Complementary and Listed Medicines – GMP 101

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GMP FORUM 2024

Agenda

- Introduction
- Product contamination
- Shelf life
- Release to market
- Control of active starting material

Lower risk medicines ⟺ Good Manufacturing Practice

Complementary and listed medicines are considered lower risk medicines as they only contain pre-approved low risk ingredients and make low level health claims.

Compliance with GMP ensures

- only the pre-approved, low risk ingredients are used in products
- no contamination or cross-contamination of product
- products meet their label claim
- the products are consistent across and between batches of the same product,
- throughout their shelf life

Manufacturing Standard

Technical guidance documents

Product contamination

Cleaning validation

Technical and organisational measure to control risk of contamination: premises, equipment, HVAC, segregation, dust control, environmental monitoring, cleaning processes, cleaning verification, gowning, and training and supervision of staff

Current TGA guidance on cleaning validation*

TGA generally expects cleaning processes for listed medicines to be validated and appropriately documented. However, due to the low toxicity of permissible ingredients used in the manufacture of listed medicines, cleaning validations can be grouped looking at worse case situations.

The acceptance criteria of 'visibly clean' will normally be accepted for listed medicines.

In addition to the acceptance criteria of 'visibly clean', cleaning validation studies should give consideration to:

- the microbiological bioburden of processed materials and cleaned equipment and their acceptable limits
- residual limits for chemical cleaning agents where used. In these cases, additional testing e.g. pH or total organic carbon (TOC) may be used where justified to demonstrate adequate cleanliness
- Give additional consideration of more stringent acceptance criteria to products containing potentially allergenic materials

*Technical guidance on the interpretation of the PIC/S Guide to GMP

Cleaning validation criteria for listed medicine manufacture

1. Visually clean product contact surfaces
2. Acceptable microbiological limits met on product contact surfaces
3. Evidence of detergent removal (where applicable)

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Ongoing stability

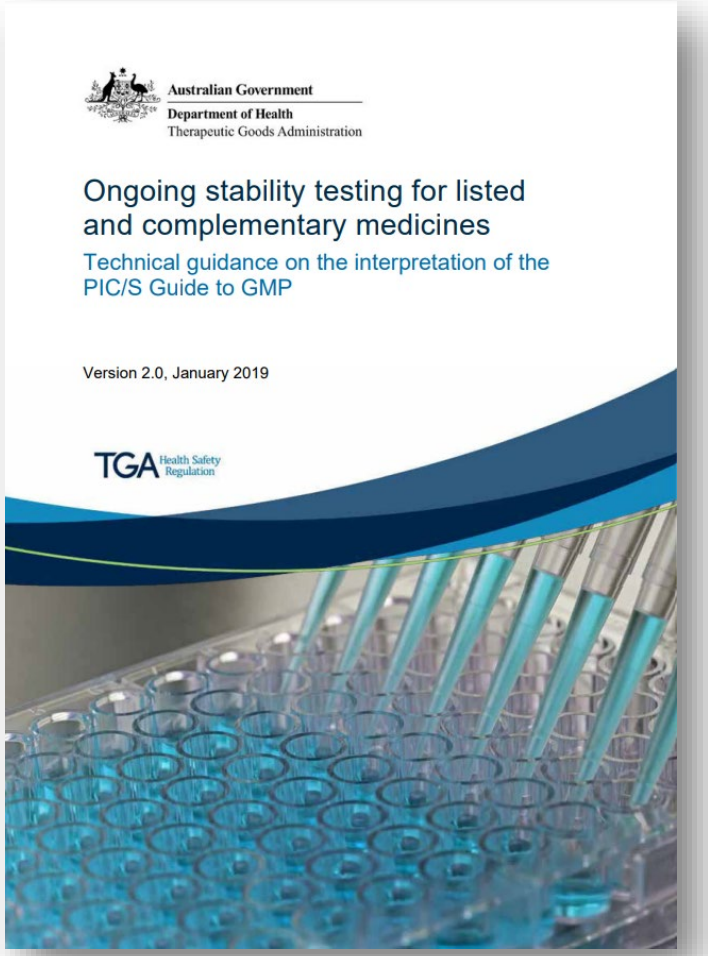
Groupings
OOS/OOT investigations

'…monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions'

Clause 6.27 PIC/S Guide to GMP

Current TGA guidance for ongoing stability

1. At least one batch of product from each group each year should be placed on the ongoing stability program
2. Types of testing – physical, micro, actives with quantitative label claims
3. Grouping of products
4. Consideration of additional testing where production batches that have undergone a significant change or deviation to the process or package, rework, reprocessing or recovery operation
5. Out of specification or significant atypical trends should be investigated*
6. Results of on-going stability studies should be available at the site of manufacture for review by the competent authority*



