



White paper:

**PIC/S GMP Guide – Annex 1
Revisions & Interpretations**

PIC/S has adopted a new sterile medicinal products annex (Annex 1) as part of recent revisions to the GMP guide. Some of the changes are significant and need to be considered carefully by sterile manufacturers subject to the PIC/S GMP guide



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MKT_TMP200_01_r06

Introduction

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) recently introduced updated versions of both their GMP guide and the associated annexes, which deal with a variety of different specific GMP subjects. There are now 20 annexes to the guide, some are new, some have received little or no change, while others have been significantly updated. Annex 1, relating to sterile medicines, was one annex to receive considerable revision as part of the update.

For manufacturers subject to the Therapeutic Goods Administration (TGA) in Australia, compliance with the new guide and relevant annexes becomes mandatory on July 1st 2010. This paper discusses all of the changes likely to have impact on manufacturers and what procedural, equipment or systems changes may be required to comply with the new annex.

The paper also considers the PIC/S Recommendation “GMP Annex 1 Revision 2008, Interpretation of Most Important Changes for the Manufacture of Sterile Medicinal Products” (PI032-2), where it is helpful in determining the requirement of the new annex.

Regulatory history of Annex 1

Specific GMP guidance on the manufacture of sterile medicines has been available from the FDA (US Food & Drug Administration) since the 1980s, and the EU (European Union) since the 1990s.

Annex 1 of the EU GMP Guide was then adopted by PIC/S, which in turn has provided the guidance to PIC/S member countries including Australia.

The TGA code of GMP has included Annex 1 since 2002 with two revisions in 2003 and 2008.

In Australia, however, sterile medicines have been regulated according to the version published with the 2002 update to the code of GMP. The legally binding *Therapeutic Goods (Manufacturing Principles) Determination no. 1 of 2009* updates the code of GMP and associated annexes to the current versions, enforceable from July 1st 2010.

Who is affected by the changes?

All manufacturers of sterile medicines who are subject to the PIC/S GMP guide (including all manufacturers subject to the TGA in Australia) are affected by the changes to Annex 1.

What are the key changes in the new Annex 1?

The new Annex 1 includes:

- around 24 changes with potential impact for manufacturers
- several grammatical changes which do not alter the intent of the document, and therefore shouldn't have impact from a compliance perspective.

The PIC/S interpretation document addresses most of the substantive changes to varying degrees. The changes and the PIC/S interpretation are discussed below and ranked as significant, moderate or low impact, based on the perceived impact to the wider sterile manufacturing industry.

Significant Impact Changes

Changes to the Requirements for Classifying and Monitoring Clean Rooms

Several changes, clarifications and additions have been made to the requirements for classifying and monitoring clean rooms:

- Section 4: Changes to limits for non-viable particles in Grade A through D environments – The changes have been made to bring the PIC/S requirements into line with those for ISO 14644. In all cases, a small increase in allowable limits has resulted, but this increase is most significant for 5 µm particle limits in Grade B (at rest) and Grade A environments.
- Section 8: Requirement to monitor clean rooms routinely 'in operation' has been expanded to require justification of monitoring locations through risk assessment – According to PI 032-2, Auditors will expect to see formal risk assessment for the selection of all monitoring locations, including justification of critical locations. Use of classification and previous monitoring data, where available, should form part of the assessment. The recommendation states that monitoring locations should NOT be based on ISO 14644.
- Section 10: Requirement for continuous monitoring for Grade B areas – The new Annex clearly requires “a similar system” to Grade A continuous monitoring in Grade B areas, however, there is some confusion as to what this actually entails. Unfortunately, PI 032-2 only serves to add to the confusion by suggesting that continuous monitoring is only required when “not fully integral containers are handled in the B zone”.

To consider: While this change relaxes the requirements and makes monitoring and classification compliance easier, it will require procedural and documentation changes to ensure the new limits have been captured within your quality management system

We can surmise from the text of the Guide that:

- Similarly to Grade A systems, the Grade B monitoring system should operate at a frequency and sample size to detect changes in contamination levels and system deterioration, including the triggering of alarms.

