Australian Government
Department of Health
Therapeutic Goods Administration

Manufacturing Investigational Medicinal Products

Legislative and GMP requirements

Lynn Talomsin
Senior Inspector
Manufacturing Quality Branch
Medical Devices and Product Quality Division
Therapeutic Goods Administration
(Thank you, Matt Davis for the materials for the presentation)

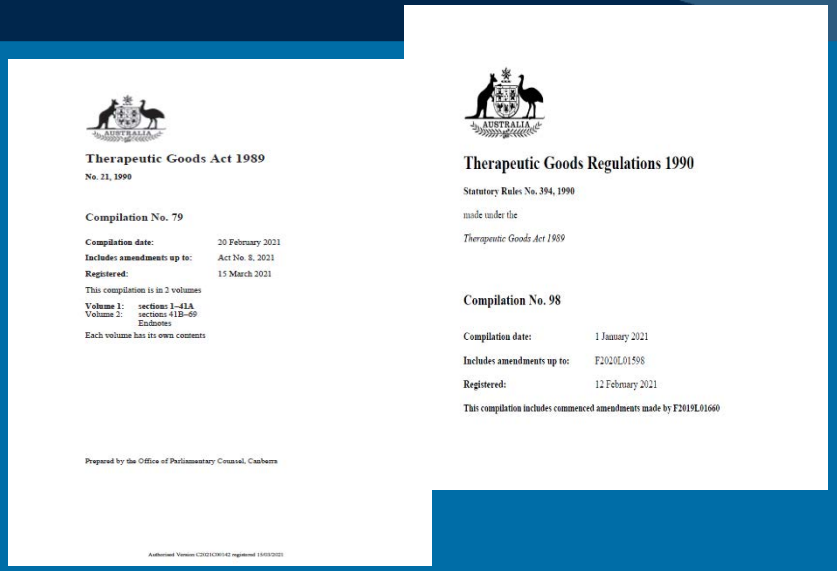
TGA Health Safety Regulation

14/05/2021

Overview

- Legislative Requirements
- Specific risks for Investigational Medicinal Product manufacturing
- Manufacturing Authorisations
- PIC/S Guide to GMP PE009-14
- Common Issues

Legislative Requirements



- ***Therapeutic Goods Act 1989***
  - **Section 18** : Provide the basis for exemption from Part 3-2 of *the Act* for IMPs

- ***Therapeutic Goods Regulations 1990***
  - **Schedule 5A – Therapeutic goods exempt from operation of Parts 3-2 and 3-2A of the *Act* subject to conditions**
    - Item 3: *"Therapeutic goods used solely for experimental purposes in humans"*
  - **Schedule 7 – Therapeutic goods exempt from the operation of Part 3-3 of the *Act***
    - Item 1: *"goods prepared for the initial experimental studies in human volunteers"*

Manufacturing Authorisation and PIC/S Guide to GMP

Manufacturing Authorisation

Manufacturing Principles

- Medicines
  - PIC/S PE009
- Blood, tissues, cellular therapies
  - Australian Code of GMP for human blood and blood components, human tissues and human cellular therapy products

Pharmacopoeia (Default Standard)

- British
- European
- United States

Therapeutic Goods Orders

- TGO 100 (microbiological Standards)
- TGO 101 (Tablets, Capsules and Pills)
- TGO 88 (Infectious Disease Testing)
- TGO87 (Labelling of Biologicals)

Manufacturing Type	Sterility	Dosage Form	Product Category	Manufacturing Step
Medicine Manufacture	Sterile and Non-sterile	Solid Unit Dosage Forms – Hard Capsules	Therapeutic Goods for Clinical Trials	Finished product manufacture
Medicine Manufacture	Sterile and Non-sterile	Solid Unit Dosage Forms – Hard Capsules	Therapeutic Goods for Clinical Trials	Packaging and labelling

Manufacturing Principles – Guide to GMP PE009-14

- Part I Manufacturing of medicinal products
- Part II Manufacturing of active pharmaceutical ingredients
- Annexes
  - Annex 13 Manufacturing of Investigational Medicinal Products

PE009-14 – Annex 13 Manufacture of IMP's

Principle:

*The application of GMP to the manufacture of investigational medicinal products is intended to ensure that trial subjects are not placed at risk, and that the results of clinical trials are unaffected by **inadequate safety, quality or efficacy arising from unsatisfactory manufacture**. Equally, it is intended to ensure that there is **consistency between batches** of the same investigational medicinal product used in the same or different clinical trials, and that **changes** during the development of an investigational medicinal product are adequately **documented and justified**.*

*The production of investigational medicinal products involves **added complexity in comparison to marketed products.***

Manufacturing risk profile - IMPs

Dynamic manufacturing

- Regular process developments & changes
- Specification changes
- Labelling requirements
- Stability data

Risk of mix-ups

- Packaging multiple products
- Blinding processes
- Randomisation processes

The unknown

- Cross contamination risks
- Vendor qualification
- Reduced process validation

Information from trial sponsor is critical!

Annex 13 – Manufacture of IMP

- **Quality Management**
- **Personnel including training** – knowledge of requirements of IMP
- **Premises and equipment** – cross contamination control
- **Documentation** – orders and product specification file
- **Production –** validation, labelling requirements and blinding and randomisation
- **Quality control** – sampling and testing
- **Release of batches**
- **Complaints**
- **Recalls and returns**
- **Destruction –** not be destroyed without authorization by the Sponsor

Annex 13 – Order

- Evidence of a request for the processing and/or packaging,
- Precise enough to avoid any ambiguity,
- Formally authorised and refer to the Product Specification File and relevant clinical trial protocol as appropriate.

