GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS

Supplementary guidelines for the manufacture of investigational pharmaceutical products for studies in humans

1. Introductory note

The legal status of investigational pharmaceutical products for human use varies from country to country: in some of them (e.g. USA, Germany and others) these products are manufactured and inspected like "normal" licensed pharmaceutical products. In most other countries the investigational pharmaceutical products are not covered by legal and regulatory provisions in the area of Good Manufacturing Practice (GMP), inspection, etc.

However, the EC Guide on GMP recommends that principles of GMP are applied as appropriate to the preparation of these products. The WHO Guide on GMP,* according to the statement in the introductory note, is applicable to the preparation of clinical trials supplies.

2. General considerations

The present guidelines supplement both WHO guidelines on GMP and Good Clinical Practice (GCP).* The application of principles of GMP to the preparation of investigational products is required for several reasons:

- to assure consistency between and within batches of the investigational product and thus assure reliability of clinical trials;
- to assure consistency between the investigational product and future commercial product and therefore relevance of the clinical trial to the efficacy and safety of the marketed product;
- to protect subjects of clinical trials from poor quality products resulting from manufacturing errors (omission of critical steps such as sterilization, contamination and cross-contamination, mix-ups, wrong labelling, etc.), or from inadequate quality of starting materials and components.
- to document all changes to the manufacturing process.

In this context, a selection of an appropriate dosage form for clinical trials is important. Whilst it is accepted that for early trials the dosage form may be very different from the anticipated final formulation (e.g. a capsule instead of a tablet), in the pivotal Phase III studies the dosage form should be similar to the projected commercial presentation. Otherwise the Phase III trials would not necessarily prove the efficacy and safety of the marketed product.

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* TRS 823, 1992, p. 18.
** WHO Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products.
In the event that there is a significant change between clinical and commercial dosage forms, data should be submitted to registration authorities in support of the equivalence of the final dosage form as opposed to that used in clinical trials regarding bioavailability and stability.

Final manufacturing methods have to be revalidated following changes in processes, scaling-up, transfer to other manufacturing sites, etc.

This annex specifically addresses those practices which may be different for investigational products, which are usually not manufactured under a set routine, and with possibly incomplete characterization of the product at initial stages of clinical development.

3. Glossary

**Clinical trial**

Any systematic study on pharmaceutical products in human subjects, whether in patients or non-patient volunteers in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study absorption, distribution, metabolism and excretion of the products with the object of ascertaining their efficacy and safety.

Clinical trials are generally classified into Phases I to IV. It is not possible to draw distinct lines between the phases, and diverging opinions about details and methodology do exist. Description (in brief) of the individual phases, based on their purposes as related to clinical development of pharmaceutical products, are given below.

(a) Phase I

These are the first trials of a new active ingredient or new formulations in man, often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of safety, and a first outline of the pharmacokinetic/pharmacodynamic profile of the active ingredient in humans.

(b) Phase II

The purpose of these therapeutic pilot studies is to demonstrate activity and to assess short-term safety of the active ingredients in patients suffering from a disease or condition for which the active ingredient is intended. The trials are performed in a limited number of subjects and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. This phase also aims at the determination of appropriate dose ranges/regimens and (if possible) clarification of dose/response relationships in order to provide an optimal background for the design of extensive therapeutic trials.

(c) Phase III

Trials in large (and possibly varied) patient groups with the purpose of determining the short- and long-term safety/efficacy balance of formulation(s) of the active ingredient, as well as to assess its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g. clinically-relevant drug interactions, factors leading to differences in effect such as age, etc.). The design of trials should preferably be randomized double-blind, but other designs may be acceptable, e.g. long-term safety studies. Generally, the circumstances of the trials should be as close as possible to normal conditions of use.

(d) Phase IV

Studies performed after marketing of the pharmaceutical product. Trials in Phase IV are carried out on the basis of the product characteristics on which the marketing authorization was granted and are normally in the form of post-marketing surveillance, assessment of therapeutic value or treatment strategies. Although methods may differ, Phase IV studies should use the same scientific and ethical standards as applied in premarketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.
**Investigational product**

Any pharmaceutical product (new product or reference product) or placebo being tested or used as reference in a clinical trial.

**Investigator**

A person responsible for the trial and for the rights, health and welfare of the subjects in the trial. The investigator must be an appropriately qualified person legally allowed to practice medicine/dentistry.