To consider: Have your monitoring locations and frequencies been critically assessed (using historical and/or classification data) and documented for all classified rooms?

- The sample frequency may be less than for Grade A systems
- The more effective the segregation between Grade A and B zones, the less important the Grade B sampling becomes.
- The capture of interventions and transient events is not paramount in Grade B monitoring.

Interpreting the requirements of this clause is very important for aseptic manufacturers, as there are potential significant costs associated with upgrading particle monitoring systems. While it is clear that regulators want to see a focus on this area, solutions are not likely to be 'one-size-fits-all' and will need to be tailored to the specific application.

To consider: Can you use your existing particle monitoring system to meet the new requirement in Grade B zones? If not, based on your zone segregation and types of operation, what is the most cost effective, compliant solution for you?

Changes to Failure Treatment for Media Fills

Section 69 provides specific and prescriptive requirement for the acceptable failure limits in media fill studies, based on filling run size. The formally specified statistical approach of >99.9% at 95% confidence interval is no longer applicable to determine acceptable failure limits. This will create tighter limits, especially for large batch sizes.

To consider: You should check to ensure that your current limits meet the new requirements and, if not, that your trending data indicates that you can meet the new standards when implemented in your quality system.

Changes to Finishing of Aseptically Filled Vials

Section 120 allows for the crimping operation as a 'clean' process outside the aseptic core. That is to say that fully stoppered vials may be removed from the aseptic core and crimped at another station which is not classified as aseptic.

It should be noted, however, that a Grade A air supply is required for vials when crimping is performed outside the aseptic core (including transport between stations). Also note that a Grade A air supply is not the same as Grade A conditions, and that partially stoppered vials must remain under Grade A conditions until fully stoppered.

PI 032-2 defines Grade A air supply as “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.” The qualification requirements for a Grade A air supply are also defined, and are summarised below:

- qualification is done only at rest
- non-viable particles are monitored to Grade A requirements
- there is no mention of viable monitoring
- smoke studies should be performed, but unidirectional (laminar) flow does not need to be demonstrated
- air velocities are to be justified by the manufacturer.

It is important to understand the implications of crimping outside the aseptic core and ensure that the appropriate equipment and controls are in place to meet the requirements of Annex 1.

After the stopper is fully inserted, the vial is still considered “non-integral” (section 118), hence the requirement for Grade A air supply. It is, however, clear that PIC/S accept there is less risk to the product at this point, which is why Grade A conditions are not required until completion of capping.

To consider: Does your current process meet the new requirements? If not, does your facility support operating in this manner, or are capital works required to bring your facility into compliance?

Moderate Impact Changes

Changes to the Requirements for Classifying and Monitoring Clean Rooms

Further to the significant impact changes relating to classifying and monitoring clean rooms, a number of moderate impact changes are noted below:

- Section 3: Added requirement to define 'in operation' and 'at rest' conditions for all cleanrooms or suites of cleanrooms – This requirement may require new or amended documentation to ensure that conditions are clearly defined. In some cases, it may also require justification of specific approaches. According to PI 032-2, these definitions should include installed equipment, running equipment and operators present. It is also suggested that clean up procedures, rest periods and any other variable conditions be nominated in the definition.
- Section 4: Classification according to ISO 14644-1 mandated – In many cases, this will have no impact, because most manufacturers already implement this. It should be noted, however, that attempts to claim classification using an alternative method would likely require significant justification.
- Section 6: Appropriate classification equipment nominated – Portable counters with short tube lengths are nominated as appropriate equipment for classification. As PI 032-2 states, this clearly implies that central units with long tube lengths are not acceptable for classification purposes. This requirement may require investment in new equipment for some manufacturers. PI 032-2 goes on to state that calibration certificates for counters should include data on tube length and material.
- Section 9: Detailed requirements for Grade A monitoring specified - Although providing significantly more detail, this section is generally in line with current standard practice. Note, however, that monitoring must be performed for all of setup and critical operations and that sample frequency/size must be such that all excursions are captured. PI 032-2 discourages the use of manifold systems for monitoring Grade A environments, due to lack of responsiveness.
- Section 11: Limitations on Particle measuring systems specified – This section is designed to prompt manufacturers to assess the performance of their monitoring systems, especially in relation to the performance of remote systems with long tube lengths (note that such systems, while unsuitable for classification, may still be used for monitoring). This assessment may result in correction factors being applied to ensure that results accurately reflect the contamination levels. PI 032-2 states that manufacturers must qualify their sampling systems for both particle sizes.

