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
- 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.)

- 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 & Abbreviatons

- **Sponsor** = responsible for the conduct of the clinical study
- **CRO** = Contract Research Organisation
  - Third Party, representative of the sponsor
- **CTA** = Clinical Trial Applicaton / Authorisation
- **IMPD** = Investigational Medicinal Product Dossier (part of CTA)
- **PSF** = Product Specification File (references for manufact.)
- **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, randomisaton 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

Inspection of the Release of Materials

- Separate releases for:
  - starting materials, packaging components
  - bulk medication, comparators, bulk placebos
  - randomisation
  - master label copy, printed labels
  - packaging (possibly various isolated stages!), kitting
  - dispatch

- incl. checks on (amongst others):
  - production conditions, process / cleaning validation
  - ID testing
  - labelling
  - retest dates, stability reports
  - compliance with PSF / IMPD

Inspection of the Distribution (1)

- Triggering by shipping order
- Defined type of shipping boxes, pack formats, coolants, temperature monitors
- Shipping staff trained [<-> e.g. risk of mix-ups!]
- Dispatch only after:
  - QP release (if sent to sponsor [rare case])
  - Release by sponsor (if sent to trial sites / depots)
  - De-coding arrangements available to resp. persons
- if shipment under quarantine, not to patients
- Detailed inventory, incl. confirmation of receipt

Inspection of the Distribution (2)

- temperature monitoring (often cold / cool chain!)
  - incl. deviation handling
- Expiry / retest date mgt
- Transfers from one trial site to another:
  - only exceptional
  - acc. to SOPs
  - only after review of product history
    (e.g. conditions of storage while outside control of manufacturer)
    - seeking of QP advice

Inspection of the Distribution (3)

- Relabelling before transfer**:**
  - only at authorised manufacturer
  - incl. re-certification by QP
- Monitoring of storage / distribution at depots / investigator sites / pharmacies (if responsibility contracted out to manufacturer)
- Returns of (unused) supplies:
  - Defined conditions for transport
  - Documentation
  - Strictly segregated
  - Destruction only after reconciliation completed
  - Reuse controlled, re-certification by QP

Inspection of Complaints & Recalls

- (Scope / details dependent on contract with sponsor)
- Designated responsibilities (acc. to contract)
- Procedure for receipt, documentation and communication of complaints
- Investigation of complaints incl. involvement of QP
- Procedures for retrieving medication and for documentation of retrievals (incl. trial sites)
- Notification of competent authority when action following potential quality problem is considered

2nd Revision of Annex 13 – Current State of Affairs

- Final text agreed by GMP/GDP Inspectors Working Group and forwarded to European Commission for adoption (June 2009)
- Major changes:
  - **Reconstitution** of IMPs only: specification of conditions for waiving need of manufacturing authorisation
  - **Separate responsibilities** for manufacture and quality control even where number of staff is small
  - Detailed provisions for taking and storage of **retain samples**
  - Detailed provisions for the **two-step release** of IMPs for use (certification by manufacturer‘s QP + sponsor)

Active Ingredients for IMPs (1)

- EC GMP-Guide part II, section 19:
  - Acknowledged that not all controls in Part II appropriate
    - Controls should be consistent with stage of development
  - Minimum requirements (1):
    - Appropriate GMP concepts
    - Independent quality unit
    - System for testing of starting materials, intermediates, finished API
      - for raw materials, supplier certificate + ID testing may suffice
    - Evaluation of process and quality problems
    - Controlled labelling
      - Incl. identification of material as ‚for investigational use‘
    - Equipment calibrated, clean, suitable [= qualified]
    - Minimsed (cross-)contamination

Active Ingredients for IMPs (2)

- EC GMP-Guide part II, section 19:
  - Minimum requirements (2):
    - Detailed documentation of production
    - Compensation of lacking process validation by combination of controls, calibration, equipment qualification
    - Every change adequately recorded
    - Analytical methods ‚scientifically sound‘
    - Documentation system for development and production
      - incl. for development of analytical methods
    - System for retaining records and documents

Up for discussion
Have you got any …?

- … questions?
- … remarks?
- … recommendations?

Teşekkür ederim!

- … for your attention
- … for your contributions