



Australian Government

Department of Health

Therapeutic Goods Administration

Guidance on release for supply

For medicinal product manufacturers

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TGA Health Safety
Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<http://www.tga.gov.au>>.

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Version history

Version	Description of change	Author	Effective date
V1.0	Draft open for industry consultation	Office of Manufacturing Quality	03/06/2013
V2.0	Revised Original publication	Office of Manufacturing Quality	21/01/2015

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About this guidance

This guidance document is published by the TGA to provide industry with guidance on release for supply of medicines. This guidance document is developed in consultation with industry involving experts from the relevant industry associations.

Industry has indicated the need for TGA guidance on release for supply, for various reasons.

- The Australian system of release for supply by an Authorised Person is different from the European system of batch release by a Qualified Person. Annex 16 of the current European Union (EU) Good Manufacturing Practice on the Qualified Person has not been adopted in the PIC/S Guide to Good Manufacturing Practice for Medicinal Products. Consequently, the PIC/S Guide to GMP provides no specific guidance in this area, leaving industry with an information gap that could be filled with a guidance document specific for the Australian situation with regards to release for supply of medicinal products.
- With the adoption of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products – 15 January 2009 - PE009-8 under the Therapeutic Goods (Manufacturing Principles) determination No 1 of 2013, the requirement to prepare regular Product Quality Reviews was newly introduced and further detail was provided on several pre-existing requirements, for example those on the on-going stability program. As these responsibilities are related to the Authorised Person's responsibility for release for supply, additional guidance was required on how to meet these responsibilities, in particular for:
 - The range of medicines regulated in the Australian Market and the level of detail that is required of each class of medicines. TGA classifies manufacture using a risk based approach. Classification for manufacturers is listed on the TGA website. The link is as follows:

§ <<https://www.tga.gov.au/manufacture-inspections-productprocess-risk-classifications>>

Complex manufacturing and supply chain situations

In order to provide a comprehensive overview on release for supply, this document contains two parts;

Part 1 describes the general requirements and responsibilities regarding release for supply by an Authorised Person applicable to all TGA licensed and/or certified manufacturers and to Australian sponsors.

Part 2 describes distinctive differences for identified categories and describes specific considerations on how the general requirements described in Part 1 above can be met for specific areas of manufacture, for example complementary medicines or sunscreens, or for different supply chains.

This guidance document is not applicable to the manufacture of Active Pharmaceutical Ingredients (APIs). Where APIs meet the definition of a medicine and the PIC/S Guide to GMP, Part II, requires APIs to be released, various release related requirements for finished medicinal products do not apply or apply only in part to APIs, for example Product Quality Reviews and GMP agreements. As the need for additional guidance was only identified for finished medicinal products, this document was developed specifically for finished medicinal products.

This guidance document is applicable to investigational medicinal products, subject to any difference in the legal provisions and more specific guidance in Annex 13 of the current PIC/S Guide to GMP.

This guidance document does not apply to products covered under the regulatory framework for biologicals (products covered in Part 3-2A of the *Therapeutic Goods Act 1989* such as products containing or derived from human cells or human plasma). However this guidance does apply to medicines from biological origin, such as vaccines and biotechnology products.

This guidance document does not address the official control authority batch release specified for certain blood and immunological products.

Nothing in this guidance document should be taken as overriding the arrangements of a medicine's Marketing Authorisation.

Part 1: General requirements and responsibilities

1. Introduction

1.1 The PIC/S Guide to Good Manufacturing Practice for Medicinal Products (PIC/S Guide to GMP), clause 1.1vii defines release for supply as: *"certification by an Authorised Person that each production batch has been produced and controlled in accordance with the requirements of the marketing authorisation and any other regulations relevant to the production, control and release of medicinal products"*.

Apart from clause 1.1vii, requirements relating to release for supply are also specified in other clauses of the PIC/S Guide to GMP, for example in clauses 1.2, 1.3vii and 2.3.

1.2 Release for supply is considered a step in medicines manufacture, as it is specifically mentioned in the definition of *manufacture* in chapter 1, section 3 of the *Therapeutic Goods Act 1989* (the Act), which reads:

Manufacture, in relation to therapeutic goods that are not medical devices, means:

- a. to produce the goods; or
- b. to engage in any part of the process of producing the goods or of bringing the goods to their final state, including engaging in the processing, assembling, packaging, labelling, storage, sterilising, testing or releasing for supply of the goods or of any component or ingredient of the goods as part of that process.