- Section 15: Requirements for Grade C & D routine monitoring detailed - As for section 8, risk management techniques are required to justify locations, number and frequency of samples for routine monitoring of Grade C & D areas. Unlike Grades A & B, however, monitoring need not be continuous. PI 032-2, however, makes it clear that monitoring episodes should be more frequent than requalification. The risk assessment should justify the frequency.

To consider: If you use central monitors with long tube lengths, do you currently employ correction factors to allow for particle absorbance? If not, you will need to determine and implement them. It may also be worth considering a risk assessment on retrospective results.

Changes to the Requirements for Bioburden Testing

Section 80: Requirements for bioburden testing have been expanded for parametrically released, terminally sterilised and aseptic product – In most cases, this section will already be met or exceeded by manufacturers but some may find that additional specifications and testing are required. PI 032-2 provides good guidance on exactly what is expected and manufacturers should review this against their current practice.

Changes to Finishing of Aseptically Filled Vials

Section 116: Environmental requirements for partially stoppered freeze drying vials detailed – As a standalone requirement, this section is clear; partially stoppered vials must be maintained in Grade A conditions until fully stoppered, even during transfer to freeze drying. However, when considered against section 34 (which allows transport in sealed containers through Grade B environments), there is some confusion.

Validation of transfer in sealed containers can be problematic, and it is suggested that section 116 be applied except where a manufacturer has complete confidence in their system and the documented justification for using it in lieu of full Grade A conditions.

To consider: If you currently transfer to freeze drying in sealed containers, you should seriously consider moving to comply with section 116.

Section 119: Crimping to be performed at separate station from filling and stoppering – This description would fit most filling setups, however, the intent of the section is to ensure that unstoppered vials are not compromised by the particle generating nature of the crimping activity. How a station is segregated (distance/physical barrier/airflow) is up to the manufacturer, but it is essential to demonstrate protection of the open vial.

Low Impact Changes

For the large majority of manufacturers, these changes will have little or no impact on current practices. They should be reviewed, however, to ensure that you are in compliance.

Changes to the Requirements for Classifying and Monitoring Clean Rooms

Section 3: Validation of laminar conditions for open clean rooms and isolators/glove boxes – Requirement is largely met through existing classification and qualification techniques. Requirement provides regulatory certainty.

Section 5: Comparative ISO levels for each clean room classification have been added - This section reiterates what can already be inferred from the particulate limit table in section 4.

Section 7: Description of when it is suitable to perform 'in operation' testing and provision of guidance reference standard - Provides options and removes ambiguity over when it is acceptable to perform such testing.

Section 12: Clarification on sample size requirements added - This section confirms that sample sizes do not necessarily need to meet full classification volumes. PI 032-2 goes further to suggest that it is undesirable to use full sample volumes in areas such as Grade A, where alarm responses need to be immediate.

Section 13: Information on how to interpret 5 micron particle counts detailed – While this information is unlikely to prompt significant changes, it is likely to be useful when investigating counts, particularly as a prompt as to what impacts and mitigations might be considered .

Section 16: Regulatory perspective on temperature and humidity requirements added - Temperature and humidity limits should be set with the product in mind, but must not compromise the room cleanliness

Changes to Failure Treatment for Media Fills

Section 70: Information on how to investigate gross media fill failures added - Investigations into gross failures must consider the risk to production batches manufactured since the last successful media fill.

Changes to Finishing of Aseptically Filled Vials

Section 118: Definition of integral container closure provided (stoppered AND capped vial) - While generally this definition would be applied in any case, it has impact with regards to ensuring crimping is conducted expediently, and with some environmental requirements as discussed in section 120 under Significant Impact Changes.