**Monitor**

A person appointed by the sponsor, and responsible to the sponsor, for the monitoring and reporting of progress of the trial and for verification of data.

**Order**

Instruction to process, package and/or ship a certain number of units of investigational product.

**Pharmaceutical product**

For the purpose of this document the same definition of the term is used as in the WHO Guidelines on GCP, see footnote on page 1: any substance or combination of substances which as a therapeutic, prophylactic or diagnostic purpose, or is intended to modify physiological functions, and presented in a dosage form suitable for administration to humans.

**Product specification file(s)**

Reference file(s) containing all the information necessary to draft the detailed written instructions on processing, packaging, labelling, quality control testing, batch release, storage conditions and shipping.

**Protocol**

A document which states the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator/institution involved and the sponsor. It can, in addition, function as a contract.

**Shipping/dispatch**

The operation of assembly, packing for shipment, and sending of ordered medicinal products for clinical trials.

**Sponsor**

An individual, a company, an institution or an organization which takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator independently initiates and takes full responsibility for a trial, the investigator then also assumes the role of the sponsor.

4. **Quality Assurance**

Quality Assurance of pharmaceutical products has been defined and discussed in detail in the main guide on GMP.

The quality of dosage forms in the Phase III clinical studies should be characterized and assured at the same level as for routinely manufactured products. The Quality Assurance System, designed, set up and verified by the manufacturer, should be described in writing, taking into account the GMP principles to the extent these are applicable to operations in question. This system should also cover the interface area between the manufacture and
the trial site (e.g. shipment, storage, occasional additional labelling etc.).

5. Validation

Some of the production processes of investigational products which have no marketing authorization may not be validated to the extent necessary for a routine production operation. The product specifications and manufacturing instructions may vary during development. This increased complexity in manufacturing operations requires a highly effective system of Quality Assurance.

For sterile products, there should be no reduction in the degree of validation of sterilizing equipment. Validation of aseptic processes presents special problems when the batch size is small; in these cases the number of units filled may be not adequate for a validation exercise. Filling and sealing is often a hand operation presenting great challenges to sterility so enhanced attention should be given to environmental monitoring.

6. Complaints

The conclusions of any investigation carried out in relation to a complaint should be discussed between the manufacturer and the sponsor (if different) or between the persons responsible for manufacture and those responsible for the relevant clinical trial in order to assess any potential impact on the trial and on the product development, to determine the cause, and to implement any necessary corrective action.

7. Recalls

Recall procedures should be understood by the sponsor, investigator and monitor in addition to the person(s) responsible for recalls, as described in Chapter 7 of the Guide to GMP.

8. Personnel

Although it is likely that the number of staff involved will be small, there should be separately designated people responsible for production and quality control. All production operations should be carried out under control of a clearly identified responsible person. Personnel from Development, involved in production and quality control, need to be instructed in the principles of GMP.

9. Premises and equipment

During manufacture of investigational products, it may be that different products are handled in the same premises and at the same time, and this reinforces the need to eliminate all risks of contamination, including cross-contamination, by using appropriate procedures.

For the production of the particular products referred to in paragraph 11.20 of the Guide to GMP, campaign working may be acceptable in place of dedicated and self-contained facilities. Because the toxicity of the materials may not be fully known, cleaning is of particular importance; account should be taken of the solubility of the product and of excipients in various cleaning agents.

* For additional advice on validation see document WHO/PHARM/93.562/rev. 3.
10. Materials

Starting materials

The consistency of production may be influenced by the quality of the starting materials. Their physical, chemical and, when appropriate, microbiological properties should therefore be defined, documented in their specifications and controlled. Existing compendial standards, when available, should be taken into consideration. Specifications for active ingredients should be as comprehensive as possible, given the current state of knowledge. Specifications for both active and non-active ingredients should be periodically reassessed.

Detailed information on the quality of active and non-active ingredients, as well as of packaging materials, should be available in order to recognize and, as necessary, allow for any variation of the production.

Chemical and biological reference standards for analytical purposes

Reference standards from reputable sources (WHO, national standards) should be used, if available. If not available, the reference substance(s) for the active ingredient(s) should be prepared, tested and released as a reference material by the producer of the investigational pharmaceutical product, or by the producer of the active ingredient(s) used in the manufacture of the investigational pharmaceutical product.

