 with the applicable limits for particle counts defined in the table in section 4 of GMP Annex 1. Probe-locations should be chosen in order to demonstrate the homogeneity across the room. A classification report should be prepared according to section 4.4 of ISO 14644-1 and section B.1.4 of ISO 14644-3.

Monitoring, on the other hand, does not need to be performed according to EN ISO 14644-1. It can be performed for a reduced number of sampling points and sampling volumes. A formal risk analysis study based on experiments and analysis of the monitoring data (over at least 6 month operation) should provide a basis for the determination of frequencies and limits. Frequencies and limits should be process-based and the results of the initial qualification and on going monitoring should be taken into account when setting operational alert and action limits. These limits and sample locations should be periodically reviewed for on-going validity of the risks initially considered.

Those frequencies and limits should be process-based and the results of the qualification should be taken into account.

Section 4:

New text: Clean rooms and clean air devices should be classified in accordance with EN ISO 14644-1. Classification should be clearly differentiated from operational process environmental monitoring.

Interpretation: Classification of clean rooms / clean air devices should be done according to provisions in EN ISO 14644-1. Compared with the prior version, the values for maximum permitted particles have been changed in this section. Especially the values for the maximum permitted number of 5 µm particles / m^3 for grade A have been changed from 1 to 20. For grade A, the corresponding ISO class is 4.8, based on the 5 µm counts.

For grade D, no in operation limits are defined; the company should establish in operation limits based on a risk analysis and on historical data where applicable.

Section 5:

New text: For classification purposes EN/ISO 14644-1 methodology defines both the minimum number of sampling locations and the sample size.

Interpretation: Minimum amount of sampling points and sampling volume and also interpretation of the results are defined in EN ISO 14644-1 (confidence interval). See also provisions for outliers in appendix B 6.2 of EN ISO 14644-1.

ISO 14644-1 Annex f has an informative section on the use of sequential sampling techniques for non-viable particle monitoring. This technique may be useful in reducing the time needed for sampling very large clean-room areas, at rest. This method would not be considered suitable for “in operation” classification.

The application of this method may be acceptable but it is unlikely to be the preferred method since most pharmaceutical facilities do not normally have the very large clean rooms of the type discussed in Annex f and therefore it is unlikely that significant time would be saved.

Section 6:

New text: Portable particle counters with a short length of sample tubing should be used for classification purposes because of the relatively higher rate of precipitation of particles ≥ 5 µm in remote sampling systems with long lengths of tubing.

Interpretation: This section implies that old central particle counters with long tube lengths will no longer be acceptable for clean room classification, as they absorb too many particles (especially 5 µm particles). Therefore, modern portable particle counters with short tubes or (even preferable when possible) those without tubes should be used for classification purposes. The certificate of calibration of the particle counter should mention the tube length and nature of material (inox or polymer). When calibration of the particle counter is performed outside by an external laboratory, the particle counting system should be qualified on site with a comparative measurement with an isokinetic probe. For impact on monitoring, see also section 11.

Section 7:

New text: EN ISO 14644-2 provides information on testing to demonstrate continued compliance with the assigned cleanliness classifications.

Interpretation: This provision concerns clean room re-qualification. The company may choose to perform re-qualification of clean rooms according to provisions in EN ISO 14644-2 (including the proposed frequencies). For re-qualification of grade A areas, it is generally expected to carry out the following activities also performed during initial classification: air velocity, filter integrity, differential pressure every 6 months. Other examples for frequencies: grade B: every 6 months at rest, once a year in operation; other grades: once a year, with maximum delay defined. If the company takes another approach, this should be justified, e.g. based on monitoring data.

4.2 Clean room / clean air device monitoring

Section 8:

New text: Clean rooms and clean air devices should be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices.

Interpretation: Frequency, location and number of monitoring locations should be based on a formal risk assessment and not on ISO 14644-1. Data obtained during classification and previous monitoring data should be considered. Critical locations should be covered.

Section 9:

New text: For grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, e.g. live organisms and radiological hazards. The grade A zone should be monitored at such a frequency and with suitable sample size that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded.

Interpretation: In critical areas with exposed product continuous monitoring, covering the duration of the operations is expected. Continuous means that the system must be able to pick up any potentially occurring event of an unusual number of particles, including an event that occurs for a short time only. Manifold systems might not be suitable for Grade A Zone monitoring due to a lack in responsiveness. It is important that monitoring in grade A comprises equipment assembly, because there is a high impact of the human operator. An SOP should be present defining alert levels and pre-defined corrective measures in cases of alerts and interventions.

Section 10:

New text: It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased. The Grade B zone should be monitored at such a frequency and with suitable sample size that changes in levels of contamination and any system deterioration would be captured and alarms triggered if alert limits are exceeded.