*PIC/S Guide to GMP

Groupings

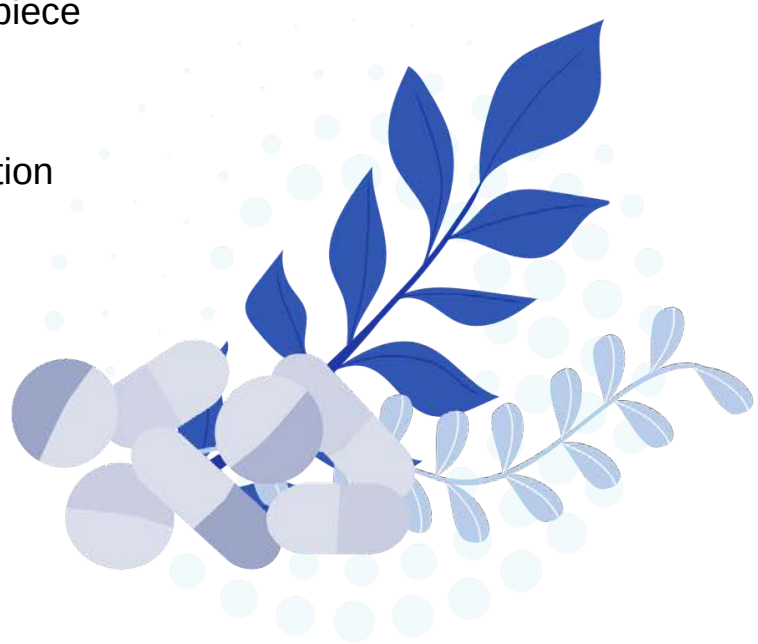
Document the scientific justification of the rationale used to establish product groupings

Base your justifications on the products having similarly constructed formulations, the same dosage form, method of manufacture and primary packaging materials

Groups that may require separate stability studies include, **but are not limited to**:

1. different dose forms – powders, solutions, suspensions, creams, ointments, tablets, two-piece capsules, softgels (solution fill), softgels (suspensions fill)
2. different formulation types
   - multi-component vitamin/mineral/herbal solid-dose tablet based on common formulation
   - vitamin tablet containing only one active, even if excipients similar to above
   - vitamin tablet containing same active, but sustained, rather than immediate-release
3. different packaging
   - glass bottle
   - specific type of plastic bottle
   - blister platform
   - laminated tube

4. different site of manufacture



Document the justification for a particular product being representative of the group

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‘Out of specification or significant atypical trends should be investigated’

Release for Supply

Adoption of Annex 16 of the PIC/S Guide to GMP

There is no substantial change in current expectations for certification by the Authorised Person and batch release

C6A: Release for Supply (Batch Certification) – Meeting your obligations as an authorised person
Goldfields Theatre Wednesday 20 November 2024 11:00am - 12:30pm

Release for supply: no substantial change in current expectations

Current TGA guidance on Release for supply*

Release for supply is normally the final step in the manufacture of therapeutic goods, during which an Authorised Person performs a thorough evaluation of the manufacturing data associated with a batch, and certifies the batch for release for supply,

- Authorised Person needs full overview of all manufacturing steps
- Release for supply includes consideration of *all* marketing authorisation requirements
- Ensure correct storage of goods prior to release for supply

*Technical guidance on the interpretation of the PIC/S Guide to GMP

Storage of goods prior to release for supply (RFS)

Requirements

- RFS is defined as a manufacturing step which requires a TGA licence.
- Release for supply is normally the final step in the manufacture of therapeutic goods.
- It is a requirement of the *Therapeutic Goods Act 1989* that steps of manufacture that precede bringing the goods to their final state must be conducted at a premises that hold a Licence to Manufacture.
- For therapeutic goods that have been fully manufactured, but not yet certified for release for supply by an AP – these goods must be held at premises that are licenced by the TGA for the storage of therapeutic goods, and the storage site must be included in the ARTG entry for the product.

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Control of ingredients

API mixes and/or blends

Control of ingredients

API mixes and/or blends

low risk ingredients

product meets label claim

ingredients uniform across and between batches of the same product

=

lower risk medicinal product

General requirements for control ingredients

- Specifications
- Supplier approval
- Sampling and testing

Manufacturing activities conducted in Australia

It is a requirement of the *Therapeutic Goods Act 1989* that all steps of manufacture of a medicinal product must be conducted at a premises that hold a Licence to Manufacture*.

This includes most herbal extracts, API premixes, and intermediate products

*some exemptions apply

Overseas manufacturing sites supplying pre-mixes to Australia

Outside Australia's legal jurisdiction: TGA cannot regulate overseas sites

Certification can be obtained via TGA inspection to confirm that manufacture occurs in line with Australian Manufacturing Principles (conducted in accordance with a certificate application made by an AU sponsor)

Clearance can be obtained if alternate evidence is available from a trusted regulator (undertaken in response to a clearance application made by an AU sponsor)

Confirmation of acceptable GMP the responsibility of the AU manufacturer

API premix or intermediate product?

Question 4

What percentage (w/w) of the finished product must a premix constitute after which it would be considered an intermediate finished product, as opposed to an API premix*?

