World Health Organization

DRAFT WORKING DOCUMENT FOR COMMENTS:

WHO good manufacturing practices for investigational products

Please send your comments to **Dr Steve Estevão Cordeiro**, Technical Officer, WHO Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (estevaos@who.int), with a copy to Ms Sinead Jones (jonessi@who.int) before **31 August 2021**. Please use the "Table of Comments" attached to this email for this purpose.

Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/current-projects) for comments under the "*Working documents in public consultation*" link. If you wish to receive all our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.

41 SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/20.863:

42 # WHO good manufacturing practices
43 # for investigational products

Description of Activity	Date
Following a recommendation by the Fifty-fifth Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP), the WHO Secretariat was recommended to revise the existing guideline on good manufacturing practices for investigational products.	October 2020
Preparation of first draft working document.	October 2020
Mailing of working document to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP) inviting comments and posting of the working document on the WHO website for public consultation	November 2020
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	January 2021
Discussion of the feedback received on the working document in a virtual meeting with an expert working group	February-March 2021
Preparation of working document for next round of public consultation.	March 2021
Mailing of revised working document inviting comments, including to the EAP, and posting the working document on the WHO website for a second round of public consultation.	April 2021
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	June 2021
Discussion of comments in the virtual meeting on *Good practices for health product manufacture and inspection*	28 June - 2 July 2021
Preparation of working document for next round of public consultation.	July 2021
Mailing of revised working document inviting comments, including to the EAP, and posting the working document on the WHO website for a second round of public consultation.	July – August 2021
Consolidation of comments received and review of feedback. Preparation of working document for discussion in the ECSPP.	September – October 2021

Presentation to the Fifty-sixth meeting of the ECSPP.	TBD
Any other follow-up action as required.	

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WHO good manufacturing practices for investigational products

Background

In view of an old publication date, and the recent need for new guidelines arising from inspections carried out for COVID-19 therapeutics, the World Health Organization (WHO) Prequalification Team - Inspection Services (PQT INS) raised the urgency for a revision of the *WHO Good manufacturing practices for investigational pharmaceutical products for clinical trials in humans* (*1*). The Fifty-fifth Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) concurred with this proposal.

The objective of this update is to bring the guideline in line with current expectations and trends in good practices and to harmonize the text with the principles from other related international guidelines.

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1. Introduction

1.1. Investigational products are used for testing purposes; as a reference in clinical trials and field trials; as a placebo; for an unauthorized indication; and to gain further information about the authorized form.

1.2. In some cases, marketed products which have been re-packaged or modified in some way, are used for investigational purposes.

1.3. The legal status of investigational products varies from country to country.

1.4. These products are sometimes not covered by legal and regulatory provisions in the areas of good practices (GxP) and inspection. These complexities, such as lack of high level good manufacturing practices (GMP) requirements, risk of contamination and cross-contamination, clinical trial designs, blinding and randomization, increase the risk related to the investigational product. In addition, there are also instances where there is incomplete knowledge of the potency and safety of the investigational product.

1.5. There are further risks associated with the production, validation, testing, control, shipping, storage and use of investigational products.

1.6. To minimize risk; to ensure the safety of the subjects participating in clinical trials; and to ensure that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture, investigational products should be manufactured and managed in accordance with an effective quality management system and the recommendations contained in this guideline.

1.7. Other guidelines and GxP should be taken into account, where relevant and as appropriate, as to the stages of development, production and control of the product.

1.8. In accordance with the quality management system, provision should be made for changes whenever necessary, as knowledge of the process increases over time, and in accordance with the stages of development of the product.

1.9. Investigational products should be manufactured in a manner:

- that is compliant to GxP, as appropriate to the stage of development;
- that ensures that subjects of clinical trials will be protected from poor quality products due to unsatisfactory manufacturing;
- to assure consistency between and within batches of the investigational product; and
- that allows for the review of the data from the investigational products used against the future commercial product.