1.3 Each batch of finished medicinal product must be released for supply by an Authorised Person (AP) before being sold or supplied in Australia or exported from Australia. This applies to registrable and listable medicines in the same manner, as well as to investigational medicinal products (phase 2 or later) that are not required to be entered in the Australian Register of Therapeutic Goods (ARTG). Release for supply must be performed through a legally valid signature.

1.4 A manufacturer can have more than one AP. The manufacturer takes responsibility to ensure the AP's level of education and expertise is appropriate using the training arrangements in the manufacturer's quality management system. This is verified by the TGA during inspections.

1.5 Production, control and release of medicines in Australia are regulated in the Act and the Therapeutic Goods Regulations 1990 (the Regulations). Consequently, release for supply to the Australian market specifically involves a verification of all production and QC testing records of a batch, for compliance with Chapters 2 and 3 of the Act. This verification should focus on compliance with the following authorisations and standards.

1. All aspects of the Marketing Authorisation. The Marketing Authorisation includes all details in the ARTG, as well as all other matters in relation to the Marketing Authorisation agreed in writing between the TGA and the Australian sponsor.
2. For domestic manufacturers: the licence to manufacture therapeutic goods, including the authorisations and conditions under the licence; the steps in manufacture granted under section 38 of the Act as well as conditions of licences as imposed under section 40 of the Act.
3. For overseas manufacturers: the TGA GMP certificate and/or GMP clearance(s), specifically their authorisations and conditions, as imposed under sections 25(1)(g), 26(1)(g) and 26A(3) of the Act.
4. The Code of Good Manufacturing Practice (GMP) as specified in the current Manufacturing Principles.
5. Default standards under Section 10 of the Act, including the British Pharmacopoeia (BP), European Pharmacopoeia (EP) and United States Pharmacopoeia (USP).
6. All applicable Therapeutic Goods Orders (TGOs).

Guidance documents available on the TGA web site provide information for specific groups of medicines on how these requirements can be complied with.

In order to effectively take responsibility for release for supply of a finished product batch, an AP should have full access and detailed knowledge and understanding of each of the above.

1.6 “Release for supply” is the preferred term as this term reflects the legal obligations under the Act. In addition, “release for supply” or “release” are internationally harmonised terminology. The term ‘release for sale’ has become obsolete since the requirement to release finished product batches also applies to medicines that are not intended to be sold, for example free samples and investigational medicines. In the context of this guidance document, release for supply is defined as:

Release of a finished product batch for supply:

- a. to the Australian market or
- b. for export or
- c. for use in a Phase 2 or later investigational medicinal product for use in human clinical studies

1.7 Release for further processing is not release for supply and is release to the next manufacturer in the manufacturing supply chain.

1.8 As release for supply is a licensable step in manufacture within Australia, an Australian sponsor who is reluctant to share the relevant information in the Marketing Authorisation with a (contract) manufacturer performing release for supply, for example due to confidentiality issues, has the following options available to them.

1. Implement a confidentiality agreement (or include confidentiality statements in the GMP agreement).
2. Contract out the release for supply to another manufacturer with which there are no confidentiality concerns provided that manufacturer holds the relevant licence or current GMP certification/GMP clearance(s).
3. Seek to obtain a TGA licence to manufacture therapeutic goods covering release for supply.

Contracting out release for supply to an independent AP is only allowed if the AP holds or works under a TGA licence or a current GMP clearance that includes release for supply.

1.9 It is the responsibility of the sponsor to ensure that each ARTG entry includes at least one TGA approved (= licensed or holding a current GMP clearance) manufacturer that is responsible for the manufacturing step of release for supply.

2. Duties of an Authorised Person (AP)

2.1 Before releasing a batch for supply, the AP should ensure, with reference to the guidance above, that at least the following requirements have been met.

