Technical Alert

Most recent TGA clarifying advice on GMP requirements for 'APIs' or 'API Active Premixes' in Listed Medicines

Members sometimes seek clarity on the requirements of GMP for active ingredients or processed materials that are used in the manufacture of complementary medicines, as the information available can be confusing and difficult to clearly understand in terms of the TGA's intended application, policy, and enforcement.

The most recent specific clarification of requirements was provided by the TGA to representative industry bodies including CMA in 2018, as part of a response to an enquiry that included examples. There have not been any changes flagged to this approach since that time to CMA and industry bodies involved, and we are aware that this has been the approach that has been taken since that time, therefore, this is as far as we are aware, both the longstanding and current approach taken by the TGA as to whether APIs and API Active Premixes are required to have evidence of GMP by way of a TGA License or a TGA Clearance.

The most recent specific advice provided by the TGA (2018) is included below, which is consistent with the advice on steps of manufacture in the '*GMP Clearance code tables guidance: Manufacturing Steps*' (Version 1.0, July 2020). It applies whether or not the 'API' or 'API active premix' is a Proprietary Ingredient. The advice confirms that evidence of GMP (by way of a TGA GMP License or Clearance) is only required to be provided by the sponsor where a manufacturing step is required to be included in the application on the ARTG for the medicine. As noted by the 'Application and submission user guide - Listed and assessed listed medicines' the following five manufacturing steps are compulsory and as such, these constitute the steps of manufacture where evidence of GMP (TGA Licensing or Clearance) is required to be provided for a Listed medicine:

- Manufacture of dosage form
- Packaging and labelling
- Release for supply
- Testing: chemical and physical testing
- Testing: microbial testing

Consequently, the advice clarifies that the types of blends provided in the examples below, are a step of manufacture but do not require that the manufacturer has evidence of GMP (TGA Licensing or Clearance as part of the compliance requirements for listed medicines.

Technical guidance on the interpretation of the PIC/S Guide to GMP that was agreed in consultation between industry and TGA is clarified in the '*Technical guidance on the interpretation of the PIC/S Guide to GMP: Supplier assessment, approval and qualification for listed and complementary medicines*' document (v2.0 January 2019) and provides that:

Establishing a GMP or technical agreement is not required

For listed and complementary medicines, it is not required to establish a formal GMP or technical agreement for suppliers and manufacturers of raw materials, packaging materials and printed artwork.

These are controlled by having the following information:

- approved specifications
- Certificate of Analysis (C of A) from manufacturing site
- a system of vendor qualification

Australian manufacturers of APIs:

However, the advice also notes that there may be requirements for Australian-based manufacturers performing a step of manufacture if the goods are not specifically exempt under the Therapeutic Goods Regulations 1990 (see Schedule 7). CMA is aware that sometimes individual manufacturers or sponsors are or have been given confusing or inconsistent advice by the TGA on whether and at what processing step, licensing of API or API active premix manufacturers in Australia is required.

CMA represents industry on the *TGA-Industry Working Group on Good Manufacturing Practice* (GMP) (TIWGG) and also runs a CMA GMP & Manufacturing Committee; please bring any unusual or process-related GMP issues arising to our attention so we may seek ongoing resolution and improvements.

TGA clarifying advice (2018):

An **active pharmaceutical ingredient (API)** is defined in the Therapeutic Goods (Manufacturing Principles) Determination 2018 [1]as: *"any substance or mixture of substances intended to be used in the manufacture of a medicine and that, when used in the production of a medicine, becomes an active ingredient of that medicine. These substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body".*

Where an active pharmaceutical ingredient contains excipients which are not a necessity and/or additional active pharmaceutical ingredients it may be considered to be an intermediate product or otherwise referred to as an **API active premix**.

Unless specifically exempt by the Therapeutic Goods Regulations 1990, an Australian manufacturer performing a step of manufacture is required to hold a TGA GMP Licence.

Similarly, overseas manufacturers of medicines supplied to Australia are required to meet an acceptable standard of GMP. Specifically

- Where manufacturing steps must be included in an application for a new medicine, evidence of GMP compliance is required and this is typically demonstrated by obtaining a GMP Clearance. You are required to keep this evidence current while the medicine remains on the ARTG.