Principles applicable to reference products for clinical trials

In studies whereby an investigational product is compared with a marketed product, attention should be paid to ensure the integrity and quality of the reference products (final dosage form, packaging materials, storage conditions, etc.). If significant changes are to be made to the product, data should be available (e.g. stability, comparative dissolution) to prove that these changes do not influence the original quality characteristics of the product.

11. Documentation

Specifications (for starting materials, primary packaging materials, intermediate and bulk products and finished products), master formulae and processing and packaging instructions may be changed frequently as a result of new experience in the development of an investigational product. Each new version should take into account the latest data and should refer to the previous version so that traceability is ensured. Rationales for changes should be stated and recorded.

Batch processing and packaging records should be retained for at least two years after termination or discontinuance of the clinical trial, or after the approval of the investigational product.

Order

The order may request the processing and/or packaging of a certain number of units and/or their shipping. It may only be given by the sponsor to the manufacturer of an investigational product. It should be in writing (though it may be transmitted by electronic means), and precise enough to avoid any ambiguity, it should be formally authorized and it should refer to the approved Product Specification File.

Product Specification File(s)

A Product Specification File (or files) should contain information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release, storage conditions and/or shipping. It should indicate who is responsible for release of batches; is it the authorized person, or a specially designated specialist trained as an authorized person? It should be continuously updated, ensuring appropriate traceability to the previous versions.

Specifications

In developing specifications, special attention should be paid to characteristics which bear on the efficacy and safety of pharmaceutical products, namely:
accuracy of the therapeutic or unitary dose: homogeneity, content uniformity;
• release of active ingredients from the dosage form: dissolution time, etc.;
• estimation of stability, if necessary in accelerated conditions, determination of the preliminary storage conditions and shelf-life of the product;

In addition packaging size should be suitable for the trial.

Specifications may be subject to change as development of the product progresses. Changes should however, be carried out according to a written procedure, authorized by a responsible person and clearly recorded. Specifications should be based on all available scientific data, current state-of-the-art technology used, and the regulatory and pharmacopoeial requirements.

Master formulae and processing instructions

They may be changed in the light of experience but allowance must be made for any possible repercussions on stability and, above all, on bioequivalence between batches of finished products. Changes should be carried out according to a written procedure, authorized by a responsible person and clearly recorded.

In certain cases it may not be necessary to produce master formula and processing instructions, but for every manufacturing operation or supply there should be clear and adequate written instructions and written records. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture.

Packaging instructions

The number of units to package should be specified prior to the start of the packaging operations, considering also the number of units necessary for carrying out quality controls and a sufficient number of samples from each batch used in the clinical trial that are to be kept as a reference for further rechecking and control. A reconciliation should take place at the end of the packaging and labelling process.

Labelling instructions

Labels should include:
• the name of the sponsor
• a statement: "for clinical research use only"
• a trial reference number
• a batch number
• the patient identification number*
• the storage conditions
• the expiry date in month/year or a retest date.

Additional information may be displayed according to the order (e.g. dosing instructions, treatment period, standard warnings etc.). When necessary for blinding purposes, the batch number may be provided separately (see also "blinding operations"). A copy of each type of label should be kept in the batch packaging record.

Processing and packaging batch records

Processing and packaging batch records should be kept in sufficient detail for the sequence of operations to be accurately traced back. These records should contain any relevant remarks which enhance existing knowledge of the product and allow improvements of the manufacturing operations and justify the procedures used.

* Not necessarily printed at the manufacturing facility (may be added at a later stage).
Coding (or randomisation) systems

Procedures should describe the generation, distribution, handling and retention of any randomization code used for packaging investigational products.

A coding system should be implemented to allow for a proper identification of the "blinded" products. The code, together with the randomization list, must allow proper identification of the product, including any necessary traceability to the codes and batch number of the product before the blinding operation. The coding system must allow in an emergency situation, determination without delay as to the identity of the actual treatment product received by individual subjects.

12. Production

Products for clinical trials (late Phase II and Phase III studies) should to the extent possible be manufactured at licensed facilities. Facilities may be of different types, e.g. as follows:

(a) a pilot plant, primarily designed and used for process development;
(b) a small-scale facility (sometimes called "pharmacy") separate both from the company's pilot plant and routine production;
(c) a larger scale production line assembled to manufacture materials in larger batches e.g. for late Phase III trials and first commercial batches;
(d) the normal production line used for licensed commercial batches, sometimes used for the production of investigational pharmaceutical products, if the number, e.g. of ordered ampoules, tablets or others is high enough.