Section 121: Information on handling of vials rejected due to missing/displaced stoppers added – This section reinforces good housekeeping and aseptic practice

Section 122: Support for the use of RABS and isolators in capping operations – This is not a requirement, but intended as advice.

A quick reference table is included below, summarising the changes which have been discussed above.

Section	ADDED (in new Guide but not old Guide) / DELETED (in old Guide but not new Guide) / CHANGED (wording/intent has been modified)	Likely Impact
3	ADDED: Requirement to define 'in operation' and 'at rest' conditions for all clean rooms or suites of clean rooms	Moderate
3	ADDED: Maintenance of laminar conditions must be demonstrated in open applications, in isolators/glove boxes, lower conditions are allowable	Low
4	ADDED: Clean rooms and clean air devices to be classified in accordance with ISO 14644-1	Moderate
4	CHANGED: Limits for non-viable particles in Grade A through D environments	Significant
5	ADDED: Comparative ISO levels for each clean room classification.	Low
6	ADDED: Description of equipment appropriate to classify clean rooms	Moderate
7	ADDED: Description of when it is suitable to perform 'in operation' testing and provision of guidance reference standard	Low
8	CHANGED: Requirement to monitor clean rooms routinely 'in operation' now requires justification of monitoring locations through risk assessment	Significant
9	ADDED: Detailed requirements for Grade A monitoring	Moderate
10	ADDED: Requirement for continuous monitoring for Grade B areas	Significant
11	ADDED: Limitations on Particle measuring systems	Moderate
12	ADDED: Clarification on sample size requirements	Low
13	ADDED: Information on how to interpret 5 micron particle counts	Low

Section	ADDED (in new Guide but not old Guide) / DELETED (in old Guide but not new Guide) / CHANGED (wording/intent has been modified)	Likely Impact
15	ADDED: Requirements for Grade C & D routine monitoring	Moderate
16	ADDED: Regulatory view on temperature and humidity requirements	Low
69	CHANGED: Details of how to determine failure limits on media fill studies. Statistical methodology has been deleted and specific limits included	Significant
70	CHANGED: Information on how to investigate media fill failures now includes additional statement on gross failures	Low
80	CHANGED: Requirements for bioburden testing has been clarified for parametrically released, terminally sterilised and aseptic product	Moderate
116	ADDED: Requirement for partially stoppered freeze drying vials to be maintained under Grade A at all times until stopper is fully inserted	Moderate
118	ADDED: Definition of integral container closure provided (vial, stopper and cap)	Moderate
119	ADDED: Crimping to be performed at separate station from filling and stoppering	Moderate
120	ADDED: Provision for aseptic or 'clean' capping operations made. Requirements for crimping when not performed aseptically detailed.	Significant
121	ADDED: Information on handling of vials rejected due to missing/displaced stoppers	Low
122	ADDED: Support for the use of RABS and isolators in capping operations	Low

What should you do?

You should review your current Quality Management System and practices against the new regulations to determine what extent of change is required to comply with the new annex. The “to consider” points raised in this paper may provide a useful starting point.

It is inevitable that some degree of change management will be required to ensure that all aspects of the new annex have been met. It is likely you will need to consider aspects of policy and procedure revision, resourcing and training in order to be fully compliant.

As leading compliance experts within Australasia, PharmOut can significantly reduce this effort and allow you to focus on your everyday business operations of making and selling quality products.

References

TGA Document: MP1/2009: Therapeutic Goods (Manufacturing Principles) Determination No. 1 of 2009

TGA Information for Manufacturers: Updated manufacturing principles for medicinal products

www.tga.gov.au/manuf/mpupdate.htm

Australian Code of GMP for Medicinal Products (16 Aug 2002) (Annex 1)

PIC/S Document: PE 009-8 (Annex 1): PIC/S Guide to Good Manufacturing Practice for Medicinal Products (15 Jan 2009)

PIC/S Document PI 032-2: PI 032-2: GMP Annex 1 Revision. 2008, Interpretation of Most Important Changes for the Manufacture of Sterile Medicinal Products (1 Dec 2009)

Sources

Links used within this document are prone to change. Please refer to the appropriate source for the most recent information. We endeavour to keep an up-to-date record of information at www.pharmout.net



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