Interpretation: Continuous monitoring (see definition under interpretation to section 9) is expected while not fully integral containers are handled in the B zone, e.g. partially stoppered vials within a laminar air flow mobile unit prior to lyophilisation. Manifold systems might not be suitable for Grade B Zone monitoring due to a lack in responsiveness.

Section 11:

New text: Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points connected by manifold to a single particle counter; or a combination of the two. The system selected must be appropriate for the particle size considered. Where remote sampling systems are used, the length of tubing and radii of any bends in the tubing must be considered in the context of particle losses in the tubing.

Interpretation: This section addresses concerns especially for the sedimentation of 5 µm particles in remote systems (as a rough example, s-shaped bent tubing of 1.5 m length can already absorb about 30% of the 5 µm particles.). The company must qualify their particle sampler and sampling system for both particle sizes, 0.5 µm and 5 µm.

Section 12:

New text: It is not necessary for the sample volume to be the same as that used for formal classification.

Interpretation: The important point for sampling during monitoring is to be able to sample quickly (especially in critical areas), to be able to link a particle excursion to an actual event and to be able to generate an alarm so that operators are immediately aware of the alarm situation. Thus sampling of 1 m^3 (which often takes 30 minutes) could be inadequate during monitoring of an A zone during operation.

Section 15:

New text: The monitoring of Grade C and D areas in operation should be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended "clean up period" should be attained.

Interpretation: The number of sampling points and the sampling frequency are to be determined by at least a risk assessment, including risk identification, risk analysis and risk evaluation (see also GMP Annex 20). There is no need for a continuous monitoring. However, the frequency should be higher than that of Re-Qualification of these areas.

4.3 Microbiological monitoring

There are no changes to the provisions for microbiological monitoring (sections 18 and 19).

However, it is important to note that for critical sampling locations in grade A areas where aseptic operations are performed, every found microorganism should result in a thorough investigation, the microorganism has to be identified and impact on batch release should be considered. An additional comment should be made on the limits for settle plates. These limits are interpreted as limit per settle plate. Also, the same limits apply when sampling time is less than 4 hours, e.g. for operations being shorter than 4 hours.

All methods indicated for a specific grade in the table of section 19 should be used for monitoring the area of that specific grade. If one of the methods is not used, this should be justified.

4.4 Media simulations

The provisions for media simulations (sections 66-71) are now fully harmonized with FDA aseptic guide. This should not give rise to problems. Section 7 includes a need for media fills to be done under worst-case conditions.

4.5 Bioburden monitoring

Section 80:

New text: The bioburden should be monitored before sterilisation. There should be working limits on contamination immediately before sterilisation, which are related to the efficiency of the method to be used. Bioburden assay should be performed on

each batch for both aseptically filled product and terminally sterilised products. Where overkill sterilisation parameters are set for terminally sterilised products, bioburden might be monitored only at suitable scheduled intervals. For parametric release systems, bioburden assays should be performed on each batch and considered as an in-process test. Where appropriate the level of Endotoxins should be monitored. All solutions, in particular large volume infusion fluids, should be passed through a micro-organism-retaining filter, if possible sited immediately before filling.

Interpretation:

General: The contribution to bioburden of the various raw materials and packaging materials together with the manufacturing processes prior to the sterilisation step should be understood and controlled. A monitoring and control strategy including periodic monitoring and trending of bioburden prior to any bioburden reduction step should be established and justified on the basis of process risks. Volumes sampled should be justified and take account of the expected level of contamination

The bioburden should at least be determined for the product prior to the final sterilization step. Acceptance criteria for bioburden must be based on the sterilising step, a sterility assurance level of 10^{-6} must be met. The results of the bioburden assays must be present before release (unless an overkill cycle is used for terminal sterilisation). This favours the use of rapid micro-methods.

A risk assessment should be performed in order to determine the need for endotoxin studies. When needed, endotoxins should be determined also for the units of product that were filled the last.

Terminal sterilisation: For terminal sterilisation the F_0 value has to be taken into account. The sampling should be performed on filled containers prior to sterilisation. For overkill sterilisation processes for terminally sterilized products, the company must justify the intervals chosen for bioburden testing.

Aseptic operations: For sterile filtration, filter efficacy studies must be taken into account when determining the acceptance criteria for the bioburden prior to filtration. This means that if two subsequent filtration steps are used, product has to be sampled prior to the last filtration step, if technically possible, e.g. first filtration into bulk tank, second filtration immediately prior to filling. However, if a system of two filters with redundancy is used (the second filter is used for security, if one fails the required SAL is still achieved), sampling should be performed upstream of these filters in order not to compromise the filtration step. The company has to justify its approach if sampling is done before the first filtration step.

