EU GMP Requirements
- Investigational Medicinal Products -

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Contents covered

- **Legislation** related to Investigational Medicinal Products (IMPs)
- IMP terminology
- Focal points of **inspections** at IMP manufacturing sites
- Revision of **Annex 13** – current status
- GMP level of **Active Ingredients** for Use in IMPs
Legal frame
for manufacture & import of IMPs

- 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
  - 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.)

- EC Guidance for Request for Authorisation of a Clinical Trial (CTA) (ENTR/FS/BL D (2003) CT1, revision 2)
- EMEA Guideline on required quality documentation for IMPs in CT’s (CHMP/QWP/185401/2004, March 2006)
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
IMP Terminology & Abbreviations

- **Sponsor** = responsible for the conduct of the clinical study
- **CRO** = Contract Research Organisation
  - Third Party, representative of the sponsor
- **CTA** = Clinical Trial Application / Authorisation
- **IMPD** = Investigational Medicinal Product Dossier (part of CTA)
- **PSF** = Product Specification File (references for manufacture)
- **Comparator** = reference product (active or placebo)
- **Randomisation** = assigning trial subjects to treatment or control groups by using an element of chance
- **Blinding** = keeping parties unaware of treatment assignment
Legal particularities related to IMPs

- 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:
  - **Labelling**
  - **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)
The Investigational Medicinal Product Dossier (IMPD)

- Source: Guidance for Request of a CTA (ENTR/F2/BL D(2003) CT1 rev 2)
- Contents:
  - Summaries of:
    - Quality, manufacture & control of the IMP (CTD format)
    - for reference medication (comparator, placebo), too
    - Data from preclinical (tox. & pharmacol) studies
    - Data from previous clinical use (if applicable)
  - Overall risk-benefit assessment of the intended use
  - Copies of manufacturing / import authorisations
  - Examples of the labels in national language
- In certain situations simplified IMPDs, e.g.
  - IMP already approved by a EU member state
  - Substantial amendments have to be notified
Contract between Sponsor/ CRO and Manufacturer

- Specific*) contents:
  - Assurance of compliance with IMPD
  - Contents of the manufacturing order
  - Randomisation management
  - Change control
  - Auditing of involved 3rd parties (e.g. suppliers, external QC labs)
  - Two-step release procedure
  - Dedicated use of medication only (commitment by sponsor)
  - Distribution
  - Monitoring of comparators for potential recalls by original distributor
  - Complaints, recalls, returns / destruction

*): basic contents of a general GMP contract see presentation on supplier qualification and outsourcing
Practical particularities of IMP manufacture

- 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 manufact. staff
Basic contents of GMP Inspections at IMP Manufacturing Sites

- Quality management system
- Personnel
- Premises & equipment
- Documentation, incl. PSF
- Production / import
- Quality Control, incl. release of materials
- Distribution
- Complaints & recalls
Inspection of the QM System

- Change mgt:
  - 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 QM effort phase dependent
Inspection of 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
  - labelling and packaging
- Capacity plans, sufficient rests
Inspection of the **Premises / Equipment**

- Design suitable to prevent cross-contamination by potentially toxic or sensitising materials
  - Cleanability
  - Containment
  - Staff / materials flow
- Warehouse:
  - sufficient space, adequate segregation
  - Freezers, refrigerators qualified
- Computerised systems validated
  - e.g. label text databases, label printers, random list generation, blister robots, interactive voice / web response systems, etc.
Inspection of 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
  - incl. specs / QC checks against unintentional unblinding
- **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 the PSF

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

Contents may vary - list is not exclusive nor exhaustive!
Complete documents not required – reference data may suffice
Inspection of the **Manufacture (1)**

- **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:
  - Effective **line-clearance**

- **Bulk** manufacture:
  - Critical parameters identified, IPCs adequate
  - Sterilisation and non-standard processes validated
  - Storage (often cold / cool chain) adequate
Inspection of the **Manufacture (2)**

- Modification of *comparators*
  - based on specification ensuring:
    - effective blinding
    - suitable biopharmaceutical properties
    - adjusted expiry date
- Manufacture of *matching placebos*
  - based on specs ensuring effective blinding
- **Randomisation / blinding**
  - Generation, documentation, security of random list
  - Blinding effective, maintained
  - Generation of emergency envelopes, suitability of code-break mechanism
Inspection of the **Manufacture (3)**

- **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!)
Inspection of the **Manufacture (4)**

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

- **Kitting**
Inspection of the Import of IMPs

- Import licence
- **Responsibility of QP** to ensure EU GMP standards
  - details dependent on country of origin, availability of EU market authorisation etc.  
  see Annex 13 Table 2
- **Technical agreement** with supplier
- **GMP certificate** of local authority
- **Audit** of supplier
- **Quality Control** of **comparators** from countries outside EU / EEA where certificate acc. to EU standards not obtainable
Inspection of the 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; incl. bulk material
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