1.10. The selection of an appropriate dosage form for clinical trials is important. While it is accepted that the dosage form may be very different from the anticipated final formulation (e.g. a capsule instead of a tablet) in early trials, in the pivotal Phase III studies, it should be similar to the projected commercial presentation; otherwise these trials will not necessarily prove that the marketed product is both efficacious and safe. If there are differences between the clinical and commercial dosage forms, scientific justification and data should be submitted to the registration authorities to demonstrate that the final dosage form is equivalent, in terms of bioavailability and stability, to that used in the clinical trials.

1.11. The quality control of investigational products should be appropriate to the stage of development. For example, dosage forms in Phase III clinical studies should be characterized and assured at a similar level, as for commercially manufactured products.

1.12. Where production and/or quality control is transferred from one site to another, the recommendations in the guideline for transfer of technology should be followed *(2)*.

1.13. This document should be read in conjunction with other WHO GxP guidelines. See section References *(1-11).*

2. Scope

2.1. The recommendations in this guideline are mainly applicable to investigational products for human use.

2.2. The principles in this guideline should be considered in early phase clinical manufacture.

2.3. Some of the principles may be applied to other investigational products.

3. Glossary

The definitions given below apply to the terms used in this guideline. They may have different meanings in other contexts.

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

Clinical trials are generally divided into Phases I-IV. It is not possible to draw clear distinctions between these phases, and different opinions about details and methodology do exist. However, the individual phases, based on their purposes as related to the clinical development of pharmaceutical products, can be briefly defined as follows:

- Phase I. These are the first trials of a new active ingredient or new formulations in humans, often carried out in healthy volunteers. Their purpose is to make a preliminary evaluation of safety, and an initial pharmacokinetic/pharmacodynamic profile of the active ingredient.
- Phase II. The purpose of these therapeutic pilot studies is to determine activity and to assess the short-term safety of the active ingredient in patients suffering from a disease or condition for which it 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 is also concerned with the determination of appropriate dose ranges/regimens and (if possible) the clarification of dose-response relationships in order to provide an optimal background for the design of extensive therapeutic trials.
- Phase III: This phase involves trials in large (and possibly varied) patient groups for the purpose of determining the short- and long-term safety-efficacy balance of formulation(s) of the active ingredient, and assessing 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). The trials should preferably be randomized double-blind but other designs may be acceptable for example,. long-term safety studies. In general, the conditions under which the trials are conducted should be as close as possible to the normal conditions of use.

- Phase IV. In this phase, studies are performed after the pharmaceutical product has been marketed. They are based on the product characteristics on which the marketing authorization was granted and normally take the form of post-marketing surveillance and assessment of therapeutic value or treatment strategies. Although methods may differ, the same scientific and ethical standards should apply to Phase IV studies as are 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, and so on, are normally regarded as trials of new pharmaceutical products.

expiry date. The date placed on the container/label of an investigational medicinal product designating the time during which the investigational medicinal product is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

investigational product. Any pharmaceutical product including a new product, existing product for a new indication, reference product or placebo being tested or used as a reference in a clinical trial.

investigator. The person responsible for the trial and for protecting 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, and responsible to, the sponsor for monitoring and reporting the progress of the trial and for the verification of data.

order. An instruction to process, package and/or ship a certain number of units of an investigational product.

pharmaceutical product. For the purpose of this document, this term is defined in the same way as in the WHO guidelines on GCP *(4),* i.e. as any substance or combination of substances which has a therapeutic, prophylactic or diagnostic purpose, or is intended to modify physiological functions, and is presented in a dosage form suitable for administration to humans.

product specification file(s). The Product specification file brings together and contains all of the essential reference documents to ensure that investigational medicinal products are manufactured according to good manufacturing practice for investigational medicinal products and the clinical trial authorisation. It should be continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions.

protocol. A document which gives 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. It should be dated and signed by the investigator/institution involved and the sponsor, and can, in addition, function as a contract.

reference sample. A sample of a batch of starting material, packaging material, product contained in its primary packaging or finished product which is stored for the purpose of being analysed, should the need arise.

retention sample. A sample of a packaged unit from a batch of finished product for each packaging run/trial period. It is stored for identification purposes: for example, presentation, packaging, labelling, leaflet, batch number and expiry date, should the need arise.

shipping/dispatch. The assembly, packing for shipment and sending of ordered medicinal products for clinical trials.

sponsor. An individual, company, institution or 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 also then assumes the role of the sponsor.