The relation between the batch size for investigational pharmaceutical products described in (a) or (b) to the planned full-size batches may vary widely depending on the demanded pilot plant or "pharmacy" batch size and the capacity available in the full-size production.

The present guidelines are applicable to operations of the first and second type (a) and (b). It is easier to assure compliance with GMP rules in the facilities of the second type (b), since processes are kept constant in the course of production and are not normally changed for the purpose of process development. The types (c) and (d) manufacture should be subject fully to GMP rules for pharmaceutical products.

Administratively the manufacturer has a fifth alternative: to contract out the preparation of investigational products. Technically however, this option will fall back into one of the above listed categories. In this case the contract must clearly state, among other provisions, the use of the pharmaceutical products in clinical trials. Cooperation between the contracting parties should be very close.

Manufacturing operations

During the development phase, validated procedures may not always be available, which makes it difficult to know in advance the critical parameters and the in-process controls that would help to control these parameters. In these cases, provisional production parameters and in-process controls may usually be deduced from experience with analogous products. Careful consideration by key personnel is called for in order to formulate the necessary instructions and to adapt them continuously to the experience gained in production.

Assurance of sterility for sterile investigational products should be no less than for licensed products. Cleaning procedures should be appropriately validated and designed in the light of the incomplete knowledge of the toxicity of the investigational product. Where processes such as mixing have not been validated, additional quality control testing may be necessary.

* Other manufacturers use the term "pharmacy" to designate different types of premises, e.g. areas where starting materials are dispensed and compounding of batches is effected.
Packaging – Packaging and labelling of investigational products are likely to be more complex and more liable to errors (which are also harder to detect) than with licensed products when "blinded" labels are used. Supervision procedures such as label reconciliation, line clearance, etc. and the independent checks by quality control staff should accordingly be intensified.

The packaging must ensure that the investigational product remains in good condition during transport and storage at intermediate destinations. Any opening or tampering of the outer packaging during transport should be readily discernible.

Blinding operations

In the preparation of "blinded" products in-process control should include a check on the similarity in appearance and any other required characteristics between the different products being compared.

13. Quality control

As processes may not be standardized or fully validated, end product testing takes on more importance to ensure that each batch meets its specification.

Product release is often carried out in two stages, before and after final packaging.*

* bulk product assessment: it should cover all relevant factors, including production conditions, results of in-process testing, a review of manufacturing documentation and compliance with the Product Specification File and the Order;

* finished product assessment: it should cover, in addition to the bulk product assessment, all relevant factors, including packaging conditions, results of in-process testing, a review of packaging documentation and compliance with the Product Specification File and the Order.

When necessary, Quality Control should also verify the similarity in appearance and other physical characteristics, smell, taste of "blinded" investigational products.

Samples of each batch of product should be retained in the primary container used for the study or in a suitable bulk container for at least for two years after the termination or completion of the relevant clinical trial. If the sample is not stored in the pack used for the study, stability data should be available to justify the shelf-life in the pack used.

14. Shipping - Returns - Destruction

Shipping, return and destruction of unused products should be carried out according to written procedures stated in the protocol.

Shipping

Shipping of investigational products is conducted according to orders given by the sponsor.

A shipment is sent to an investigator only after a two-step release procedure: the release of the product after quality control ("technical green light") and the authorization to use the product, given by the sponsor ("regulatory green light"). Both releases should be recorded.

The sponsor should ensure that the shipment is to be received and acknowledged by the right addressee as stated in the protocol.

A detailed inventory of the shipments made by the manufacturer should be maintained. It should particularly mention

* This practice also exists at certain large companies with regard to licensed products.
the addressee's identification.

**Returns**

Investigational products should be returned on agreed conditions defined by the sponsor, specified in written procedures, and approved by authorized staff members.

Returned investigational products should be clearly identified and stored in a dedicated area. Inventory records of the returned medicinal products should be kept. Responsibilities of the investigator and the sponsor are further elaborated in the WHO GCP, Section 10.

**Destruction**

The sponsor is responsible for the destruction of unused investigational products. Investigational products should therefore not be destroyed by the manufacturer without prior authorization by the sponsor. Destruction operations should be in accordance with environmental safety requirements.

Recording of destruction operations should be carried out in such a manner that all operations are documented. The records should be kept by the sponsor.

If the manufacturer is requested to destroy the products, he should deliver a certificate of destruction or a receipt for destruction to the sponsor. These documents should allow the batches involved to be clearly identified.

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