



White Paper

# TGA GMP Update: New Manufacturing Principles for Medicinal Products

On the 29th July 2009, the TGA determined new manufacturing principles for medicinal products that effectively replace the current TGA code of GMP with the 2009 version of the PIC/S GMP Guide. The new code becomes mandatory on 1st July 2010.

## Introduction

The Therapeutic Goods Administration (TGA) currently licenses the manufacture of medicinal products in Australia in accordance with the Australian code of Good Manufacturing Practice for Medicinal Products (dated 16th August, 2002).

On the 29th July 2009, the Australian government legislated the implementation of a new set of manufacturing principles under the Therapeutic Goods (Manufacturing Principles) Determination No. 1 of 2009.

This determination (with some minor exceptions) effectively replaces the current code with the Guide to Good Manufacturing Practice for Medicinal Products (PE009-8) (dated 15th January, 2009) published by the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

The updated principles are scheduled to become mandatory for all manufacturers of medicinal products (who are subject to the TGA) on 1st July 2010. In the interim, the TGA will accept compliance with either the existing manufacturing principles, or the updated principles.

**Table 1: Implementation dates for Therapeutic Goods (Manufacturing Principles) Determination No. 1 of 2009**

Date	Active TGA code of GMP for Medicinal Products
Prior to 29th July 2009	Australian code of GMP (Aug 2002)
29th July 2009 to 30th June 2010	Australian code of GMP (Aug 2002) or PIC/S Guide to GMP (Jan 2009)
1st July 2010	PIC/S Guide to GMP (Jan 2009)

What does this mean for your company?

You will need to answer this for yourself, but history has shown that companies that react quickly and effectively to change are well placed to succeed.

## Why is the TGA changing to the PIC/S GMP guide?

The change to the PIC/S Guide has been an ongoing process for the TGA over many years; the existing code is actually a slightly modified version of the PIC/S Guide published in January 2002. There are currently 35 national authorities participating in the PIC/S scheme, as well as several international authorities, including the World Health Organisation (WHO).

From the TGA's perspective, participation in PIC/S is useful in several ways; most importantly:

- It preserves Australia's equivalence with international regulatory partners required under Mutual Recognition Agreements (MRAs) for GMP certifications. This allows TGA certification of Australian companies to be recognised internationally, and certification by authorities with MRAs to be recognised in Australia. To put it simply, different national authorities can audit on behalf of each other.
- It reduces the regulatory burden on Australian manufacturing companies competing overseas, by minimising the requirement to comply with different codes for different countries.

*The mission of PIC/S is 'to lead the international development, implementation and maintenance of harmonised Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products'.*

## Who is affected by the changes?

The updated principles apply to all medicinal product manufacturers previously subject to the Australian Code of GMP (2002). Active Pharmaceutical Ingredient (API) manufacturers under TGA jurisdiction are also affected, however they are not addressed by this white paper.

The updated principles do not apply to manufacturers of the following product types:

- Blood, blood components, plasma and haematopoietic progenitor cells - For these products, there is no change to existing compliance arrangements. The related Annex 14 of the new guide will not come into force with the rest of the document.
- Veterinary products - Annexes 4 & 5 (veterinary products) have been published in full in the new guide, but are not enforceable by the TGA. The Australian Pesticides and Veterinary Medicines Authority (APVMA) is still the regulatory authority for veterinary medicines in Australia.
- Human tissue - There is no change to existing compliance arrangements for these products. The new guide makes no reference to human tissue products.
- Therapeutic devices - There is no change to existing compliance arrangements for these products. The new guide makes no reference to therapeutic devices.

## What are the key changes in the new code?

There are numerous changes in the updated code—some will have little impact on manufacturers, while some changes are significant. The key changes are summarised below.

### Product quality review

The new code includes product quality reviews—companies with experience in FDA compliance will be familiar with these. This is the first time that the TGA has required such reviews. Product quality reviews should be performed annually for all licensed medicinal products (including export only products). The new code includes prescriptive details of the review requirements.

Reviews, as a minimum, must consider starting materials (including packaging), in-process and finished product results, batch failures, significant deviations, changes to process and analytical methods, marketing authorisation variations, stability results, complaints and recalls, corrective actions, post-marketing commitments, equipment qualification status and contractual arrangements (for contract manufacturers).

It is also expected that each review is evaluated and assessments made on need (or otherwise) for corrective and preventative action, including re-validation.