4. Quality management

4.1. There should be a comprehensively designed, clearly defined, documented and correctly implemented quality management system in place. Senior management should assume responsibility for this as well as the quality of the investigational product.

4.2. All parts of the quality system should be adequately resourced and maintained.

4.3. The quality system should incorporate GMP which would be applied appropriately to the stages of the development, including the technology transfer and the interface (e.g. shipment, storage, labelling) between the manufacture and the trial site.

4.4. The quality management system should ensure that:

- products are designed and developed in accordance with the requirements of this document and other associated guidelines such as good laboratory practice (GLP) *(3)*, good clinical practice (GCP) *(4)*, good manufacturing practices (GMP) *(5, 6)* and good storage and distribution practices (GSDP) *(7)*, where appropriate;
- responsibilities are clearly defined in job descriptions;
- operations are clearly described in a written form;
- arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
- all necessary controls on starting materials, intermediate products, bulk products and other in-process controls should be in place;
- maintenance, calibrations and validations are carried out where necessary;
- the finished product is correctly processed and checked according to the defined procedures;
- changes are appropriately managed;
- deviations are investigated and recorded with an appropriate level of root cause analysis done and appropriate corrective actions and/or preventive actions (CAPAs) identified and taken; and
- investigational products are stored, distributed and subsequently handled in accordance with relevant good practices guidelines.

5. Quality risk management

5.1. There should be a system for quality risk management *(8).*

5.2. The system for quality risk management should cover a systematic process for the assessment, control, communication and review of risks to the quality of the product and, ultimately, to the protection of the trial subject and patient.

5.3. The quality risk management system should ensure that:

- the evaluation of the risk is based on scientific knowledge and experience with the process and product;
- procedures and records for quality risk management are retained; and
- the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

5.4. Quality risk management should be applied both prospectively and retrospectively, as appropriate.

6. Personnel

6.1. There should be a sufficient number of appropriately qualified personnel available to carry out all the tasks for which the manufacturer of investigational products is responsible.

6.2. Individual responsibilities should be clearly defined, recorded as written descriptions and understood by the persons concerned.

6.3. A designated person, with a broad knowledge of product development and clinical trial processes should ensure that there are systems in place that meet the requirements of this guideline and other relevant GxP guidelines.

6.4. Personnel involved in the development, production and control of investigational products should have appropriate qualifications. They should be trained in relevant GxP and the

requirements specific to investigational products. Records should be maintained.

6.5. Persons responsible for production and quality should be clearly identified and independent, one from the other where applicable.

6.6. A responsible person should be designated for the release of batches.

6.7. Appropriate protective garments should be worn, based on operations and risk.

6.8. Smoking, eating, drinking, chewing and keeping plants, food, drink, smoking material and personal medicines should not be permitted in any area where they might adversely influence product quality.

6.9. Visitors and untrained persons should only be allowed into production and quality control areas as a rare exception and should then be instructed and closely supervised at all times.

7. Documentation

7.1. Good documentation is an essential part of a quality management system. Documents should be appropriately designed, prepared, reviewed and distributed. They should also be appropriate for their intended use.

7.2. Documents should be approved, signed and dated by the appropriate responsible persons. No authorized document should be changed without the prior authorization and approval.

Specifications

7.3. Specifications with limits for impurities where applicable should be available; for example, raw materials, starting materials, placebo, intermediate, bulk and finished products. There should be specifications for primary packaging materials.

7.4. In developing specifications, attention should be paid to the characteristics which affect the efficacy and safety of products, namely:

- the assay of the therapeutic or unitary dose (content uniformity can be used for quantitation of drug product assay or unitary dose);
- the release of active ingredients from the dosage form: dissolution time, etc.;
- the package size should be suitable for the requirements of the trial, where applicable;
- the estimated stability, if necessary, under accelerated conditions; and
- the preliminary storage conditions and the shelf life of the product.

7.5. As a result of new experience in the development of an investigational product, specifications may be changed by following a documented procedure. Changes should be authorized by a responsible person. Each new version should take into account the latest data and information, current technology, regulatory and pharmacopoeia requirements. There should be traceability of the previous version(s). The reasons for changes should be recorded. The impact of the change on any on-going clinical trials, on product quality, stability, bio-availability, and bio equivalence (where applicable) should be considered based on risk.

Order

7.6. An order should be available for the request of a certain number of units for processing, packaging, storage and their shipping.

7.7. The order should be given by or on behalf of the sponsor to the manufacturer of an investigational product.

7.8. The order should be in writing (e.g. by paper or electronic means, or a combination thereof), be authorized and contain sufficient detail including reference to the approved product specification file (see below) and the relevant clinical trial protocol, as appropriate.

7.9. Where commercially available products are obtained to be used as reference products, such as for use in bio-equivalence studies, the relevant documentation, such as a purchase order, an invoice, storage and transport records, should be maintained and available for inspection.

Product specification file(s)

7.10. A product specification file (or files) should contain, or refer to files containing all the information necessary to prepare detailed written instructions on processing, packaging, quality control testing, batch release, storage conditions and/or shipping.

7.11. The information should form the basis for assessment of the suitability for certification and release of a particular batch by the designated responsible person. It should include or refer to the following documents:

- specifications for starting materials, packaging materials, intermediate and finished product;
- analytical procedures for starting materials, packaging materials, intermediate and finished product;
- manufacturing methods;
- in-process testing and methods;
- approved label;
- relevant clinical trial protocols;
- randomization codes, as appropriate;
- relevant technical agreements, as appropriate;
- stability data; and
- storage and distribution conditions.

Note: The contents will vary depending on the product and stage of development. Where different manufacturing steps are carried out at different locations, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations.

Manufacturing formulae and processing instructions

7.12. Every manufacturing operation or supply should have clear written instructions for personnel, based on the relevant product specification file and trial details, and written records to enable the details of activities to be reconstructed .

7.13. As a result of new experience in the development of an investigational product, manufacturing

formulae and processing instructions may be changed by following a documented procedure. Each new version should take into account the latest data and information, current technology, regulatory and other requirements. There should be traceability to previous versions. The reasons for changes should be recorded. The impact of the change on any on-going clinical trial, product quality, stability, bio-availability and bio equivalence (where applicable) should be considered based on risk. Changes should be authorized by a responsible person.

7.14. Batch processing and packaging records as well as product specification files should be retained for at least five years after the termination or discontinuance of the clinical trial, or after the registration of the investigational product.

7.15. Where the data are intended for inclusion in an application for product registration (marketing authorization) purposes, the records should be maintained for 25 years from authorization or until the end of the life cycle of the product, whichever is shorter.

Packaging instructions

7.16. The theoretical number of units to be packaged should be specified before the start of the packaging operation. This should include the number of units necessary for carrying out quality controls and the number of samples from each batch used in the clinical trial to be kept as retention samples. Reconciliation should be carried out at defined intervals, where required, and at the end of the packaging and labelling process.

7.17. Investigational products should normally be packed individually for each subject included in the clinical trial.

Labelling instructions

7.18. Investigational products should be labelled in accordance with relevant legislation or best practices. Examples of information that the label should include:

- the name, address and telephone number of the sponsor, contract research organization or investigator;
- the statement: "For clinical research use only" or similar wording;

- a reference number indicative of the trial, site, investigator and sponsor, if not given elsewhere;
- a batch or code number;
- the trial subject, patient identification number and /or a treatment code;
- a reference to the directions or instructions for use;
- information on storage conditions;
- an expiry date, use-by date or re-test date (month and year) or similar where appropriate;
- a dosage form and route of administration;
- whether for single or multiple use;
- the quantity of dosage units and, in the case of open trials, the name/identifier and strength/potency; and
- the statement: “Keep out of reach of children”.

7.19. Additional information may be displayed in accordance with the order (e.g. treatment period, standard warnings).

7.20. When necessary for blinding purposes, the batch number may be provided separately (*see also "Blinding operations"*).

7.21. A copy or electronic record of each type of label should be kept in the batch packaging record.

7.22. The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not appear on the label where the subject has been given a leaflet or card which provides these details and who has been instructed to keep this in their possession at all times.

7.23. Particulars should appear in the official language(s) of the country in which the investigational medicinal product is to be used. This may be provided electronically.

7.24. Where all the required information cannot be displayed on primary packaging, secondary packaging should be provided bearing a label with those particulars. The primary packaging should nevertheless contain information such as the name of sponsor, contract research

organization or investigator; route of administration; batch and/or code number; trial reference code and the trial subject identification number or treatment code. Where required such as in open label trials, the product name and strength of the product should be displayed.

7.25. Symbols or pictograms may also be used or included to clarify certain information. Warnings and/or handling instructions may be displayed.

7.26. If it becomes necessary to change the use-by date, an additional label should be affixed to the investigational medicinal product. This additional label should state the new use-by date and repeat the batch number. The original batch number should remain visible. This labelling activity should be performed in accordance with GMP principles, standard operating procedures and should be checked by a second person. This additional labelling should be recorded in both the trial documentation and in the batch records.

Batch manufacturing, packaging and testing records

7.27. Processing, packaging and testing records should be kept in sufficient detail for the sequence of operations to be accurately traced.

Coding (or randomization) systems

7.28. Procedures should be established for the generation, security, distribution, handling and retention of any randomization code used in packaging investigational products and code-break mechanisms. The appropriate records should be maintained.

7.29. The coding system must permit the determination of the identity of the actual treatment product received by individual subjects, without delay, in an emergency situation.

8. Premises

8.1. Premises, where investigational products are manufactured, should be located, designed, constructed and maintained to suit the operations to be carried out.

8.2. The layout and design of premises should aim to minimize the risk of errors and mix-ups and permit effective cleaning and maintenance in order to avoid contamination, cross-contamination and, in general, any adverse effect on the quality of the products.

8.3. Attention should be paid to line clearance in order to avoid mix-ups.

8.4. Validated or verified cleaning procedures, as appropriate, should be followed in order to prevent cross-contamination. Since the characteristics and toxicity of some investigational materials may not be fully known, cleaning is of particular importance to avoid cross-contamination. The visual inspection after cleaning, sampling and test procedures should be appropriate and the acceptance limits applied should be scientifically justifiable.

8.5. Where identified through risk assessment, campaign production should be considered. In other cases based on risk, dedicated and self-contained facilities should be used.

9. Equipment and utilities

9.1. Equipment and utilities should be selected, located, constructed and maintained to suit the operations to be carried out.

9.2. The layout, design, installation and use of equipment and utilities should aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, a build-up of dust or dirt and, in general, any adverse effect on the quality of products.

9.3. Computerized systems should be validated. The extent of validation should be based on risk assessment *(8).*

10. Materials

Starting materials

10.1. The consistency of the production of investigational products 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.

10.2. Existing compendial standards, when available, should be used.

10.3. Specifications for active ingredients and excipients should be as comprehensive as possible, given the current state of knowledge.

10.4. Specifications for both active ingredients and excipients should be reassessed and updated when required.

10.5. In addition to the specifications, detailed information on the active ingredients, excipients and packaging materials should be available. This includes materials from animal origin.

Chemical and biological reference standards for analytical purposes

10.6. Reference standards (WHO or national standards) should be used, if available. Otherwise, the reference substance(s) for the active ingredient(s) should be prepared, tested and authorized for use as reference material(s) by the producer of the investigational pharmaceutical product, or by the producer of the active ingredient(s) used in the manufacture of that product *(9)*.

Principles applicable to reference products for clinical trials

10.7. In a study where an investigational product is being compared to a marketed product, the integrity and quality of the reference (final dosage form, packaging materials, storage conditions, etc.) should be ensured.

10.8. If significant changes are to be made in the product, data should be available (e.g. on

stability, comparative dissolution) that demonstrate that these changes do not influence the original quality characteristics of the product.

11. Production

11.1. Products intended for use in clinical trials should be manufactured in accordance with the requirements of this guideline, and where required by national legislation, in licensed facilities. Manufacturing operations should be controlled as appropriate to the phase of development and scale of manufacture.

11.2. Facilities, as listed below, should be subject to all GMP requirements for pharmaceutical products;

- a large-scale production line assembled to manufacture materials in larger batches (e.g. for late Phase III trials and first commercial batches);
- sterile product manufacturing; and
- the normal production line used for commercial batches and sometimes for the production of investigational products if the number of, for example, ordered ampoules, tablets or other dosage forms, is large enough.

11.3. Where activities are outsourced to contract facilities and the product(s) to be manufactured or controlled are intended for use in clinical trials, the contract must then clearly state, inter alia, the responsibilities of each party, compliance with this guideline and WHO GMP *(5).* Close cooperation between the contracting parties is essential.

Manufacturing operations

11.4. As process validation may not always be complete during the development phase of products, provisional quality attributes, process parameters and in-process controls should be identified, based on risk management principles and experience with the products or analogous products.

11.5. The necessary processing instructions should be identified and may be adapted based on

the experience gained in production.

11.6. Where processes such as mixing have not been validated, additional quality control testing may be necessary.

11.7. For sterile investigational products, the sterility assurance should be no less than for commercial products (*see GMP for sterile products (10)*).

Packaging and labelling

11.8. The packaging and labelling of investigational products are likely to be more complex and more liable to errors (which are also harder to detect) when "blinded" labels are used than for commercial products. Supervisory procedures such as label reconciliation, line clearance, and other controls, including independent checks by quality unit personnel, should be intensified accordingly.

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

Blinding operations

11.10. In the preparation of "blinded" products, the blind should be maintained until it is required to allow for the identification of the “blinded” product. The label expiry date should be assigned to ensure that the ‘blind’ is not broken.

11.11. A coding system should be introduced to permit the proper identification of "blinded" products. The code, together with the randomization list, must permit the proper identification of the product, including any necessary traceability to the codes and batch number of the product before the blinding operation.

11.12. Controls should be applied to verify the similarity in appearance and other physical characteristics such as the odour of "blinded" investigational products. Maintenance of

blinding during the study should be ensured and verification of effectiveness of blinding should be performed and recorded.

12. Quality unit (including quality control)

12.1. Quality control should cover, for example, the sampling and testing of materials and products. The analytical procedures should be suitable for their intended purpose, ensuring that materials and products are not released for use or supply until their quality has been judged to be compliant with the specifications.

12.2. Each batch of product should be tested in accordance with the specifications included in the Product Specification File and should meet its acceptance criteria.

12.3. Bulk product release should cover all relevant factors including production conditions, the results of in-process testing, a review of manufacturing documentation and compliance with the Product Specification File and the order. Finished product release should cover, in addition to the bulk product assessment, all relevant factors including packaging conditions, the results of in-process testing, a review of packaging documentation and compliance with the Product Specification File and the order.

12.4. Reference and retention (control) samples of each batch of product should be retained.

12.5. Samples should be retained in the primary container used for the study or in a suitable bulk container for at least two years after the termination or completion of the clinical trial.

12.6. Retention samples should be kept until the clinical report has been submitted to the regulatory authorities or at least two years after the termination or completion of the relevant clinical trial, whichever is longest. This is in order to enable the confirmation of product identity in the event of, and as part of an investigation into, inconsistent trial results.

12.7. The storage location of reference and retention samples should be defined in a technical agreement between the sponsor and manufacturer(s) and should allow for timely access by

the competent authorities.

12.8. The reference sample should be of sufficient size to permit the carrying out on, at least, two occasions of the full analytical controls on the batch in accordance with the Investigational Product dossier submitted for authorization in order to conduct the clinical trial.

12.9. Where data and information are stored as electronic records, such systems should comply with the requirements of *WHO guidelines for computerized systems (8)*.

12.10. The release of a batch of an investigational product should only occur after the designated responsible person and sponsor, as required, have certified that the product meets the relevant requirements. These requirements include the assessment of, as appropriate:

- batch records, including control reports, in-process test reports, changes, deviations and release reports demonstrating compliance with the product specification file, the order, and randomization code;
- production conditions;
- the qualification status of facilities, validation status of processes and methods, as appropriate;
- the examination of finished packs;
- where relevant, the results of any analyses or tests performed after importation;
- stability reports;
- the source and verification of conditions of storage and shipment;
- audit reports concerning the quality system of the manufacturer, where applicable;
- documents certifying that the manufacturer is authorized to manufacture investigational medicinal products or comparators for export by the appropriate authorities in the country of export; and
- where relevant, regulatory requirements for marketing authorization, GMP standards applicable and any official verification of GMP compliance.

Note: The relevance of the above elements is affected by the country of origin of the product, the manufacturer and the marketed status of the product.

13. Qualification and validation

13.1. The extent of qualification and validation may be different to that necessary for routine commercial production operations.

13.2. The scope of qualification and validation required should be determined based on risk assessment.

13.3. For sterile products, there should be no reduction in the degree of validation of sterilizing equipment required. Validation of aseptic processes presents special problems when the batch size is small due to the low number of units filled for a validation exercise. Filling and sealing, which is often done by hand, can compromise the maintenance of sterility. Enhanced attention should be given to operator training and the qualification of their aseptic technique. Greater attention should also be given to environmental monitoring.

14. Complaints

14.1. There should be a written procedure describing the managing of complaints.

14.2. Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated.

14.3. Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.

14.4. All decisions made and measures taken as a result of a complaint should be recorded.

14.5. The competent authorities should be informed if a manufacturer is considering action following the identification of serious quality problems with a product that may be impacting trial subjects or patients.

14.6. The conclusions of the investigations carried out in response 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, in order to determine the cause, and to take any necessary corrective action.

15. Recalls

15.1. There should be a written procedure describing the managing of a recall of investigational products.

15.2. Recall procedures should be understood by the sponsor, investigator and monitor, in addition to the person(s) responsible for recalls.

15.3. The recall of a product should be documented and inventory records should be kept.

15.4. The recall process should be tested routinely and the results of mock recall should be recorded to demonstrate effectiveness.

16. Returns

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

16.2. Returned investigational products should be clearly identified and stored in a dedicated area in a controlled manner.

16.3. Inventory records of returned products should be kept.

17. Shipping

17.1. The shipping of investigational products should be carried out in accordance with written

procedures laid down in the protocol or shipping order given by the sponsor.

17.2. Shipping studies should be performed to establish acceptable shipping conditions, including temperature and light protection, based on product attributes. If required, a temperature monitor should be situated adjacent to the product, and the product shipment should be packaged appropriately to ensure that it will reach its destination intact and maintain the appropriate temperature profile during that time.

17.3. A shipment is sent to an investigator after following the defined release procedures, for example, quality control, certification and authorization by the sponsor and responsible person, as appropriate. Releases should be recorded.

17.4. The sponsor should ensure that the shipment will be received and acknowledged by the correct addressee as stated in the protocol.

17.5. A detailed inventory of the shipments made by the manufacturer should be maintained and should make particular mention of the addressee's identification.

17.6. The transfer of investigational products from one trial site to another should be done in exceptional cases only. Such transfers should be justifiable, documented and carried out in accordance with a written procedure. Repackaging or relabelling should normally be done by the manufacturer or by authorised personnel at a hospital, health centre or clinic that meet the requirements. Records should be maintained and provide full traceability of the product, batch and activities.

18. Destruction

18.1. The sponsor is responsible for the destruction of unused, partially used or returned investigational products. These should normally not be destroyed by the manufacturer without prior authorization by the sponsor.

18.2. Destruction operations should be carried out in accordance with written procedures and environmental safety requirements.

18.3. The delivered, used and recovered quantities of a product should be recorded, reconciled and verified by or on behalf of the sponsor for each trial site and each trial period. The destruction should be carried out only after any discrepancies have been investigated, satisfactorily explained and the reconciliation has been accepted.

18.4. Destruction operations should be recorded in such a manner that all operations are accounted for. These records should be kept by the sponsor.

18.5. A Certificate of Destruction should be available.

Abbreviations

CAPA	corrective actions and/or preventive actions
GCP	good clinical practices
GLP	good laboratory practices
GMP	good manufacturing practices
GSDP	good storage and distribution practices
GxP	good practices

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Further reading

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