Annex 13 – Product Specification File

- Specifications and analytical methods for starting materials, packaging materials, intermediate, bulk and finished product;
- Manufacturing methods;
- In-process testing and methods;
- Approved label copy;
- Relevant clinical trial protocols and randomisation codes, as appropriate;
- Relevant technical agreements with contract givers, as appropriate;
- Stability data;
- Storage and shipment conditions.

Forms the basis for assessment of the suitability for certification and release of a particular batch by the Authorised Person.

Annex 13 – Validation

Production processes for IMP's are not expected to be validated to the extent necessary for routine production.

Process validation should be commensurate with process understanding.

However:

- Premises, utilities and equipment must be fully qualified
- For sterile products:
  - Sterilisation processes must be fully validated
  - Media fills must be conducted as per Annex 1
- Virul inactivation/removal or similar treatment other impurities of biological origin must be demonstrated

Annex 13 - Labelling

TABLE 1. SUMMARY OF LABELLING DETAILS (§26 to 30)

a) name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding);

b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials[3], the name/identifier and strength/potency;

c) the batch and/or code number to identify the contents and packaging operation;

d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

e) the trial subject identification number / treatment number and where relevant, the visit number;

f) the name of the investigator (if not included in (a) or (d);

g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product

h) "for clinical trial use only" or similar wording;

i) the storage conditions;

j) period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity.

k) "keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.

GENERAL CASE
For both the primary and secondary packaging (§26)

Particulars
a[4] to k

PRIMARY PACKAGE
Where primary and secondary packaging remain together throughout (§29)[5]

a[6] b[7] c d e

PRIMARY PACKAGE
Blisters or small packaging units (§30)[5]

a[6] b[7,8] c d e

Annex 13 – Blinding & Randomisation

Blinding and randomisation are risky activities

- Clear processes and controls to ensure products are effectively blinded, whilst avoiding any mix-up.
- Effective controls for allocation and control of randomisation codes and label generation controls.
- System validation expected.
- Method of un-blinding or code-breaking in case of emergency.

Annex 13 – Sampling & Testing

Increased emphasis on sampling and QC testing

- Increased sampling plans and test plans for in-process and finished goods
- Full method validation expected
- Laboratory controls for data integrity required
- Product specification file outlines agreed testing specification

Common Issues Observed in Inspections

Common issues……..

Product Specification File

- The company did not maintain **product specification files** for clinical trial products handled by the site. E.g. for IMP XXX for which “Manufacturer” performed release for supply.
- **Specifications** for finished products were not generated and held by the company.
- There were **no formalised agreed formulae** between the manufacturer and sponsor for products for clinical trials.

Orders

- The **order** for IMP XXX was a purchase order (P/O) and **did not contain sufficient information** for the products ordered.
- While there was an order for the clinical trial products for IMPXXX available, there was no evidence in the order that the order was from the sponsor of the clinical trial.

Common issues……..

Controlled Introduction

- There was no procedure or system in place for the **introduction of new products/clinical trial material**. The actions required for ensuring the safe introduction and control of new materials was not covered by the pharmaceutical quality system.
- The risk assessment (RA) and validation master plan (VMP) for the **cross contamination** for the clinical trial products (class A potent actives) did **not include** a detailed assessment of the potential cross contamination issues associated with the use of non dedicated HVAC systems for impact and any mitigating circumstances.

Labelling

- The manufacturer's current redressing process required the **addition** of a clinical trial **label** onto the **secondary container only**, and not of the immediate container.
- The "Country" label on the immediate container **did not include** all **labelling requirements** as specified by clause 26 and table 1 of Annex 13, e.g. address and telephone number of the sponsor, CRO or investigator, "for clinical trial use" or similar wording, storage conditions.

Common issues……..

Qualification and Validation

- Equipment was not fully **qualified**.
- The **cleaning validation** for equipment shared across different products/clinical trial materials was **not available.**
- There were **no process validation** requirements in the Validation Master Plan for IMPs, and not all processes had been validated e.g. blister packaging process.

Qualification and Validation

- In relation to “IMP XXX” sterile eye drop manufacture;
  - The **sterilising filter was not fully validated** in relation to chemical compatibility and microbial retention capacity;
  - For batch sizes less than 60 litres, a sterilising filter pre-integrity check was not performed. Furthermore, a bubble point for the solvent used was not determined.
- The **computerised system** used to merge the electronic randomisation protocol with the label printing application **had not been validated**, and there was no manual checking to ensure that the printed labels were in accordance with the randomisation protocol provided.

Common issues……..

Testing

- **Starting materials/bulk products** were not always adequately checked to ensure **correct identity and appropriate quality** before released for further processing.

Release for Supply

- There was no requirement in the release for supply procedure and checklist to have **evidence that, if the product was manufactured by a third party contractor, that the product was manufactured in accordance with the relevant clinical trial requirements**.
- The company did not have any evidence to demonstrate that the bulk product manufactured by a contractor was manufactured in compliance with the **PIC/S code of GMP and the relevant clinical trial requirements**, prior to release the batch for supply.

Summary

- Be aware of legislative provisions for the manufacture of IMPs
  - Act and Regulations
  - Specific GMP requirements
- Knowledge management is critical
  - Relationship between sponsor and manufacturer
  - Sharing data and information

Contact us

General & Australian manufacturing enquiries:
gmp@health.gov.au

Overseas manufacturing enquiries:
gmpclearance@health.gov.au

Thank you for your attention

Australian Government

Department of Health

Therapeutic Goods Administration