Federal Agency for Medicines and Health Products (FAGG-AFMPS)

Implementation of GMP in Early Phase Clinical Trials

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Good Manufacturing Practices: What?

Different chapters of GMP:
• quality management
• personnel
• premise and equipment
• documentation
• production
• quality control
• contract manufacture and analysis
• complaints and recalls
• self inspection
Good Manufacturing Practices: What?

• Documentation of every aspect of processes and operations related to the production of a medicinal product.

• All equipment for manufacturing and analysis must be suited for intended use.

• All operational methods and procedures for manufacturing, cleaning and analytical testing used in the fabrication process are validated according to predefined specifications.
Good Manufacturing Practices: What?

• GMP is a system to ensure that products are consistently produced and controlled according to quality standards.
• It is also designed to minimize the risks related to the use of IMP’s that cannot be eliminated through testing of the final product.
• GMP covers all aspects of production from the starting materials, premises and equipment to the training and personal hygiene of staff.
GMP for IMPs: Why?

• Protect study participants against risks that may arise from inadequate manufacturing, manipulation, storage or administration of wrong product or dose

• Make sure that results of clinical trials are not be influenced by inadequate safety, mistakes in the administered product, insufficient quality or changed efficacy because of poor fabrication
GMP for IMPs: Why?

• Assure consistency between different batches of a medicinal product

• Changes made during development should be adequately documented and justified to allow comparison between the effects observed in early and later phases.

• Clinical trials should follow GCP rules and this implies that medicinal products used should be produced, manipulated and stored according to GMP
Considerations for Clinical Trials

- No established routines yet
- Different trial designs
- Randomisation and blinding
- Risk for cross contamination and mix up
- Potency and toxicity not yet completely known
- No complete process validation
- Modification of authorised medicinal products (repackaging, blinding, overencapsulation)
Good Manufacturing Practices: Law

• The production of medicinal products for investigational use is governed by the guidelines in Eudralex volume IV, annex 13
• Eudralex volume IV, annex 13 not fully adjusted to reality in early phase clinical trials
Considerations for Early Phase Trials

- In early phases there is a need to take into account:
  - Flexible dose adjustments
  - Ex temporaneous preparation
  - Highly trained staff performs very limited production activities
  - No QP present in phase I center or hospital pharmacy
Good Manufacturing Practices: Law

• Law of 7 May 2004, Art. 24. § 1 For the production and importation of medicinal products for research an authorisation is required from the minister.

• An authorisation is also required for the production of medicinal products that will be exported.

• How can GMP be implemented in phase I units?
Authorisation

- Pharmaceutical companies, phase I units, hospital pharmacies can ask for an authorisation according to the Royal Decree of 30/06/2004.
- This means that an inspection will take place to determine whether all conditions for the production of IMP’s are met.
Authorisation

- Obtaining an authorisation to produce IMP’s may in the end be the most desirable situation.
- It should be recognised that at present this may be an impossible burden in early phases.
- It can even be questioned whether a full authorisation is always needed for the limited production that is required in phase I clinical trial units.
- There is need for a pragmatic approach.
Hospital pharmacies

• Directive 2005/28/EC: authorisation not 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 investigational medicinal products are intended to be used exclusively in those institutions.
Reconstitution (Vol IV, Annex 13)

- Dissolving or dispersing the investigational medicinal product (IMP) for administration of the IMP to a trial subject
- Or diluting or mixing the IMP with some other substance used as a vehicle for the purposes of administering it.
- This process is defined in the Clinical Trial Application/IMP Dossier or clinical trial protocol
Reconstitution

• This process is undertaken as soon as practicable before administration

• A finished investigational medicinal product (released by a Qualified Person) must exist before a process can be defined as reconstitution.

• Reconstitution is NOT the mixing of several ingredients, including the active substance together to produce the IMP
Limitations

• A phase I unit is not recognised by law in Belgium

• When a phase I unit is not an integral part of a hospital, health centre or clinic it cannot rely on the hospital pharmacy even if situated in the same building

• A pharmacist must be on the site, which is not always the case in a phase I unit

• Even if a hospital pharmacy is available the manipulations of the IMP’s that are allowed are limited
Limited production of IMP

- Phase I units or hospital pharmacies can apply for the procedure
- Inspection will take place
- A limited production as specified in the inspection report can take place
- This report will reassure the FAMHP that a clinical trial involving the specified manipulations can safely be conducted at the site involved
Limited production of IMP

• Without such inspection report or if the outcome was negative, the conduct of a clinical trial requiring production will be denied because of non compliance with GMP and as a consequence GCP

• The proposed procedure will only be possible for production operations for internal use

• The procedure will also be limited to clinical trials in early phase
Limited production of IMP

• Early phase clinical trial is defined as:
  - Exploratory, microdose or phase 0 clinical trial
  - phase I trials
  - phase II trials:
    1) first exposure to patients
    2) exploring therapeutic effect / maximum tolerated dose
    3) therapeutic dose finding in patients
Temporary measure

- Evaluation of the procedure will take place based on the experience gained.
Important aspects of the project

• There are three important definitions in order to clarify the temporary measures in Belgium
  - Inspected location
  - Responsible person
  - Quality agreement
Inspected location

• A dedicated area, or an area providing equivalent protection, of the hospital pharmacy or the phase I unit inspected by the National Competent Authority for the preparation of investigational medicinal products under minimum GMP conditions described in guidance document, intended for use on site.

• The inspection report will clearly indicate what are the limited production operations and required conditions at the site.
Responsible Person

• An individual who takes responsibility for pharmaceutical operations performed in the inspected location.

• This should be a health care professional legally authorised to perform these activities.

• Thus the Responsible Person could be a pharmacist, or in case of cell or tissue based medicinal products a medical doctor.
Quality agreement

• A written agreement between the Qualified Person of the sponsor and the Responsible Person describing procedures and responsibilities of each party and in accordance with applicable legislation.

• This document should be part of the clinical trial application
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