Implementation of annex 13 of the EU GMP guide

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Outline

- Legal frame for manufacturing and importing IMP
- What is an IMP ?
- Legal particularities related to IMP
- Special particularities for manufacturing IMP
- Contents of GMP inspection at IMP manufacturing site
- Conclusion

Based on material edited by Bernd Boedecker (GMP inspectorate of Hannover/ Germany)

Legal frame for manufacturing and importing IMP

- Directive 2001/20/EC (Good Clinical Practice basics)
  - Article 9: conduct of a clinical study subject to ethical evaluation and authorisation
  - Article 13: manufacture and import of IMPs subject to holding of an authorisation
- Directive 2005/28/EC (Clinical Trials Directive)
  - Article 10: requirements for obtaining the manufacturing / import authorisation
- Directive 2003/94/EC (GMP basics)
- EC GMP-Guide (detailed guidance)
  - Part I (Finished Products) + Annex 13 (IMPs)
  - Part II Section 19 (APIs for Use in Clinical Trials)
  - other Annexes as applicable (e.g. Annex 1 for Steriles, Annex 2 for Biologicals etc.)
- Eudralex Volume 10 on CT guidelines
  - Chapter I related to application and application form
  - Chapter III related to the quality of IMP
  - Chapter IV related to inspections (GCP inspections)

What is an Investigational Medicinal Product (IMP)

Definition in Directive 2001/20/EC article 2 d):

- a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial?
- including products already with a marketing authorisation but:

✓ used or assembled (formulated or packaged) in a way different from the authorised form,
✓ or when used for an unauthorised indication,
✓ or when used to gain further information about the authorised form

Legal particularities related to IMP

- Use of IMP only after CTA approval,
- Only use of IMPs being compliant with IMPD, as submitted with CTA application (or as later amended),
- Overlap of GCP and GMP requirements,
- Ultimate responsibility with the sponsor (+ CRO),
- Specific provisions for:
  - ☛ Labeling,
  - ☛ Retain samples,
  - ☛ GMP compliance,
- Two-tier release of IMP prior to use:
  1) by qualified person of manufacturer (for GMP/ PSF compliance),
  2) by sponsor (for CTA/ IMPD compliance)

Special particularities for manufacturing IMP

- Manufacture more complex than commercial production (especially packaging)
- No routine production (often only *one batch per formula)*
- Large proportion of manual operations
- Increased risk of mix-up and cross-contamination (e.g. blinding)
- Incomplete knowledge of potency / toxicity of the product
- Limited validity of analytical test methods
- Quality system not only to ensure patient safety, but also to support scientific validity of the clinical trial (as far as determined by IMP identity/ quality) e.g. level of detail / traceability of documentation-
- Frequent changes of specifications and/or methods
- Delicate supply chain, prone to disturbances
- high economic risk of study high mental pressure on manufacturing staff

Main chapters of annex 13

- Principles
- Glossary
- Quality management
- Personnel
- Premises and equipment
- Documentation
- Production
- Quality control
- Release of batches
- Shipping
- Complaints
- Recalls and returns
- Destruction

Principles

- In clinical trials there may be added risk to participating subjects compared to patients treated with marketed products. The application of GMP to the manufacture of IMP 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.

- The production of investigational medicinal products involves added complexity in comparison to marketed products by virtue of the lack of fixed routines, variety of clinical trial designs, consequent packaging designs, and the need, often, for randomisation and blinding and increased risk of product cross-contamination and mix up.

Quality Management System

- Do not forget part I of the GMP guide (chapter 1 and 2).

Personnel

- All personnel involved with investigational medicinal products should be appropriately trained in the requirements specific to these types of product.
- The Qualified Person should ensure that there are systems in place that meet the requirements of GMP and should have a broad knowledge of pharmaceutical development and clinical trial processes. Guidance for the Qualified Person in connection with the certification of investigational medicinal products is given in paragraphes 38 to 41.

Documentation

- Specifications and instructions,
- Order,
- Product specification file,
- Manufacturing formulae and processing instructions,
- Packaging instructions,
- Processing, testing and packaging batch records.

Production

- Packaging materials,
- Manufacturing operations,
- Principles applicable to comparator product,
- Blinding operations,
- Randomisation code,
- Packaging,
- Labeling.

Contents of GMP inspection at IMP manufacturing site

Regarding the QMS :

- Change management:
  - Traceability,
  - Notification of competent authorities (if applicable).
- Specific standard procedures, e.g. for:
  - Prevention of cross contamination and mix-ups,
  - Compensation of lacking validation,
  - Comparator handling (e.g. stability, if modified),
  - Blinding / randomisation, prevention of unblinding.
- Level of QMS is phase dependent.