1. The batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation¹.
2. The batch has been produced and controlled in accordance with the Code of GMP as defined in the Manufacturing Principles (for domestic sites) or, in the case of a batch manufactured in an overseas country, in accordance with good manufacturing practice standards at least equivalent to that Code of GMP.
3. All manufacturers involved in producing the batch:
 - a. hold a TGA licence or are covered by a current GMP clearance for all of the manufacturing steps they have performed
 - b. are included in the ARTG entry for the manufacturing steps performed.¹
4. The principal manufacturing and release testing processes (as per finished medicinal product specifications) have been validated; account has been taken of the actual production conditions, manufacturing and test records.
5. All the necessary checks and tests have been performed; including any additional sampling, inspection, tests or checks initiated because of deviations or planned changes.
6. All necessary production and quality control documentation has been completed and endorsed by the staff authorised to do so. For quality control documentation this includes out of specification (OOS) investigations.
7. Any significant deviations or planned changes in production or quality control have been authorised by the persons responsible in accordance with a defined system. Any changes requiring variation to the Marketing Authorisation or (for domestic manufacturers) to the manufacturing licence or (for overseas manufacturers) to the GMP clearance have been notified to and authorised by the TGA.
8. The GMP internal audits and supplier audits systems of the manufacturers involved are operational.

The AP should in addition take into account any other factors of which he/she is aware which are relevant to the quality of the batch.

The AP may delegate tasks to verify these requirements have been met to appropriately trained personnel or third parties. It is recognised that the AP will need to rely on a quality management system. The AP should have on-going assurance that this reliance is well founded.

2.2 An AP should have detailed knowledge of the steps in manufacture for which responsibility is taken and keep this knowledge up to date in the light of technical and scientific progress and changes in quality management relevant to the products which he/she is required to release.

¹ Consistent with Annex 13, investigational medicinal products should be produced in accordance with the principles and the detailed requirements of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products.

2.3 The PIC/S Guide to GMP identifies some responsibilities that are shared between the manufacturer and the sponsor (marketing authorisation holder) and that involve the AP.

1. The responsibility to ensure that the quality review is performed in a timely manner and is accurate, as outlined in GMP clause 1.4.
2. The responsibility to monitor product stability in an on-going stability program, as outlined in GMP clauses 6.23 – 6.33.

The AP responsible for release for supply has appropriate information in regard to PQRs and the on-going stability program, to undertake the release for supply step. Appropriate information will be provided and clarified in Part 2.

3. Manufacture in different locations

3.1 Manufacture, including quality control testing, of a batch of medicines takes place in stages which may be conducted at different sites and by different manufacturers that may be located within Australia or overseas. In all cases, each stage should be conducted in accordance with the requirements outlined above in section 2.1.

3.2 Each site located in Australia should be licensed under the Act for the manufacturing steps performed, while each site located overseas should be covered by a current TGA GMP clearance. Regardless whether located in Australia or overseas, each site should have at its disposal the services of at least one AP.

3.3 The AP responsible for release for supply of the finished product batch cannot always be closely involved with every stage of manufacture, specifically where different steps in manufacture occur in different locations. Therefore, under the conditions outlined in section 3.4 below, the AP performing release for supply of the finished product batch is allowed to rely on decisions(s) of one or more other APs to release the bulk or intermediate for supply to the next step in manufacture. This can be either an AP working within the same company (on the same site or on a different site) or an AP working with another manufacturer. Regardless of how many sites are involved, the AP performing batch release for supply of the finished product must ensure that all necessary steps have been completed through an appropriate quality management system.

3.4 The AP responsible for release for supply of the finished product batch can only rely on decisions by other APs to release an intermediate or bulk for supply to the next step in manufacture (i.e. partial manufacture) if all of the following conditions are met.

1. All partial manufacturers in the supply chain are covered by valid GMP agreements in accordance with chapter 7 of the PIC/S Guide to GMP. These agreements should each define the release for supply to the next manufacturer in the supply chain as applicable.
2. All AP(s) involved, including the APs at sites of partial manufacture are provided full access to all parts of the Marketing Authorisation that are relevant for the steps in manufacture performed at the site for which they are the AP.
3. Additional details regarding the release process are provided in the relevant release procedures in the quality management systems of the manufacturers involved.
4. All decisions to release for supply to the next step in manufacture are recorded through a legally valid signature, for example a full written signature on a paper document or an electronic signature in a validated electronic environment.
5. The AP performing release for supply of the finished product batch has accepted the quality management system used for this release for supply to the next step in manufacture, for example through the supplier qualification programme.