[1] CMA note: The same definitions are included in the 2020 legislative document that has superseded the 2018 document: Therapeutic Goods (Manufacturing Principles) Determination 2020.

- Where a manufacturing step is not recorded in an ARTG entry, evidence of GMP compliance does not need to be submitted in an application, however, adherence to GMP principles is still required.

Using [the] examples below, we confirm that they constitute a step in manufacture, and have clarified the definition of each 'blend' and the GMP evidence requirements, in support of product registration or listing:

1. ***One non herbal active with excipients for use in Listed or Registered medicines***:
   a. If the excipient was necessary for the purpose of the stability of the non-herbal active ingredient, then this would be considered to be an API. In accordance with the requirements for Listed medicines, Registered Complementary Medicines (RCM) and OTC products, the manufacturer of APIs does not need to be included on the ARTG and thus, GMP evidence is not required to be provided to the TGA, as part of the product registration or listing.

      For prescription medicines, sponsors are required to hold and provide GMP evidence to support the product registration, therefore a GMP licence (for Australian manufacturers) or GMP clearance (for overseas manufacturers) would need to be obtained to support the product registration.

   b. If the excipient was not necessary for the purpose of the stability of the non-herbal active ingredient, then this would be considered to meet the definition of an API Active Premix.
      - For Listed medicines: In accordance with the requirements for Listed medicines, the API Active Premixes manufacturer is not currently required to be declared at the time of Listing therefore evidence of GMP for these manufacturers are not required to be provided to the TGA to support a product listing application.

      - For registered OTC medicines, the complexity of the process required to produce the 'blend/mixture/substance' may also be considered in determining the requirement for GMP evidence. If a sponsor is unsure of whether the extent of complexity (of preparation of the 'blend/mixture/substance') is sufficient to require a GMP clearance etc., the sponsor is encouraged to contact OTC Medicines Evaluation for further advice.

      - For Registered complementary medicines and prescription medicines: In accordance with the requirements GMP evidence for API Active Premix manufacturers is required to be submitted to the TGA to support the product registration.

2. ***One herbal active with excipients for use in Listed or Registered medicines***
   As per above.

3. ***Two herbal actives with excipients for use in Listed or Registered medicines***
   Where two or more active ingredients are blended/granulated together, it is no longer considered to be an API; it is by definition an API Active Premix. GMP evidence for premixes is not required to be submitted for a listed medicine, however it would be required for OTC, RCM and prescription medicines.

Please note that recognition of a substance as an 'API Active Premix' is not to be confused with use of the term 'Active premix' in relation to Proprietary Ingredients.

July 2020 guidance on GMP Clearance code tables: Manufacturing Steps

In July 2020, TGA Guidance for GMP Clearance code tables for Manufacturing Steps also provides clarity that correlates with the above information from 2018. The below excerpt from this guidance contains similar clarification to the 2018 advice around manufacturing steps as it relates to Listed medicines and requirement for evidence of GMP (TGA Licensing or Clearance). It clarifies that the step '**Manufacture of dosage form**' includes any or all processing steps in the *manufacture of a dosage form*. Does this description include a requirement for GMP Licensing or Clearance on APIs and API Active Premixes used in Listed medicines? This guidance appears to correlate with the advice from 2018, which is that this step does not include the manufacture of APIs or API Active Premixes, by way of comparison with other types of medicines. For example:

- Registered Complementary medicines and OTC medicines require the manufacturing step of **API Active Premix** to be recorded on the GMP and therefore require evidence of GMP.
- Prescription medicines also provides that **Active material manufacture** is required to be on the application for those medicines, a step which 'Includes any or all processing steps in the manufacture of an API or drug substance.'

Relevant excerpt from the document, '*GMP Clearance code tables guidance: Manufacturing Steps*' (Version 1.0, July 2020):

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Listed and assessed listed medicines

The following list of manufacturing steps and the respective codes are associated with the product listing and variation related to listed and assessed listed medicines. Complementary medicines may be either listed or registered, depending on their ingredients and the claims made. Most complementary medicines are listed, however it is important to be certain before proceeding with your GMP clearance or certification application. For further guidance, refer to Pathways for complementary medicine products.
The steps and codes below are those which will validate within the listed and assessed listed medicines system. It is not necessary to have all the below steps in a GMP clearance or certificate in order to support a product registration/listing or variation.
For more information for listed and assessed listed medicines, refer to the Australian Regulatory Guidelines for Listed Medicines and Registered Complementary Medicines.