- 20%
- 50%
- 85%
- 95%
- 98%
- None of the above

*Think multi-strain probiotics, mixed herbal extracts, stabilised vitamin pre-mixes, multi-active vitamin/mineral blends

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Control of starting materials (single component)

Identification	Complete ID on each lot and/or delivery received (mandatory)
Verification that starting material meets established specification	Testing + review of supplied CoA to ensure material meets specification
Evidence that material manufactured under acceptable controls e.g. consistent processes, contamination control, quality system	Supplier approval (questionnaires / audits of manufacturer of material)

Control of API premix

Identification of each active ingredient in API premix, on each lot received (actives & excipients)	Mandatory ID of all components at receipt to site
Verification that API premix meets established specification - Specific limit tests, applicable to any active ingredient in the premix, have been met - concentration of each active is within specification	Testing of critical quality attributes + review of supplied CoA to ensure material meets specification
Evidence that material manufactured under acceptable controls e.g. consistent processes, contamination control, quality system	Supplier approval process
Control of ingredients used in each lot of API premix received (actives & excipients)	Supplier approval process On-going testing for possible contaminants e.g. heavy metals, micro, solvents
Ensure uniformity of blend	Supplier approval process, or Testing at receipt to demonstrate blend uniformity on every batch Blend uniformity in finished product on every batch

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Onsite audits of API suppliers, manufacturers and/or 3rd party laboratories* (not mandatory for listed medicines)

‘...Audits should be carried out at the manufacturers and distributors of active substances to confirm that they comply with the relevant good manufacturing practice and good distribution practice requirements...’

– Clause 5.29 PE-009-15

‘The medicinal product manufacturer should perform audits, either itself or via third parties, at appropriate intervals based on risk at the site(s) carrying out the testing (including sampling) of the starting materials...’

– Clause 5.36 (ii) PE-009-15

* requirements introduced in PIC/S Guide to GMP, version 14 (1 July 2018)

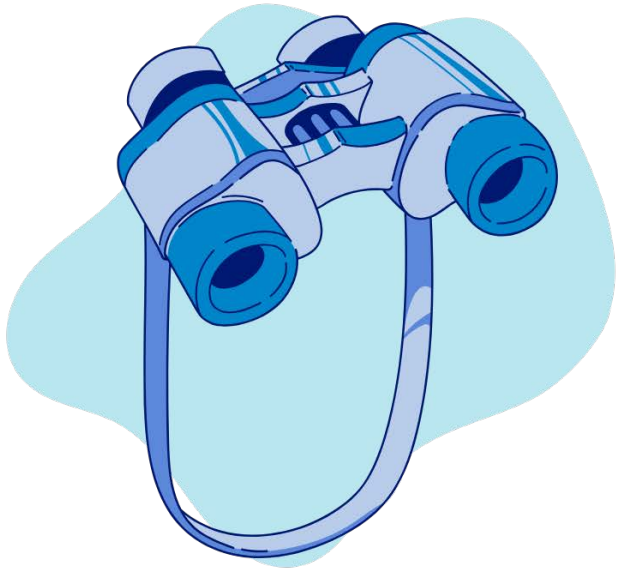
What areas should the audit/inspection cover?

Raw material manufacturers:

- Quality Management System
- Manufacturing areas (inc. risk of cross contamination)
- Manufacturing processes & control of starting materials (inc. source of APIs, process verification)
- QC Laboratories
- Supply chain traceability

3rd Party QC Laboratories:

- Distribution controls
- Applicable test methods/validation
- Data management
- Issuance and authorisation relating to Certificates of Analysis (CoA)



Audits must be satisfactorily completed

3rd party contractors, or evidence from independent regulators, can be used

Effective remote inspections acceptable

Control of API premixes post site-based audit

Identification of each active ingredient in API premix on each lot received	Verification of laboratory testing during audit, and/or ID of all components at receipt to your site and/or
Verification that API premix meets established specification - Specific limit tests applicable to any active ingredient in the starting material have been met - concentration of each active within specification	Verification of laboratory testing during audit, and/or Testing at receipt + review of supplied CoA to ensure material meets established specification
Evidence that material manufactured under acceptable controls e.g. consistent processes, contamination control, quality system	Verified at audit
Control of ingredients used in each lot of API premix received (actives + excipients)	All ingredients permitted for use in listed medicines – checked pre-audit & verified at audit Control of ingredients verified at audit – material controls, BMR
Ensure uniformity of blend	Process validation verified at audit, and/or Blend uniformity testing on 1st 3 lots, and/or Blend uniformity in finished product via process validation studies

Lower risk medicines ⟺ Good Manufacturing Practice

In summary

Scorecard for Australian industry (and you)

Updated guidance information

Compliance with GMP ensures

- low risk ingredients are used in products
- no contamination or cross-contamination of product
- products meet their label claim
- the products are constituent across and between batches of the same product,
- throughout their shelf life

Questions?

Scan this QR code with your device to submit a question

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Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration