Annex 7

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: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans* (*1*). The fifty-fifth Expert Committee on Specifications for Pharmaceutical Preparations 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 of other related international guidelines.

Contents

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; or to gain further information about the authorized form.

1.2 In some cases, marketed products that have been repackaged 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 and inspection. In such circumstances, risks related to investigational products are increased by lack of adherence to good manufacturing practices (GMP), risk of contamination and cross-contamination, and shortcomings in clinical trial designs, blinding and randomization. In addition, there are 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, packaged, tested, handled, stored and distributed in accordance with an effective quality management system, applicable good practice guidelines and the recommendations contained in this guideline.

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

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

1.9 Investigational products should be manufactured in a manner:

- that is compliant with GMP, as appropriate to the stage of development;
- that ensures that subjects of clinical trials will be protected from poor-quality products resulting from unsatisfactory manufacturing;

- that ensures consistency between and within batches of the investigational product;
- that enables a review of the data derived 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 used in early trials may be very different from the anticipated final formulation (for example, a capsule instead of a tablet), 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 trial dosage form 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 or quality control is transferred from one site to another, the recommendations in the guideline for transfer of technology should be considered (*2*).

1.13 This document should be read in conjunction with other WHO good practice guidelines (*3–11*).

2. Scope

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

3. Glossary

The definitions given below apply to the terms used in this guideline. They have been aligned as much as possible with the terminology in related WHO guidelines and good practices and included in the WHO *Quality Assurance of Medicines Terminology Database: list of terms and related guideline*,[1] but may have different meanings in other contexts.

[1] https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/mqa-terminology-sept-2020.pdf?sfvrsn=48461cfc_5.

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, or identify any adverse reaction to, investigational products; and 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 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 formulation in humans, often carried out in healthy volunteers. Their purpose is to make a preliminary evaluation of safety, and an initial pharmacokinetic and 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 (for example, placebo-controlled) design. This phase is also concerned with the determination of appropriate dose ranges and 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 and efficacy balance of formulations 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 (for example, clinically relevant drug interactions and factors leading to differences in effect, such as age). The trials should preferably be randomized double-blind trials, but other designs may be acceptable, such as 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 pre-marketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations are normally regarded as trials of new pharmaceutical products.

expiry date. The date placed on the container or label of an investigational product designating the time during which the investigational 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 or dentistry.

monitor. A person appointed by the sponsor who is responsible for monitoring and reporting the progress of the trial and for the verification of data.

order. An instruction to process, package and 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 handbook for good clinical research practices* (*4*), that is, as any substance or combination of substances that 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. The product specification file brings together and contains or refers to all of the essential reference documents to ensure that investigational products are manufactured according to good manufacturing practice for investigational products and the clinical trial authorization. It should be continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions.

protocol. A document that 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. The protocol should be dated and signed by the investigator or 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 that is stored for the purpose of being analysed, should the need arise. This may include storage in a suitable bulk container.

retention sample. A sample of a packaged unit from a batch of finished product for each packaging run or 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 packing for shipment and sending of ordered products for clinical trials.

sponsor. An individual, company, institution or organization that takes responsibility for the initiation, management and 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 for 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 the principles of GMP, which should be applied appropriately to each stage of the development, including technology transfer and the interface between the manufacture and the trial sites (for example, with regard to shipment, storage and labelling).

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 practices (*3*), good clinical practices (*4*), GMP (*5*, *6*) and good storage and distribution practices (*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, calibration, qualification and validation are carried out where necessary;
- the finished product is correctly processed and checked according to the defined procedures;
- changes are appropriately managed and documented, and records are maintained;
- deviations are investigated and recorded with an appropriate level of root cause analysis done and appropriate corrective and preventive actions identified and taken;
- investigational products are stored, distributed and subsequently handled in accordance with relevant good practice 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 subjects and patients.

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;
- 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 good practice guidelines.

6.4 Personnel involved in the development, production and control of investigational products should have appropriate qualifications. They should be trained in relevant good practices and the requirements specific to investigational products. All personnel, prior to and during employment, as appropriate, should undergo health examinations. Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials, in-process materials or products until the condition is no longer judged to be a risk. Records should be maintained. No cosmetics or jewellery should be worn.

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

6.6 A person should be designated to be responsible 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 normally not be allowed into production and quality control areas. When entry is required, it should then be under instruction and close supervision.

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 (*12*).

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

7.1 Specifications

7.3 Specifications with limits for impurities and degradation products, where applicable, should be available (for example, for raw materials, starting materials, placebos, and intermediate, bulk and finished products). There should be specifications for packaging materials.

7.4 In developing specifications, attention should be paid to the characteristics that affect the efficacy and safety of products, such as:

- the sterility, potency, assay and other quality attributes of the product (content uniformity can be used for quantitation of drug product assay or unitary dose, where appropriate);
- the release of active ingredients from the dosage form (for example, dissolution profile);
- the suitability of the package size for the requirements of the trial, where applicable;
- the stability of the product, including expected stability where data have been obtained from accelerated conditions, if needed;
- the preliminary storage conditions;
- 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, and regulatory and pharmacopoeial requirements. There should be traceability of the previous version or versions. The reasons for changes should be recorded. The impact of the change on any ongoing clinical trials, product quality, stability, bioavailability and bioequivalence (where applicable) should be considered, based on risk.

7.2 Order

7.6 An order should be available for the request of a certain number of units for processing, packaging, storage and 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 (for example, 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 (for example, for use in bioequivalence studies), the relevant documentation, such as a purchase order, an invoice, and storage and transport records, should be maintained and available for inspection.

7.3 Product specification file

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 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 (*13*):

- specifications and analytical methods for starting materials, packaging materials, intermediate product, bulk product and finished product;
- manufacturing methods;
- in-process testing and methods;
- approved label copy;
- relevant clinical trial authorizations and amendments thereof, clinical trial protocol and randomization codes, as appropriate;
- relevant technical agreements with contract givers and acceptors, as appropriate;
- stability plan and reports;
- storage and distribution conditions;
- details of the supply chain, including manufacturing, packaging, labelling and testing sites for the investigational products, preferably in the format of a comprehensive diagram.

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.

7.4 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, and 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 ongoing clinical trial, product quality, stability, bioavailability and bioequivalence (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 a defined period of time.

7.15 Where the data are intended for inclusion in an application for product registration (marketing authorization) purposes, the records should be maintained for 30 years from authorization or until the end of the life cycle of the product, whichever is shorter.

7.5 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 of units packed and primary labels 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.

7.6 Labelling instructions

7.18 Labelling should be performed by a site authorized by the sponsor, under the supervision of an appropriately qualified individual (for example, a health care professional or clinical trial monitor) and checked by a second person, in accordance with GMP principles and standard operating procedures. This additional labelling should be recorded in both the trial documentation and in the batch records.

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

- 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 a treatment code;
- a reference to the directions or instructions for use;
- information on storage conditions;
- an expiry date, use-by date or retest date (month and year) or similar, where appropriate;
- a dosage form and route of administration;
- whether for single or multiple use, where applicable;
- the quantity of dosage units and, in the case of open trials, the name or identifier and the strength or potency.

7.20 Additional information may be displayed in accordance with the order (such as treatment period, standard warnings).

7.21 When necessary for blinding purposes, the batch number may be provided separately (see also section 11.3 below).

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

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

7.24 Particulars should appear in the official language or languages of the country in which the investigational product is to be used. This may be provided electronically.

7.25 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 or code number; trial reference code; and the trial subject identification number or treatment code. Where

required, for example in open label trials, the product name and strength of the product should be displayed.

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

7.27 If it becomes necessary to change the use-by date, an additional label should be affixed to the investigational 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 and standard operating procedures and should be checked by a second person. This additional labelling should be recorded both in the trial documentation and in the batch records.

7.7 Batch manufacturing, packaging and testing records

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

7.8 Coding (or randomization) systems

7.29 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.

7.30 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. Where possible, the use of unidirectional flows for personnel, materials, products and waste should be established and maintained.

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

8.4 Validated or verified cleaning and sanitization 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. Cleaning and sanitizing agents should not become a source of contamination.

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 considered.

8.6 Ingress of contaminants should be avoided and controls should be implemented to prevent contamination of the environment, as required.

9. Equipment and utilities

9.1 Equipment and utilities should be selected, located, constructed, qualified (as appropriate) 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, and should support reproducibility and robustness of the process.

9.3 Computerized systems used to acquire, process and store GMP data should be validated. The extent of validation should be based on risk assessment (*8*).

10. Materials

10.1 Starting and packaging 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 of animal origin.

10.2 Chemical and biological reference standards for analytical purposes

10.6 Reference standards (WHO or national standards) should be used, if available. Otherwise, the reference substances for the active ingredients should be prepared, tested and authorized for use as reference materials by the producer of the investigational product, or by the producer of the active ingredients used in the manufacture of that product (*10*).

10.3 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 (such as final dosage form, packaging materials or storage conditions) should be ensured.

10.8 If significant changes are to be made in the product, data should be available (for example, on stability and comparative dissolution) that demonstrate that those 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 Where activities are outsourced to contract facilities and the products to be manufactured or controlled are intended for use in clinical trials, the contract must then clearly state the responsibilities of each party in compliance with this guideline and WHO GMP (*5*). Close cooperation between the contracting parties is essential.

11.1 Manufacturing operations

11.3 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.

11.4 The necessary processing instructions should be identified and may be adapted, based on the experience gained in production.

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

11.6 For sterile investigational products, the sterility assurance should be no less than for commercial products (*11*).

11.2 Packaging and labelling

11.7 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.

11.8 The packaging must ensure that the investigational product remains in good condition during transport and storage, within specified limits of temperature, relative humidity and light, as appropriate. Any opening of, or tampering with, the outer packaging during transport should be readily visible.

11.3 Blinding operations

11.9 In the preparation of blinded products, the blind should be maintained until it is required to enable its identification.

11.10 A coding system should be introduced to permit the identification of blinded products, also in the case of an emergency. The code, together with the randomization list, must enable the identification of the product, including any necessary traceability to the codes and batch number of the product before the blinding operation.

11.11 Controls should be applied to verify the similarity in appearance and other physical characteristics, such as the odour and colour of blinded investigational products. Maintenance of blinding during the study should

be ensured and verification of the 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 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.

12.6 The storage location of reference and retention samples should be defined in a technical agreement between the sponsor and manufacturer and should enable timely access by the competent authorities.

12.7 The retained sample should be of sufficient size to perform the full analytical controls at least twice on the batch in accordance with the investigational product dossier submitted for authorization in order to conduct the clinical trial.

12.8 Where data and information are stored as electronic records, such systems should comply with the requirements of WHO guidelines for computerized systems (*9*).

12.9 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 and the 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 products or comparators for export by the appropriate authorities in the country of export;
- 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 scope of qualification and validation required should be determined based on risk assessment.

13.2 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. Sterility testing methods should be validated.

13.3 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, and to determine the cause and 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 or persons 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 There should be a written procedure describing the managing of returns of investigational products. The returns should be under agreed conditions, as defined by the sponsor.

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 Acceptable shipping conditions, including temperature and light protection, based on product attributes, phase-appropriate stability data and risk assessment, should be observed. If required, a calibrated temperature monitor should be kept 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 authorized personnel at a hospital, health centre or clinic that meets 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 and 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 containing the necessary detail to enable traceability of the product, batch and related information.

References

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Further reading

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