The AP performing release for supply of the finished product batch is ultimately responsible to ensure these conditions are being met when relying on other AP's release decisions. The level of detail of evidence the AP should obtain to review these conditions depends on the type of products manufactured. Further detail will be provided in part 2.

3.5 The GMP agreement should comply with the requirements of GMP chapter 7, specifically clause 7.11 to specify the way in which the AP responsible for release for supply of the finished product batch ensures that each batch has been manufactured and checked for compliance with the Marketing Authorisation.

3.6 Where bulk or intermediate product is manufactured on a different site, the GMP agreement should include an obligation on the part of the provider of a bulk or intermediate product to notify the recipient(s) of any significant deviations, out-of-specification results, non-compliance with GMP, investigations, complaints or other matters which should be taken into account by the AP who is responsible for release for supply of the finished product batch.

3.7 Where computer systems are used for recording release for supply decisions, particular note should be taken of Annex 11 of the PIC/S Guide to GMP.

3.8 Whatever particular arrangements are made for release for supply, it should always be possible to identify and recall without delay all products which could be rendered hazardous by a quality defect in the batch.

3.9 Where the ARTG entry of a medicine allows more than one site for release for supply of the finished product batch, the Australian sponsor should be able to identify the site at which any particular batch has been released for supply to the Australian market and the AP who was responsible for releasing that batch. These details should be specified in the batch records reviewed by the AP for release for supply.

4. Release for supply at manufacturing sites outside Australia

4.1 Release for supply by an AP located at an overseas manufacturer is recognised within Australia provided all of the following conditions are met.

1. The manufacturing steps performed are covered by a current GMP clearance.
2. A GMP agreement is in place clearly defining mutual responsibilities between the contract giver (which can be the sponsor or a manufacturer) and the contract acceptor (contract manufacturer). Alternatively, where both are part of one multinational organisation and covered by the same corporate quality system, an arrangement within that quality system achieving the same would be acceptable.
3. The ARTG entry reflects the release for supply step being performed by the overseas manufacturer.

4.2 The TGA assesses and verifies release for supply arrangements with overseas manufacturers through on-site GMP inspection and/or the Compliance Verification (CV) process, except for CVs based on evidence from MRA regulators in their own country. These assessments are done via the GMP agreement(s) with the contract givers and the assessment of the release for supply procedures including marketing authorisation requirements.

5. Responsibilities of the AP in relation to product quality review (PQR)

5.1 The preparation of PQRs is a shared responsibility between the sponsor and the manufacturer(s) of a product. The mutual responsibilities with regards to PQRs should be detailed in the relevant GMP agreements between the sponsor and the manufacturer(s).

5.2 Sponsors are also expected to have access and contribute to the PQRs, specifically in relation to marketing authorisation variations and market complaints, to ensure product compliance with the Marketing Authorisation.

5.3 PQRs are expected to be available for review during TGA on-site GMP inspections of manufacturers of products for which the inspected manufacturer is responsible to perform release for supply.

5.4 During TGA GMP inspections of (contract) manufacturers performing manufacturing steps prior to release for supply but not the actual release for supply itself, the PQR data relevant to that manufacturing step submitted to the manufacturer performing release for supply are expected to be available for review.

5.5 Where multiple manufacturers are involved in the manufacture of a product, each (contract) manufacturer will normally prepare the data for the PQRs of the manufacturing steps performed by that manufacturer and submit this data to the manufacturer performing release for supply of the finished product batch. The manufacturer responsible for release for supply will then collate the data into complete PQRs. The AP performing release for supply must consider the results within the context of the PQR findings. Other arrangements can be considered, as long as all the relevant data are provided to one manufacturer in the supply chain or to the sponsor who prepares complete PQRs. In that case, the other arrangements must be clearly defined in all applicable GMP agreements.

6. Responsibilities of the AP in relation to on-going stability testing

6.1 The responsibility to run an on-going stability program of the finished product is shared between the manufacturer responsible for release for supply and the sponsor. Actual studies in the on-going stability program can be contracted out to third parties, but both the manufacturer responsible for release for supply and the sponsor are expected to have access to results and review those.

