



PIC/S GMP Guide Annex 1 - Manufacture of sterile medicinal products

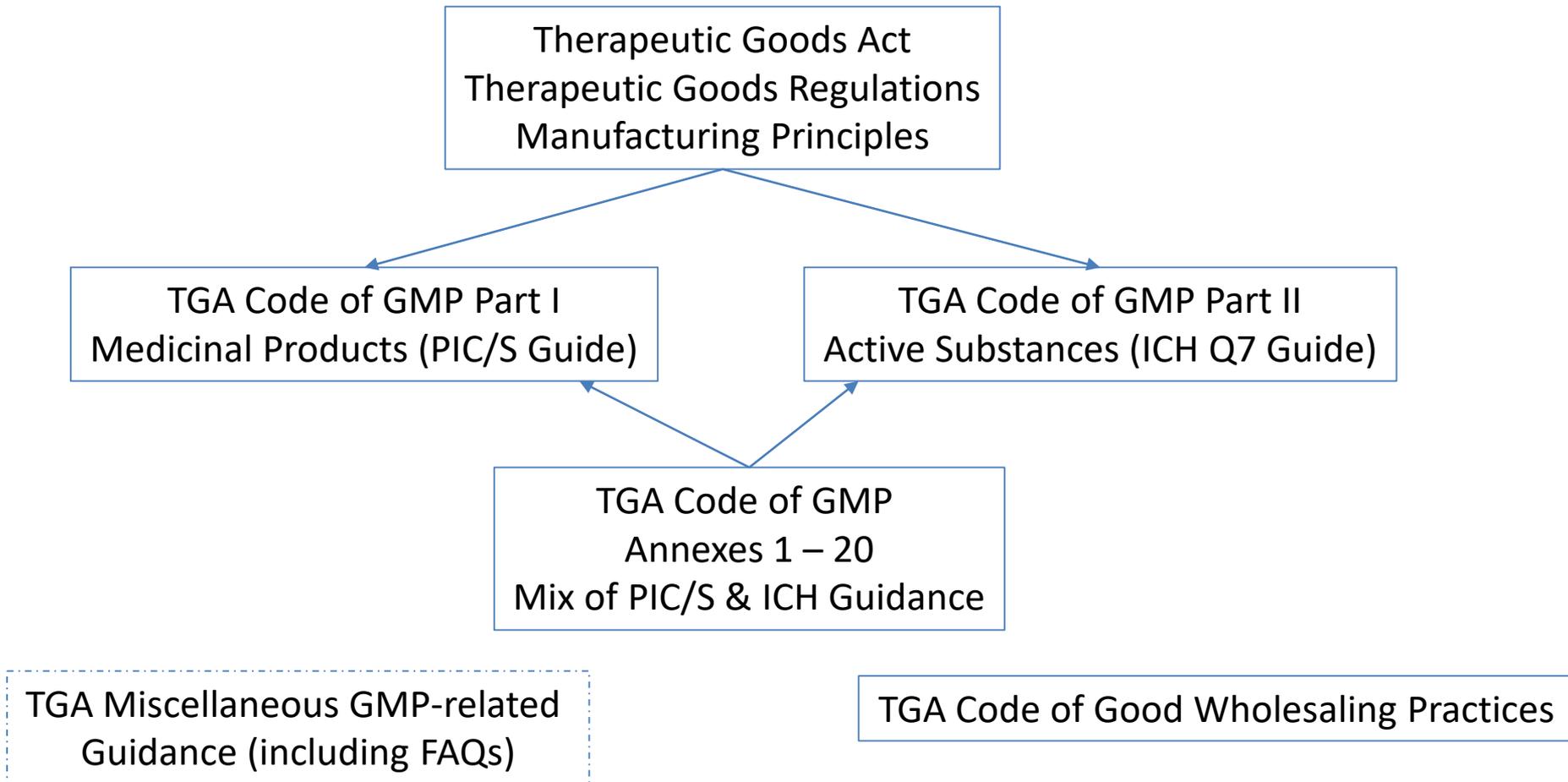
Current Version vs. Draft –
Comparing the Changes and
Differences

SP6530 Ver 1.0

Revision History

- Annex 1 was last revised in the release of PIC/S 009-08 in January 2009.
- PIC/S 009-08 was the version adopted by TGA until 31 Dec 2017 (and still being adopted by Medsafe)
- Therefore, no updates since PIC/S 009-08 for Australian (and NZ) manufacturers

Australian GMPs for Medicinal Products



Supporting 'Recommendation' for Annex 1

TGA Code of GMP
Annex 1 – Manufacture of Sterile Medicinal Products

PI 032-2 GMP ANNEX 1 REVISION 2008, INTERPRETATION OF
MOST IMPORTANT CHANGES FOR THE MANUFACTURE OF
STERILE MEDICINAL PRODUCTS (8 Jan 2010)

Will PIC/S Prepare an interpretation
for the new Annex 1?