4.6 Provisions for environmental conditions for the handling of aseptically filled vials after leaving the aseptic processing area up until final sealing

General interpretation: these provisions are valid not only for freeze-dried vials but for all aseptically filled vials. If crimp-capping is done as a “clean process” (see section 120) these provisions define requirements for the environment for vials from the moment they leave the aseptic processing area until the crimp cap has been crimped into place on the stoppered vial. Grade A air supply is required for conveyor tunnels connecting the aseptic processing area with the crimp capping machine for liquid products and powder, and the transport of freeze-dried vials from the freeze dryer to the crimp capping machine and the crimp capping machine itself.

Grade D classification is considered to be the minimal requirement for the clean room in which the crimp-capping machine is located. The company has to justify their approach for choosing the appropriate room class.

It is important to note that in order to avoid contamination of the product at this stage, not only one but several factors are important such as the design of the vial stopper combination, a thoroughly validated detection systems of misplaced or missing stoppers, restricted access of operators, good training of operators, thorough procedures for manual interventions and follow-up actions and adequate environmental conditions.

Section 116:

New text: Partially stoppered freeze drying vials should be maintained under grade A conditions at all times until the stopper is fully inserted.

Interpretation: There should be no problem with this point, which is basically equivalent with the provisions in section 12 of the prior version of the Annex.

Section 118:

New text: The container closure system for aseptically filled vials is not fully integral until the aluminium cap has been crimped into place on the stoppered vial.

Interpretation: This is to be used as a definition. It does not mean that the product is considered open prior to crimp capping and therefore it is not a requirement for aseptic conditions up to crimp capping. However, for more detail on specific requirements see section 120.

Section 120:

New text: Vial capping can be undertaken as an aseptic process using sterilized caps or as a clean process outside the aseptic core. Where this latter approach is adopted, vials should be protected by grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a grade A air supply until the cap has been crimped.

Interpretation: For lyophilized products: product transfer from filling machine to freeze dryer should be done under grade A conditions (e.g. laminar air flow mobile unit) with grade B surroundings. Transfer to the crimp-capping machine should be done under grade A air supply. For liquid products and powders: transfer from the aseptic processing area to the crimp capping machine should be done under grade A air supply. For all products: Crimp capping should be done under grade A air supply. Sterilization of crimp caps is only mandatory, when crimp capping is performed in the aseptic core.

The new revision of Annex 1 mentions a new term, Grade A air supply, but no definition of this new term is given in the revised Annex. Inspectors and Industry therefore need an interpretation of this term, especially as a provision of a grade A air supply is one of the most significant changes in Annex 1.

The term grade A air supply is specifically used to describe a supply of air which is HEPA filtered, and at the point of supply meets when tested, the non-viable particulate requirements of a grade A area, as defined in paragraph 4 of the revised Annex 1. It is important to differentiate between the terms grade A air supply and

grade A area. A grade A air supply should be qualified and monitored as follows:

Qualification requirements:

- Qualification is done only under at rest conditions: For the crimp-capping machine the at-rest state is achieved when the air supply is switched on, the crimp-capping machine is operating (feeding of vials and crimp caps is not considered necessary) and there is no interference by operators. For the conveyor tunnel for liquid products the at-rest state is achieved when the air supply is switched on, the conveyor belt is switched on and there is no interference by operators.
- Non-viable particles should be measured and are expected to meet grade A requirements. The probe should be located at the point of supply of the filtered air.
- Smoke studies should be performed. Whilst unidirectional air flow is not required, efficient protection of the vials should be demonstrated and the absence of air entrainment from the surrounding room should be demonstrated.
- Limits for air velocity should be in place and justified.

Monitoring requirements:

- Monitoring requirements for non-viable particles and microbiological contamination should be defined by the company following a risk assessment.

Section 121:

New text: Vials with missing or displaced stoppers should be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology should be used to prevent direct contact with vials and to minimise microbial contamination.

Interpretation: It is essential that there is a robust system, capable of detecting with a very high probability displaced or missing stoppers prior to capping. These vials should be rejected prior to capping. For thoroughly validated systems, a physical ejection of rejected vials after the capping station is acceptable although physical ejection prior to capping is preferred. The better the controls are for correctly set stoppers and demonstration of integrity, the lower the dependence is for the monitoring of the capping environment. If there is no such detection and rejection system in place, capping must be performed as an aseptic process rather than as a clean process.

Procedures must be in place defining manual interventions, avoiding unnecessary contamination and measures in case of manual interventions. This is true also for the handling of the transport tunnel for liquid products.

Section 122:

New text: Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimising direct human interventions into the capping operation.

Interpretation: The use of RABS or isolators is not a direct requirement; human impact can be reduced by other means as well.

5. Revision history

Date	Version Number	Reasons for revision
1 January 2010	PI 032-2	Revision of points below following parallel discussions within EEA and PIC/S: - 2.3 Relevant international norms; - 4.1 Clean room / clean air device classification: general interpretation and section 5; - 4.5 Bioburden monitoring: sections 80, 120 and 121.

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