Manufacturing steps and codes for listed and assessed listed medicines

Manufacturing step	Code
Manufacture of dosage form*	MDD
Packaging and labelling*	MXP
Secondary packaging#	MXS
Testing chemical and physical*	TCC
Testing microbial*	TMM
Release for supply*	MXR

* Steps required in a listed or assessed listed medicine application and covered by appropriate GMP evidence

[#] Secondary packaging may also require a GMP clearance if the step of manufacture is undertaken for the product.

Interpretation of common manufacturing steps for listed and assessed listed medicines

The following table provides interpretation of the common manufacturing steps across the ARTG, licences and clearances that validate in the listed and assessed listed medicine application system.

Interpretation of manufacturing steps for listed and assessed listed medicines

Manufacturing step	Interpretation
Manufacture of dosage form	Includes any or all processing steps in the manufacture of a dosage form. Does not include packaging, labelling, testing or release for supply. For sterile products, this term includes primary packaging.
Packaging and labelling	Refers to placing and sealing of the medicinal product within the finished product packaging material which is in direct contact with the product as well as labelling operations.
Secondary packaging	Refers to the placing of the medicinal product, which is already sealed within its primary packaging material within an outer packaging material.
Testing chemical and physical	Tests which identify, quantify or characterise chemical and physical properties of a substance or finished dosage form. A chemical test is a qualitative or quantitative procedure designed to identify, quantify, or characterise a chemical compound or chemical group.
Testing microbial	Test to determine the presence or absence of specific objectionable organisms in a product. For sterile products, testing microbial includes sterility testing.
Release for supply	Refers to batch certification by an Authorised Person (AP) where 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 the product. For more information refer to Release for supply of medicines in Australia.

Unless specifically exempt by the Therapeutic Goods Regulations 1990, an *Australian manufacturer* performing a step of manufacture is required to hold a TGA GMP Licence. *Overseas manufacturers* of medicines supplied to Australia are required to meet an acceptable standard of GMP:

- Where manufacturing steps must be included in an application for a new medicine, evidence of GMP compliance is required and this is typically demonstrated by obtaining a GMP Clearance. You are required to keep this evidence current while the medicine remains on the ARTG.
- Where a manufacturing step is **not** recorded in an ARTG entry, evidence of GMP compliance does not need to be submitted in an application, however, adherence to GMP principles is still required.

TGA Interpretation of manufacturing steps for listed and assessed listed medicines

Manufacturing step	Interpretation
Manufacture of dosage form	Includes any or all processing steps in the manufacture of a dosage form. Does not include packaging, labelling, testing or release for supply. For sterile products, this term includes primary packaging.
Packaging and labelling	Refers to placing and sealing of the medicinal product within the finished product packaging material which is in direct contact with the product as well as labelling operations.
Secondary packaging	Refers to the placing of the medicinal product, which is already sealed within its primary packaging material within an outer packaging material.
Testing chemical and physical	Tests which identify, quantify or characterise chemical and physical properties of a substance or finished dosage form. A chemical test is a qualitative or quantitative procedure designed to identify, quantify, or characterise a chemical compound or chemical group.
Testing microbial	Test to determine the presence or absence of specific objectionable organisms in a product. For sterile products, testing microbial includes sterility testing.
Release for supply	Refers to batch certification by an Authorised Person (AP) where 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 the product. For more information refer to Release for supply of medicines in Australia.

Resources

- Manufacturing principles for medicinal products
- Manufacturing medicines
- Australian manufacturing licences and overseas GMP certification
- GMP Clearance code tables guidance
- TGA webpage Proprietary ingredients Proprietary ingredient formulations and how they are used and TGA eBS Proprietary Ingredients
- Australian Regulatory Guidelines for Listed and Registered Complementary Medicines.
- CMA Vendor qualification guidelines and tools for industry
- CMA Code of practice and other guidelines/tools including Modern Slavery