What are the Changes in the Draft Annex 1?

- 18 pages is now 50 pages
- Should consider this as a new document, not an update of existing Annex 1
- **Scope** may include non-sterile *‘where the control of microbial, particulate and pyrogen contamination....is considered important’*

Is There More Regulation?

Word Count	Must	Shall	Should	May
Existing Annex 1 (PE009-08)	9	0	251	27
New Draft Annex 1	19	3	602	55

Table: The number of occurrences of each word in Annex 1 of the GMP Guide

PDA's Response on Behalf of its Members

Clarify the intent of statements. It is not always clear if the authors intended for a statement to be read as a requirement, a recommendation, a suggestion, or an opinion. Words and phrases such as “encouraged”, “in alignment with”, “typically” or “in consideration of” lack clarity of intent and should be avoided or better defined. Where words such as “should”, “must”, “shall”, “may” and “can” are used, it would be helpful to have a better idea which of these words denotes a requirement, a recommendation, or a suggestion. Qualifying words such as “sufficient”, “appropriate”, “optimized”, “similar”, and “suitable”, lack definable criteria and should also be avoided, as they are difficult to objectively define and will likely be different for different companies.

Scope

Impact of Scope

- *‘This Annex provides general guidance that should be used for all sterile medicinal products and sterile active substances...’*
- *‘The intent of the Annex 1 is to provide guidance for sterile medicinal products.’*
- *‘However some of the principals and guidance, such as contamination control strategy, room qualification, classification, monitoring and gowning, may be used to support the manufacture of other products that are not intended to be sterile (such as certain liquids, creams, ointments and low bioburden biological intermediates) but where the control of microbial, particulate and pyrogen contamination, to reduce it as far as possible, is considered important.’*

PDA's Response on Behalf of its Members

Comment: It is stated in the Scope that the requirements 'principles and guidance ... products that are not intended to be sterile (such as....)'; we acknowledge the inclusion of this statement; however, it may not always be possible to apply such requirements to 'non-sterile products'. It is suggested to remove any 'non-sterile' products from the 'scope' of this guidance. This may lead to unnecessary confusion when the document is only aimed at 'sterile' products. Nonetheless, once adopted by PIC/s it may trigger translation to other languages and hence may lead to additional confusion and lead to increased requirement for non-sterile products.

Proposed change: Clarify intent by replacing line with: "~~However~~ While it is not a requirement, some of the principles and guidance, such as contamination control strategy, room qualification, classification, monitoring and gowning, may be used to support the manufacture of other products that are not intended to be sterile (such as certain liquids, creams, ointments and low bioburden biological intermediates) but where the control of microbial, particulate and pyrogen contamination, to reduce it as far as possible, is considered important."

Impact of Scope – Annex 2

PIC/S PE009-13

- **Annex 2** – Manufacture of Biological Medicinal Substances and Products for Human Use
 - ‘The environmental monitoring program in addition to **Annex 1** should be supplemented by the inclusion of methods to detect the presence of specific microorganisms (e.g. host organism, anaerobes, etc.) where indicated by the QRM process’
 - ‘These QRM principles should take into account the principles and requirements from the appropriate sections of **Annex 1** when selecting environmental classification cascades and associated controls.’

Impact of Scope – Annex 2 (cont.)