Contents of GMP inspection at IMP manufacturing site

Regarding the personnel:

- Project management (especially for complex studies),
- Communication lines with sponsor / CRO,
- Structures such that QP can assume his/her responsibility,
- Specific training, e.g. on:
  - aseptic processing,
  - labeling and packaging,
- Capacity plans, sufficient rests.

Contents of GMP inspection at IMP manufacturing site

Regarding the premises and equipment:

- Design suitable to prevent cross-contamination by potentially toxic or sensitising materials:
  - Cleanability,
  - Containment,
  - Staff / materials flow,
- Warehouse:
  - sufficient space, adequate segregation,
  - Qualified freezers, refrigerators,
- Computerised systems validated e.g. label text databases, label printers, random list generation, etc.

Contents of GMP inspection at IMP manufacturing site

Regarding the documentation:

- PSF: complete [next slide], up-to-date, compliant with IMPD,
- Specifications & instructions (manufacturing, packaging, shipment / distribution etc.) up-to-date, compliant with PSF,
- Manufacturing order: detailed (<-> ref. to PSF), authorised,
- Changes: rationales recorded, consequences investigated,
- Records (manufacturing, packaging, testing, shipping):
  - sufficiently detailed (e.g. reconciliation of amounts),
  - changes / deviations logged.

Contents of GMP inspection at IMP manufacturing site

Regarding the product specification file (PSF):

- Specifications, analytical methods (for all kinds of materials / processing steps),
- Manufacturing / IPC testing methods,
- Approved label copy,
- (relevant) clinical trial protocols, randomisaton codes,
- Technical agreements with contract givers,
- Stability data,
- Storage and shipment conditions.

Contents may vary - list is not exclusive nor exhaustive!

Contents of GMP inspection at IMP manufacturing site

Inspection of the manufacture:

- Procurement of materials, e.g:
  - APIs: GMP conditions, sterility, TSE/ viral safety, bio purity,
  - Comparators: reliable origin, sufficient shelf-life,
  - Labels: dimensions, colour etc. (<-> blinding!),
- All manufacturing steps e.g. effective line-clearance,
- Bulk manufacture:
  - Critical parameters identified, IPCs adequate,
  - Sterilisation and non-standard processes validated,
  - Storage (often cold / cool chain) adequate.

Contents of GMP inspection at IMP manufacturing site

Inspection of the manufacture:

- Modification of **comparators** based on specification ensuring:
  - effective blinding,
  - suitable biopharmaceutical properties,
  - adjusted expiry date,
- Manufacture of **matching placebos** based on specifications ensuring effective blinding,
- **Randomisation / blinding:**
  - Generation, documentation, security of random list,
  - Blinding effective, maintained,
  - Generation of emergency envelopes, suitability of code-break mechanism.

Contents of GMP inspection at IMP manufacturing site

Inspection of manufacture:

- Label printing
  - Data complete, according to CTA, right language,
  - (Core and translated) label text approved,
  - Printing process, e.g.:
    - each printing run and collection of printed labels separately,
    - measures to avoid misprinting,
    - reconciliation of amounts,
    - change of use-by date: usually at authorised site, no superimposing batch ID,
  - Control of printed labels:
    - subsequent to printing, 100% check,
    - incl. cross-check compliance to master label, legibility,
    - incl. positioning of text, color, perforation (<-> blinding!).

Contents of GMP inspection at IMP manufacturing site

Inspection of manufacture:

- Packaging & labeling:
  - Handling of different products on same packaging line at same time,
  - Dealing multiple packaging and labeling runs (e.g. per treatment arm),
  - Prevention of mislabeling (position, random code),
  - Adequate and sufficiently frequent IPCs (incl. check similarity of appearance for different treatment arms),
  - Component / label reconciliation.

Contents of GMP inspection at IMP manufacturing site

Inspection of quality control:

- Compensation for absence of full process validation,
- Incl. effectiveness of blinding (placebos, modified comparators, labels, packaging materials, final packs),
- Comparators imported from 3rd countries: adequate scope,
- Modified comparators incl. stability, dissolution,
- Validation of test methods: scope commensurate with level of risk / stage of development,
- Handling of out-of-specification results: not as formal as in routine QC but scientifically sound,
- Retain samples incl. blinded product, each packaging run / trial period,
- Stability testing: simulative; including bulk material.

Contents of GMP inspection at IMP manufacturing site

Inspection of batch release:

- Duties of the qualified person,
- Duties of the sponsor,

Inspection of shipping,

Inspection of complaints,

Inspection of recalls and returns,

Inspection of destruction.

Conclusion

- Manufacture of IMPs is a major challenge for both the sponsor and the qualified person. The last one is in charge to ensure quality and compliance of the IMP to the CT authorisation.
- This is a critical point that needs to pay special attention to avoid, later on, any questioning of the clinical trial data.
- Beyond the manufacturing itself, points like shipping and recall process should be clearly defined.
- All outsourced activities should be defined in a contract that clearly determines the responsibilities of each party.

Thank you for your attention

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