RACI Presentation

Specifications, Manufacture and Quality Requirements of Dose Form and Placebos for Clinical Trials -

5th October 2022

Introduction

- Trial Phase and General Requirements
- Manufacturing Facility
- Manufacturing Process
- Labelling of Investigational product
- Specifications and Release for Supply
- Stability Testing
- Quality Requirements

Trial Phase

- Phase 0 and I Trials
  - Manufacture of medicines for initial experimental studies in human volunteers (which generally means first-in-human trials) is not subject to inspection and licensing by the TGA (specified in item 1, Schedule 7, *Therapeutic Goods Regulations 1990*).
  - Still should take a risk based approach when considering key quality and manufacturing controls for these products
- Phase II onwards regulated by TGA and subject to TGA cGMP Licensing of the manufacturing facility
  - PE009, the PIC/S guide to GMP for medicinal products, Annex 13 Investigational Product Manufacture

Manufacture (Facility)

- Facility needs to have a current GMP Licence that includes
  - The product type to be manufactured for the trial (e.g. coated tablets)
  - Specify manufacture of investigational products
  - Include the manufacturing step of Release for Supply for the Client to arrange a TGA licenced 3rd party to perform this step
- cGMP Agreement and Service Agreement
  - Client and manufacturing site require a cGMP agreement
  - Details responsibilities including Release for Supply, Recalls etc
  - Normally separate to the Service Agreement and often a simplified 2-3 page tick box document detailing client and manufacturer responsibilities
  - Scope of services to be clear including Warehouse and Distribution, Stability (and shelf life extensions)

Manufacture (Process)

- Manufacturing
  - Sourcing of raw material, packaging materials and other product contact consumables needs to be considered
    - Identifying suppliers (MOQs, Lead Time)
    - Supplier Qualification
    - Release testing of materials, extent, qualification, suitability for human/cGMP use
  - Manufacturing Batch Records to be clear, unambiguous and err on the side of collecting more information than less
    - Manufacture placebo first to avoid possible cross contamination with active
    - dedicated equipment for active and placebo manufacture
    - Consider cleaning requirements (including facility and equipment)
  - Comparator Selection
    - Select white active tablets to avoid complexity with colour matching
    - Consider active livery and capacity to make matching placebo tooling
    - Best approved shelf life of comparators and stock availability (e.g. is there a possibility the product will be withdrawn from the market ?).
    - Will the trial involve overseas sites and if so what impact does Australian sourced comparator have on use in other territories ?

Manufacture (Process)

- Product Considerations
  - Over Encapsulation (1 month development)
    - Tablet size (what size capsule and can the participant swallow this)
    - Capsule type
      - DB Capsules versus Conisnap, HALAL, Colour, Opaqueness versus colour of tablet
      - Rattle and use of fillers (e.g. Microcrystalline Cellulose)
      - Capsule make e.g. HPMC, enteric coated, gelatine (water content, gelatine cross linking)
  - Powder In Capsule (3 months development)
    - API Characteristics (bulk density, hygroscopicity, colour, moisture content)
    - Placebo powder (e.g. MCC, DCP etc)
    - Blend excipient selection and development work
    - Fill weights and release testing (uniformity of content by weight or assay)
    - Method Development (dissolution versus disintegration)
  - Tablets (> 6 months development)
    - Development Work requirements including excipient selection
    - Method development (discriminative dissolution method)
    - R&D Stability requirements
    - Increased API needs

Manufacture (Process)

- Product Considerations
  - Injectable Product
    - Excipient selection
    - Container closure selection (integrity, stability)
    - Placebo manufacture (colour, pH, osmolarity etc)
    - Formulation considerations
      - pH, osmolarity, filter compatibility
    - Manufacture
      - Sterility, endotoxins, particulates
      - Shelf life setting and stability
      - In-use stability considerations