PIC/S PE009-13

- **Annex 2** – Manufacture of Biological Medicinal Substances and Products for Human Use
 - ‘Given that the risks from the introduction of contamination and the consequences to the product is the same irrespective of the stage of manufacture, establishment of a control strategy to protect the product and the preparation of solutions, buffers and other additions should be based on the principles and guidance contained in the appropriate sections of **Annex 1**. ‘

Impact of Scope – Annex 3

PIC/S PE009-13

- **Annex 3** Manufacture of Radiopharmaceuticals
 - ‘Radiopharmaceuticals to be administered parenterally should comply with sterility requirements for parenterals and, where relevant, aseptic working conditions for the manufacture of sterile medicinal products, which are covered in PIC/S GMP Guide, **Annex 1.**’
 - ‘For manufacture of sterile products the working zone where products or containers may be exposed to the environment, the cleanliness requirements should comply with the requirements described in the PIC/S GMP Guide, **Annex 1.**’

Impact of Scope – Annex 9

PIC/S PE009-13

- **Annex 9** Manufacture of Liquids, Creams and Ointments
 - No reference to Annex 1
 - Yet scope **may** be relevant to this group of products.

Personnel

Personnel

4.3 Personnel Training

What and
how

‘All personnel (including those performing cleaning and maintenance) employed in such areas should receive regular training, *qualification (including sampling of the operators bioburden, using methods such as contact plates, at key locations e.g. hands, arms and chest) and assessment* in disciplines relevant to the correct manufacture of sterile products. This training should include reference to hygiene, *cleanroom practices, contamination control, aseptic techniques, and potential safety implications to the patient of a loss of product sterility and in the* basic elements of microbiology.’

Why

Personnel (cont.)

4.4 Grade A/B cleanroom aseptic gowning and aseptic practice training

- *‘...aseptic gowning procedures should be assessed and confirmed and ... periodically reassessed **at least annually** and should involve both visual and microbiological assessment (using additional locations such as arms and chest).*
- *Only trained personnel who have **passed the gowning assessment** and have participated in a **successful aseptic process simulation (APS) test**, ..., should be authorized to enter any grade A/B area, ..., whilst unsupervised.’*

Personnel (cont.)

4.4 Grade A/B cleanroom aseptic gowning and aseptic practice training

- *‘The microbial monitoring ... should be performed to assess their aseptic behaviour... **immediately after completion of a critical intervention** and upon **each exit from the cleanroom**. ...also be an ongoing continuous monitoring program for personnel ... under the supervision of the quality unit.’*

PDA's Response on Behalf of its Members

Comment: Section 4.4 requirement for personnel to participate in a successful aseptic process simulation as a prerequisite for unsupervised entry to the Grade A/B is unnecessary and in conflict with PDA published positions, in PDA Technical Report 22 (2011) and Aseptic Processing Points to Consider Part 1 (2015). Each person entering the aseptic processing area has the potential to introduce microbiological contamination; however, the risk to product may vary with the specific job function. Personnel within an aseptic processing area present the greatest potential of microbial contamination and as such require extensive training, monitoring and on-going training to reduce the likelihood of viable particulate shedding/contamination. The critical aspects of qualification involve the ability of personnel to understand and perform their job functions, and should assure that aseptic processing area personnel have the proper training and knowledge for their respective functions. **Testing through Aseptic Process Simulation is not sensitive enough to fully qualify personnel to work in the Grade A/B area.** Participation in media fills does not provide additional assurance of adherence to proper clean room behavior. And mere adherence to this requirement may result in clean room personnel allowed to work in Grade A/B areas without proper knowledge and demonstration of clean room behavior. Instead we recommend an emphasis on training and monitoring, as noted in the aforementioned Technical Report and Points to Consider. In addition, as currently written, the requirement would be burdensome and limiting for certain ATMP (Advanced Therapy Medicinal Product) aseptic processes.

PDA's Response on Behalf of its Members

Proposed change: “4.4 Only trained, **qualified** personnel who have passed the gowning assessment and **have demonstrated their proficiency in aseptic technique by either successfully performing a qualification test entailing manual media manipulation not associated with a full aseptic process simulation (APS), or** have participated in a successful aseptic process simulation test, in both cases simulating or performing their normal duties, should be authorized to enter any grade A/B area, in which aseptic operations will be conducted, or are being conducted, whilst unsupervised.”

Personnel (cont.)

4.5 Disqualification and requalification of staff entering cleanrooms

- *‘Disqualification of personnel from entry into cleanrooms, based on aspects including ongoing assessment and/or the identification of an **adverse trend** from the personnel monitoring program.*
- *Once disqualified, retraining and requalification is required before permitting the operator to have any further involvement in aseptic practices.*
- *This should include consideration of participation in a successful Aseptic Process Simulation (APS)’*

Personnel (cont.)