6.2 Where studies in the on-going stability program are contracted out to third parties, these laboratories do not necessarily have to be TGA approved. Other certificates may be used in lieu of a GMP certification, such as a current Good Laboratory Practice (GLP) certificate or licence issued by a regulatory authority acceptable to the TGA or a current ISO 17025 accreditation certificate. Stability test methods used by the laboratory should be appropriately validated and documented according to the requirements of the PIC/S Guide to GMP.

6.3 The Code of GMP requires manufacturers performing manufacturing steps but not performing release for supply of finished product batches to consider inclusion of the intermediate product in the steps they perform, in an on-going stability program. This could be their own on-going stability program, or the program run by the manufacturer responsible for release for supply as defined in the relevant agreement.

Part 2: Specific considerations for specific areas of manufacture

This will be a separate and living document where further information will be added as required and agreed between TGA and the industry associations.

Glossary

In the context of this guidance document, certain words and phrases are used with the particular meanings defined below. Reference is also made to the Glossary in the PIC/S Guide to GMP.

Authorised Person (AP)/Authorised Persons (APs): an employee or employees authorised by a TGA approved manufacturer through a statement in the manufacturer's quality management system to perform release for supply. The person nominated under section 37(1)(e) of the Act to have control of quality control would be an obvious choice to be an AP, but other arrangements can be considered including delegation.

Bulk production batch: a batch of product, either ready for assembly into final containers or in individual containers ready for assembly to final packs. (A bulk production batch may, for example, consist of a bulk quantity of liquid product, of solid dosage forms such as tablets or capsules, or of filled ampoules).

Finished product batch: with reference to the control of the finished product, a finished product batch is the batch of product in its final pack for release for supply to the market.

GMP agreement: a written contract to meet the requirements of chapter 7 of the code, covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it to meet the requirements of Chapter 7 of the PICS Guide to GMP for Medicinal Products.. Also termed a Technical agreement or a Sponsor Contract Manufacturer Agreement

Marketing authorisation: the details of the medicine involved in the Australian Register of Therapeutic Goods (ARTG), as well as all other matters in relation to the product registration or listing agreed in writing between the TGA and the sponsor.

PIC/S Guide to GMP: The Guide to Good Manufacturing Practice for Medicinal Products, published by the Pharmaceutical Inspection Cooperation Scheme (PIC/S) under document number PE 009 in its version as determined in the current Manufacturing Principles.

Release for supply: certification by an Authorised Person that each production batch has been produced and controlled in accordance with the requirements of the marketing authorisation and any other regulations relevant to the production, control and release of medicinal products. Release for supply can be distinguished in the following categories.

1. Release of a finished product batch for supply:
 - a. to the Australian market or
 - b. for export or
 - c. for use in a Phase 2 or later investigational medicinal product for use in human clinical studies

Release for further processing: Release of an intermediate or bulk product or finished product that requires alteration for distribution into the Australian Market.

TGA approved manufacturer: a domestic manufacturer holding a TGA licence to manufacture therapeutic goods or an overseas a manufacturer covered by a current TGA GMP clearance.

References

Some useful references are attached.

1. Supplier Qualification

<<https://www.tga.gov.au/technical-guidance-interpretation-manufacturing-standards-supplier-qualification>>

2. On going Stability

<<https://www.tga.gov.au/technical-guidance-interpretation-manufacturing-standards-going-stability-testing-listed-complementary-medicines>>

3. Product Quality Reviews

<<https://www.tga.gov.au/technical-guidance-interpretation-manufacturing-standards-product-quality-review-listed-complementary-medicines>>

4. Manufacturer inspections - product/process risk classifications

<<https://www.tga.gov.au/manufacturer-inspections-productprocess-risk-classifications>>

List of acronyms used

AP: Authorised Person

API: Active Pharmaceutical Ingredient

ARTG: Australian Register of Therapeutic Goods

BP: British Pharmacopoeia

EP: European Pharmacopoeia

GLP: Good Laboratory Practice

GMP: Good Manufacturing Practice

ISO: International Organisation for Standardisation: <<http://www.iso.org/>>

OOS: Out-of-specification (result)

PIC/S: Pharmaceutical Inspection Cooperation Scheme: <<http://www.picscheme.org/>>

PQR: Product Quality Review

TGA: Therapeutic Goods Administration

TGO: Therapeutic Goods Order

USP: United States Pharmacopoeia

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