Allowance is given for the grouping of reviews by product type (e.g. solid dose, sterile, etc.) where 'scientifically justified'. It should be understood, however, that each individual licensed product must be reviewed and assessed fully, even when part of a grouped report.

### **Ongoing stability program**

The previous code briefly mentions the expectation that stability monitoring should form part of a GMP compliant quality control program. The new code expands considerably on this concept and provides detailed instructions on what is expected, leaving little to interpretation.

The new code includes requirements for protocol content, number of batches, frequency of testing, reporting and investigation.

The expanded requirements for an ongoing stability program are complimented by the new Annex 19 (Reference & Retention Samples), which provides information on the reference and retention samples.

### **Manufacture of sterile medicines**

Annex 1 (Manufacture of Sterile Medicinal Products) of the new code has been revamped. Several changes with significant impact have been made and include:

- requirement to classify clean rooms in accordance with ISO 14644
- changes to allowable non-viable particle count limits in all grades (A-D) of clean room environments (limits are now typically slightly more lenient)
- changes to monitoring and measurement of clean room environments (in particular, the expectation of continuous monitoring in both Grade A and B environments)
- detailed new requirements for container closure of freeze-dried vials
- changes to acceptable failure limits for process simulations (media fill studies) which are more clearly defined and typically tighter than previously allowed.

### **Quality risk management**

Detailed information on quality risk management has been included as a new, voluntary approach, to demonstrate compliance with the code.

The new Annex 20 (Quality Risk Management) provides more than 25 pages of information detailing quality risk management concepts, methodology, applications, definitions, references and examples.

Note that, at this stage, quality risk management is considered a voluntary part of a GMP compliant quality management system. Its inclusion in the code indicates that early adoption of this approach is likely to be beneficial in the future.

### **Other changes**

Below is a summary of the changes recognised to have potential compliance impact for manufacturers. Note that the table does not include minor changes, such as spelling, grammar or terminology updates, unless they change the intent or interpretation of the document.

**Table 2: Summary of changes**

Section	Changes	Potential impact
Introduction	ADDED: details of the two-part nature of the new guide, revision details and adoption information	None
Introduction	DELETED: explanations of the changes made through the original harmonisation process	None
Introduction	DELETED: interpretation section - specifically the applications of terms 'should', 'shall' and 'must'. 'Should' is now defined in MP1/2009	Low
1 (Quality Management - Principle)	ADDED: "quality risk management" as part of system of quality assurance	Significant
1.1 (Quality Assurance)	DELETED: "good laboratory practice" ensured by system of quality assurance	Low
1.3 (vii) (Quality Control)	CHANGED: release for sale to be approved in accordance with 'relevant authorisations' instead of 'marketing authorisations'	None
1.4 (Product Quality Review)	ADDED: entire section, sub-points (i) to (xii) and additional information	Significant
1.5-1.6 (Quality Risk Management)	ADDED: definition and requirements of quality risk management within overall quality management	Significant
6.23-6.33 (Ongoing Stability Program)	ADDED: detailed requirements for stability program for medicinal products	Significant
7 (Contract Manufacture & Analysis)	ADDED: explanatory note clarifying intent of section	None
7.15 (Contract Manufacture & Analysis)	DELETED: reference to the TGA as the competent inspection authority in Australia	None

Section	Changes	Potential impact
8.4 (Complaints)	CHANGED: action post defect from 'other batches should be checked' to 'consideration should be given to checking other batches'	Low
8.7-8.8 (Complaints)	ADDED: statements identifying counterfeiting as a specific cause of customer complaint, worthy of special attention	Low
Annex 1 (Steriles) Item 3	ADDED: requirement to define internally 'in operation' and 'at rest' conditions for all clean rooms or suites of clean rooms	Low
Annex 1 (Steriles) Item 3	CHANGED: laminar flow air velocity specs for open clean rooms changed from 0.45 m/s $\pm$ 20% to 0.36 – 0.54 m/s and must be validated	Low
Annex 1 (Steriles) Item 3	ADDED: in isolators and glove boxes, lower air velocities than those specified above are permissible	Low
Annex 1 (Steriles) Item 4	ADDED: clean rooms and clean air devices to be classified in accordance with ISO 14644	Significant
Annex 1 (Steriles) Item 4	CHANGED: limits for non-viable particles in Grade A through D environments	Significant
Annex 1 (Steriles) Items 5-16	ADDED: detailed information relating to the measurement and monitoring of clean rooms and clean air devices. Includes concepts of continuous monitoring, particle counter configurations, when to perform in-operation testing and more.	Significant
Annex 1 (Steriles) Item 69	CHANGED: details of how to determine failure limits on media fill studies. Statistical methodology has been deleted and specific limits included. These limits are typically tighter than previously allowed.	Significant
Annex 1 (Steriles) Item 70	CHANGED: requirements for failure investigation are expanded to detail the type of investigations required under different circumstances	Low