4.7 Personal Hygiene

- ‘Personnel involved in the manufacture of sterile preparations should be instructed to report any specific health conditions or ailments which may cause the shedding of abnormal numbers or types of contaminants and therefore preclude clean room access; periodic health checks for such conditions ~~are desirable~~ *should be performed.*’

Personnel (cont.)

4.9 Personal Items

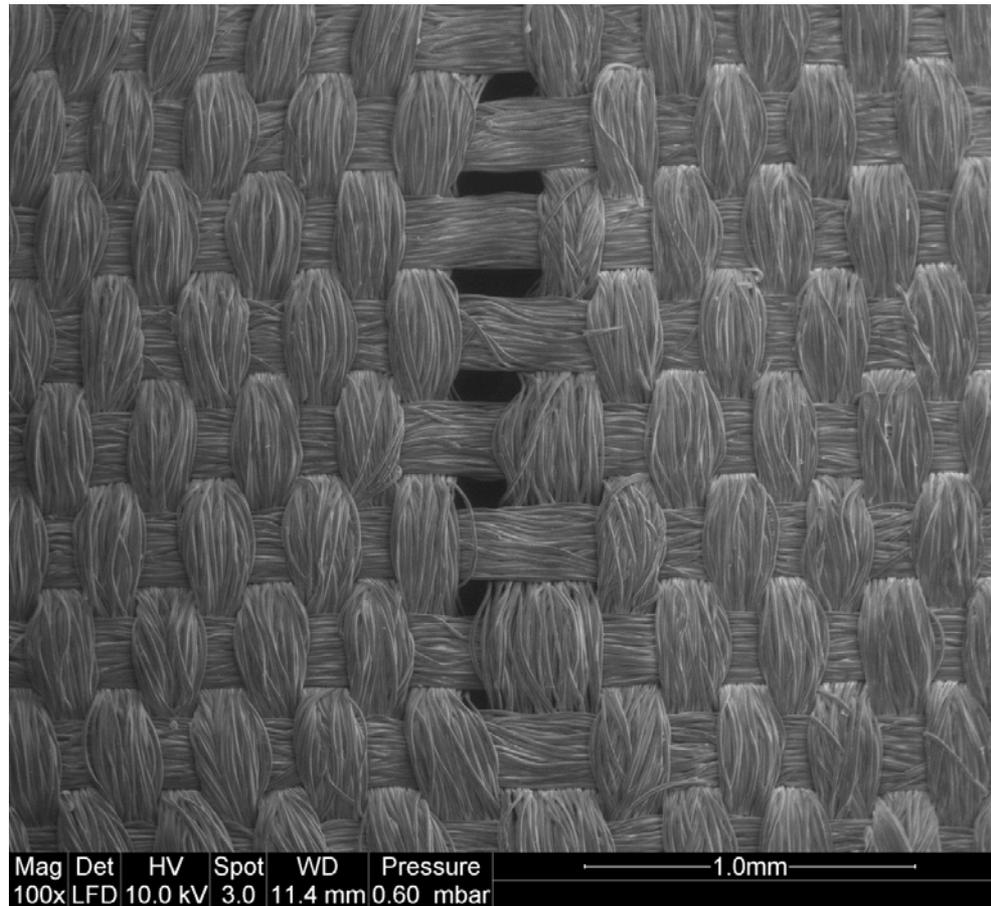
- Wristwatches, make-up and jewellery *and other personal items such as mobile phones* should not be allowed in clean areas.

Personnel (cont.)