Labelling

- Labelling
  - Label proofs/Text
    - Must be assessed against TGA requirement for clinical trials
    - Combined labels with O/S (e.g. NZ, EU etc)
    - Position of retest/expiry date with respect to future shelf life extensions
  - Need control of randomisation List. How will it be sent to manufacturer, have they experience in randomisation/blinding. Will they conduct 100% double check against read only copy of list etc…
    - Where will they store the list, who has access to this ?
  - Label type
    - direct thermal transfer, rub test etc
    - Product storage and label integrity at RT/2-8°C,-20 °C
  - Secondary packaging requirements
    - carton type, thickness, tamper evidence, pack out design and integrity when stored at RT/2-8°C,-20 °C

Specifications

- Finished Product Specifications
  - If the product is described in a compendial specification this should be used as starting point for specification development.
  - Tablets and capsules should comply with standard monographs (e.g. USP) for the dosage form e.g. dissolution, disintegration, uniformity of content etc. Should also comply with relevant TGOs e.g. TGO 101 Tablets Capsules and Pills
  - Injectables must comply with TGA requirements for sterility and endotoxins
    - Including sterility and endotoxin validation
    - TGO 100 Microbial Standards
  - Specifications should be agreed upfront and signed off by Client and Manufacturer
  - Finished product assay/impurity methods should be validated and by Phase III should be validated for stability indicating
  - Placebo usually includes absence of active, appearance and for sterile products sterility, endotoxins, particulates and any other relevant tests described in the relevant TGO.

Specifications

- Finished Product Specifications
  - A Product Specification file must be created for all investigational product manufacture and available on release of the product. We would normally include:
    - 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/GMP agreements with contract givers, as appropriate;
    - Stability data;
    - Storage and shipment conditions.

Stability

- Finished Product Stability Testing
  - Stability Testing and Proposed Shelf Life
    - cGMP TGA Licensed facility should undertake testing
    - Reference standards and columns can often be rate limiting, need to consider early
    - Methods should be validated commensurate for the stage of development
    - Storage conditions should be in line with product use in the clinical trial
      - Accelerated conditions should be considered in order to extrapolate to longer shelf life 2x-4x real time with accelerate data
      - In Use studies should be planned in particular with injectables
        - Syringe and infusion line compatibility
        - In-use stability post reconstitution and drawing up into syringe
        - Filter compatibility
    - Shelf life extensions need to be planned
      - Minimum data requirements
      - Who will prepare and sign off on the memo to extend
      - Who will conduct the shelf life extension
    - Contingency for shelf life failures should be considered
      - Ideally start stability on R&D batch to obtain real time and accelerated data in advance
      - Conduct accelerated stability and use this to extrapolate to predicted shelf life
      - Monitor real time stability against predicted/extrapolated stability
      - Consider re-manufacture capacity and timelines
  - Consider need placing placebo on stability
    - Country requirements (e.g. EU often require placebo stability)
    - Limited to physical characteristics (e.g. appearance, disintegration, hardness, friability)

Quality Requirements

- Dedicated Quality Group for release of product independent of manufacture
- Experience in reviewing investigational product manufacturing batch records and associated documents
- Undertake independent check of randomised labels against lists and can maintain secure storage of the randomisation list
- Performs line clearance prior to and after manufacture to reduce risk of miss haps
- Recommends increased in process and product controls to minimise limited process qualification in upfront review of master batch records
- Is there an Authorised Person with respect to release of investigational product under the TGA and is this individual included in the licence to undertake this role
- Retention of records including executed batch records, randomisation lists and retention samples is appropriate to the trial and consistent with GMP/Technical Agreement
- Maintenance of blind in particular when sharing documentation with 3rd party e.g executed batch records with client

Quality Requirements

- Manage facility audits, in particular with overseas auditors charged with assessing suitability of IMP new territories (e.g. QP Audit)
- If required initiate or participate in recalls including
  - Mock recalls
  - Liaising with TGA and Sponsor within agreed time frames
  - Emergency unblinding when specified in client/GMP/Technical Agreements