Section	Changes	Potential impact
Annex 1 (Steriles) Item 80	CHANGED: requirements for bioburden assay have been expanded to define requirements for aseptic processing, terminal sterilisation and parametric release. Also, the term 'absence of pyrogens' has been changed to 'level of endotoxins'.	Significant
Annex 1 (Steriles) Item 116	ADDED: requirement for partially-stoppered freeze drying vials to be maintained under Grade A at all times until stopper is fully inserted	Significant
Annex 1 (Steriles) Items 118-120	ADDED: new requirements regarding vial capping in aseptic processes. (118) it must be performed as soon as possible after stoppering. (119) It must be done at a separate station from the filling/stoppering functions with adequate air extraction. (120) It may be done aseptically or as a 'clean' operation but, either way, the stoppered vial must be protected by Grade A air until the completion of crimping.	Significant
Annex 1 (Steriles) Items 121-122	ADDED: information on minimising human intervention in finishing (stoppering/ capping) aseptically produced product	Low
Annex 4 (Veterinary - non immunological)	ADDED: the full text of the annex is included in the code, however, the Manufacturing Principles Determination 2009 excludes this annex from the definition of 'the code'. That is, the TGA will not administer this part of the Guide. Veterinary products remain under the jurisdiction of the APVMA.	None
Annex 5 (Veterinary - immunological)	ADDED: the full text of the annex is included in the code, however, the Manufacturing Principles Determination 2009 excludes this annex from the definition of 'the code'. That is, the TGA will not administer this part of the Guide. Veterinary medicines remain under the jurisdiction of the APVMA.	None
Annex 6 (Medicinal gases) section 1	ADDED: scope has been clarified by expressly excluding the manufacture and handling of gases in hospitals from the scope of the annex	Low

Section	Changes	Potential impact
Annex 14 (Human blood or plasma products)	ADDED: the full text of the annex is included in the code, however, the Manufacturing Principles Determination 2009 excludes this annex from the definition of 'the code'. That is, the TGA will continue to assess blood products against the existing code).	None
Annex 18 (Active Pharmaceutical Ingredients)	CHANGED: Annex 18 is now Part II of the new code	None
Annex 19 (Reference and retention samples)	ADDED: new annex, adopted in full and previously not part of the code	Significant
Annex 20 (Quality risk management)	ADDED: new annex, adopted in full and previously not part of the code. Note, however, that this annex is marked as 'voluntary'	Significant

## What should you do?

You should review your current quality systems against the new regulations to determine what extent of change is required. It is likely you will need to consider 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

Reference	Title
TGA Document: MP1/2009	Therapeutic Goods (Manufacturing Principles) Determination No. 1 of 2009
<a href="http://www.tga.gov.au/manuf/mpupdate.htm">www.tga.gov.au/manuf/mpupdate.htm</a>	TGA Information for Manufacturers: Updated manufacturing principles for medicinal products
N/A	Australian Code of GMP for Medicinal Products (16 Aug 2002)
PIC/S Document: PE009-8 & Annexes	PIC/S Guide to Good Manufacturing Practice for Medicinal Products (15 Jan 2009)

## About PharmOut

PharmOut is a boutique consultancy to the Pharmaceutical, Medical Device, and Veterinary drug industries.

PharmOut specialises in GMP compliance, validation and continuous improvement consulting and training.

## How PharmOut can help

We offer a range of services to assist companies with their compliance programs while maintaining operational efficiencies.

### **GMP Gap Analysis**

We can assess your current quality system and identify potential compliance gaps and operational inefficiencies. We achieve this through in-depth knowledge of the codes of GMP and practical experience in implementing workable solutions through a risk-based approach.

The advantage to companies is that precious internal resources are not diverted from core business activities, and it alleviates the pressure to set the high compliance levels to avoid mis-interpretations of the GMP requirements.



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