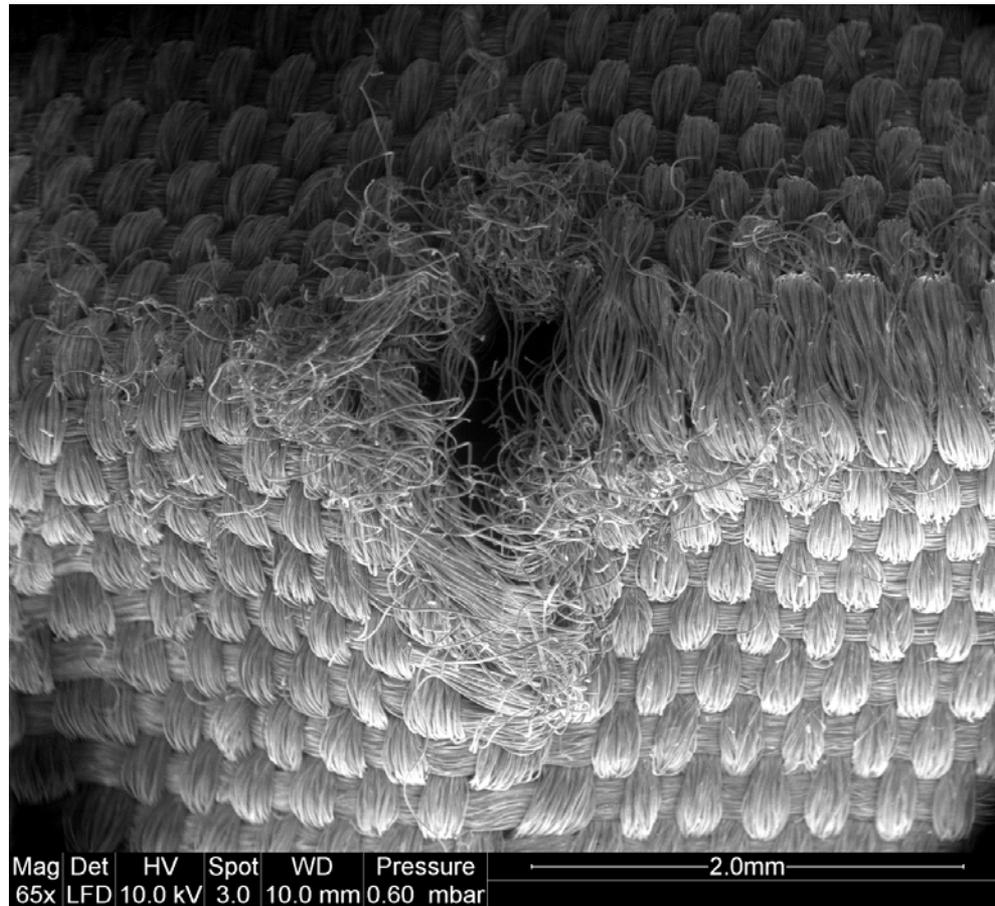
4.10 Garments

- *‘Garments should be visually checked for cleanliness and integrity prior to entry to the cleanroom. For sterilized garments, particular attention should be taken to ensure that garments and **eye coverings** have been sterilized and that their packaging is integral before use. Reusable garments should be replaced based at a set frequency determined by qualification or if damage is identified.’*

Stretch



Hole



Personnel (cont.)

4.12 Garments

- Grade D:
 - ‘hair, ~~and where relevant~~ beards *and moustaches* should be covered’
 - ‘...appropriately *disinfected* shoes or overshoes should be worn.’
- Grade C:
 - ‘hair, ~~and where relevant~~ beards and moustaches should be covered’
 - ‘...appropriately *disinfected or sterilized* shoes or overshoes should be worn.’

Personnel (cont.)

4.12 Garments

- Grade A/B:
 - *Sterile* headgear should totally enclose hair and where relevant beards and moustaches *and facial hair*; it should be tucked into the neck of the *sterile* suit; a *sterile* face mask *and sterile eye coverings* should be worn to *cover all facial skin and* prevent the shedding of droplets *and particles*. Appropriate sterilized, non-powdered rubber or plastic gloves and sterilized or ~~disinfected~~ footwear should be worn. Trouser-legs should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body. *Garments should be packed and folded in such a way as to allow operators to change into the garments with contact to the outer surfaces of the garment reduced to a minimum.*

Personnel (cont.)

4.13 Garments

- Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. *It is recommended that facility suits, including dedicated socks be worn before entry to change rooms for grade C and B. Where clothing is reused this should be considered as part of the qualification.*

Personnel (cont.)

4.14 Garments

- For every worker in a grade A/B area, clean sterilized (or adequately sanitized) protective garments (*including eye coverings and masks of an appropriate size*) should be provided at each work session. Gloves should be regularly disinfected during operations. *Garments* masks and gloves should be changed at least for every working session.

Personnel (cont.)

4.15 Garments

- Clean area clothing should be cleaned, handled *and worn* in such a way that it does not gather additional contaminants which can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibres and may increase the risk of shedding of particles. *After washing and before sterilization, garments should be checked for integrity.*