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An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

IMP Management

Frequently asked questions

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HPRA Information Day – GCP for IMP clinical trials

Dublin, 23 October 2018

Frequently asked questions – IMP management

- Key requirements that apply to sponsors regarding IMP management
- Aspects of IMP management considered during a GCP inspection
- Scope of the ‘hospital exemption’
- Points to consider if investigator site activities, for IMP management, are delegated to a third party

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Key Legislation

- Directive 2001/20/EC & 2005/28/EC
- S.I. No. 190 of 2004 - European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004, as amended *(IMP labelling)*
- S.I. No. 273/2012 - Medicinal Products (Control of Manufacture) (Amendment) Regulations 2012, as amended *(Exemptions, manufacturer's authorisation, obligations, qualified person etc.)*

Key Guidance

- ICH GCP E6 (R2) e.g. 5.14, Supply and Handling IMPs
- EudraLex:
  - Volume 10 - Clinical trials guidelines, Chapter III
  - Volume 4 - Good Manufacturing Practice (GMP) guidelines, including Annex 13, Manufacture of Investigational Medicinal Products (IMP)
- HPRA Guidance:
  - Reporting and Initial Investigation of Quality Defects in Medicinal Products for Human and Veterinary Use
  - Recall of Medicinal Products for Human and Veterinary Use

Key requirements that apply to sponsors regarding IMP management

- Considered during planning stage for a trial
- Clearly identify which medicines are ‘IMPs’ and which are not
- Need to consider the IMP sourcing strategy
- Need to determine which rules apply
- If IMP not sourced from medicine(s) already available on market, the process will be more complex

IMP Sourced Internally

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Marketed medicinal product, available at Investigator site for routine use, in marketed form

IMP dispensed according to routine practice

If, additional GMP activities required (such as labelling):
Performed at Inv. Site under Exemption (S.I 539 of 2007 (5))
Performed to GMP standards

Investigator site (Compliance with ICH GCP E6, 4.6 – Investigational Products)
(Inventory, storage, accountability, destruction, and associated records etc.)

For illustrative purposes, other rules may apply

IMP Sourced Externally

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IMP no marketed form

Manufacture to GMP

Medicinal product (marketed/sourced from within EU/EEA)

Designated IMP for trial: Additional activities (repackaging, labelling –performed to GMP)

1st Step Release: Qualified Person at Authorised Manufacturing site has certified that the requirements of Article 13.3 of Dir. 2001/20/EC have been met (GMP Related Activity)

2nd Step Release: Regulatory Release (GCP/GMP Related Activity) ICH GCP E6 (R2), 5.14.2

Investigator Site: Compliance with ICH GCP E6 (R2), 4.6 (Investigational Products)

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Key aspects examined during a GCP inspection

- Regulatory Release (Green Light Procedure)
- Supply, shipment, accountability, returns & destruction
- Blinding & un-blinding
- Randomisation & code breaking
- Outsourcing of activities
- Written procedures
- Non-commercial financial arrangements

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Hospital exemption

- The term ***'hospital exemption'*** is used to refer to the exemption from the requirement to hold a Manufacturer's / Importer's Authorisation for certain manufacturing activities which are carried out in a hospital which is participating in a clinical trial

- HPRA Guide to Clinical Trial Applications: *'no authorisation is needed for labelling, packaging or re-packaging (including re-constitution) of a product by a doctor, pharmacist or other person acting under the supervision of a pharmacist, when the product is for use only in the hospital by a resident patient or an out-patient'.*

Legal provisions

- Commission Directive 2005/28/EC, Chapter 3, Manufacturer's authorisation, Article 9(2). Authorisation, as provided for in Article 13(1) of Directive 2001/20/EC, shall not be required for ***reconstitution prior to use or packaging***, where those processes are carried out in ***hospitals, health centres or clinics***, by pharmacists or other ***persons legally authorised in the Member States*** to carry out such processes and if the IMPs are intended to be used ***exclusively in those institutions***

Exemption as reflected in S.I. No. 273/2012 - Control of Manufacture (Amendment) Regulations 2012

- *Exemptions*. 5. (1) The provisions of Regulation 4 shall not apply to:

  (*b*) the preparation, dividing up, changes in packaging or in the presentation of a medicinal product, where these processes are carried out

  (i) **in a dispensing pharmacy by or under the personal supervision of a pharmacist, for supply in or from such pharmacy**, or

  (ii) by a **registered medical practitioner or registered dentist** for supply to a patient under his or her care.

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Hospital exemption

- Most commonly used for re-labelling associated with extension of ‘use-by’ date and/or simple reconstitution
- At present, IMPs must be used ‘exclusively’ at the investigator site
- Use of the hospital exemption for more complex GMP activities, or at centres not part of the same legal entity as the investigator site, should be carefully considered and compliance advice sought

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Points to consider

- Observed increasing trend whereby sponsor contracts a 3rd party pharmacy, on behalf of investigator site
- IMP shipped to 3rd party pharmacy
- 3rd party pharmacy used to perform routine investigator site IMP related activities, including IMP accountability, allocation, returns etc. (ref. GCP E6, 4.6)
- When this arrangement is used, common deficiencies have been identified in the following areas:
  - Records of delegation
  - Arrangements for insurance/indemnity
  - General deficiencies regarding GCP compliance
  - Supervision

Delegation to a 3rd party

- Non compliance with GCP 4.2.5, 4.2 (qualification, supervision) & GCP 4.1.5 (delegation)
- Contract/written agreement: typically only between sponsor and third party
- No record on delegation log
- Deficiencies in qualification process: not performed, or investigator not aware of the process and outcome
- No specific procedures for PI supervision and oversight foreseen
- Indemnity/insurance not considered

GCP procedures

- All of the same GCP requirements apply to the 3rd party pharmacy
- Includes 4.6 (Investigational Product) & 4.9 (Records & Reports)
- Same expectations for temperature monitoring, IMP accountability, source records, records of shipment, receipt, dispensing, returns, compliance checks, destruction
- Common deficiencies:
  - Communication of subject compliance issues from 3rd party pharmacy back to the investigator site
  - Unclear roles/responsibilities with regard to prohibited medication checks
  - PI not aware of sponsor monitoring visits and any issues identified

Points to consider

- Needs to be considered during the planning stage
- Any change from routine practices at a clinical site require consideration, and the impact of the changes on GCP compliance needs to be taken into consideration
- The same principles and requirements apply to the third party as they would to the investigator site
- Consider also description of these arrangements in the application for ethics opinion

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Thank You and Safe Home