第１３条　回収処理

（質問４３）
第２号「回収した治験薬を区分して一定期間保管した後、適切に処理すること。」でいう一定期間について説明されたい。（回収の記録と同様に、承認を受ける日までの保存が必要となるのか。）

回収した治験薬が治験の成績に影響を及ぼさないことが明らかな場合を除き、回収処理記録と同一の期間、保存すること。

第１６条　委託製造

（質問４４）
治験原薬製造業者は、自らが治験依頼者とならない場合には、受託製造者に該当すると考えてよいか。

よい。
なお、治験原薬製造業者が、自らが製造する治験原薬について他社に製剤化させたうえで治験の依頼をする場合には、当該原薬製造業者は治験依頼者となり、また製剤化工程については本条でいう委託製造となる。

治験薬の製造施設の構造設備基準について

全般的事項

（質問１）
医薬品製造業の許可施設で治験薬を製造しても差し支えないとのことだが、この場合、医薬品の製造設備を用いて治験薬を製造してもよいか。

差し支えない。

（質問２）
治験薬を、他社の製造施設を借りて自ら製造することは認められるか。

認められる。ただし、製造期間中の製造施設の管理は治験依頼者の責任で実施すること。
なお、薬事法の許可を受けている医薬品製造所を他社に貸すことを認めるものではない。

（質問３）
放射性治験薬について、薬局等構造設備規則第９条に相当する基準がないのはなぜか。

「放射性同位元素等による放射線障害の防止に関する法律」による規制が適用されるため、治験薬ＧＭＰでは規定していない。

（質問４）
薬局等構造設備規則第５条（製造管理及び品質管理の基準を適用しない医薬品の製造所の構造設備）に相当する規定がないのはなぜか。

治験薬ＧＭＰが適用となるかどうかは、ＧＣＰ省令第１７条が適用されるかどうかにより判断されるものであり、当該治験薬が承認された場合に医薬品ＧＭＰが適用となるかどうかによるものではないため、薬局等構造設備規則第５条に相当する規定を設ける必要はないものである。

第１条　治験原薬以外の治験薬の製造施設の構造設備

（質問５）
第３号リ「飛散しやすく、微量で過敏症反応を示す治験薬又は交叉汚染することにより他の治験薬に重大な影響を及ぼすおそれのある治験薬」とは、具体的にはどのようなものをいうのか。

前臨床試験の成績から判断すること。
なお、ペニシリン系抗生物質の治験薬は、「飛散しやすく、微量で過敏症反応を示す治験薬」の一例である。

（質問６）
第６号「他の試験検査設備又は試験検査機関を利用して自己の責任において当該試験検査を行う場合」とあるが、「自己の責任において試験検査を行う」とはどのような意味か。

自社の職員に外部試験検査機関等の設備を利用させ試験検査を行わせること、又は外部試験検査機関等へ試験検査を依頼し、この試験検査成績について自己の責任で判定をすることをいう。

第５条　治験生物学的製剤の製造施設の構造設備

（質問７）
第５号に掲げる設備については、治験生物学的製剤の種類により製造に必要のない設備は有していなくてもよいか。

よい。

1. Introductory note

The legal status of investigational pharmaceutical products for human use varies from country to country; in some of them (e.g. Germany, the United States and others), these products are manufactured and inspected like "normal" licensed pharmaceutical products. In most other countries, however, they are not covered by legal and regulatory provisions in the areas of good manufacturing practice (GMP) inspection, etc.

However, the EC guide on GMP (*1*) recommends that the principles of GMP should be applied, as appropriate, to the preparation of these products, and the WHO guide on GMP, according to the statement in the general considerations, is applicable to "the preparation of clinical trials supplies" (2, page 18).

2. General considerations

The present guidelines supplement both the WHO guide on GMP and the guidelines on good clinical practice (GCP) for trials on pharmaceutical products (*3*). The application of the principles of GMP to the preparation of investigational products is necessary for several reasons:

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[1] Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.* Geneva, World Health Organization, 1996, Annex 7 (WHO Technical Report Series, No. 863).

- To assure consistency between and within batches of the investigational product and thus assure the reliability of clinical trials.
- To assure consistency between the investigational product and the future commercial product and therefore the 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 starting materials and components of inadequate quality.
- To document all changes in the manufacturing process.

In this context, the selection of an appropriate dosage for clinical trials is important. While it is accepted that in 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 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 significant differences between the clinical and commercial dosage forms, 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. Final manufacturing methods must be revalidated following changes in processes, scaling-up, transfer to other manufacturing sites, etc.

This Annex specifically addresses those practices that may be different for investigational products, which are usually not manufactured in accordance with a set routine, and which may possibly be incompletely characterized during the initial stages of clinical development.

3. Glossary

The definitions given below apply to the terms used in these guidelines. 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, e.g. 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, etc., are normally regarded as trials of new pharmaceutical products.

investigational product

Any pharmaceutical product (new product or 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 practise 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 Annex, this term is defined in the same way as in the WHO guidelines on GCP (*3*), 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)
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 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.

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 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 guide on GMP (*2*, pages 25–26).

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

5. Validation[1]

Some of the production processes for investigational products that have not received 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 the manufacturing operations requires a highly effective quality assurance system.

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, since the number of units filled may not be adequate for a validation exercise. Filling and sealing, which is often done by hand, can compromise the maintenance of sterility. Greater attention should therefore be given to environmental monitoring.

6. Complaints

The conclusions of any investigation 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, to determine the cause, and to take 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 the guide on GMP (*2*, pages 28–29).

8. Personnel

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

9. Premises and equipment

During the manufacture of investigational products, different products may be handled in the same premises and at the same time, and this reinforces the need

[1] For additional advice on validation, see *Validation of manufacturing processes*, pp. 53–71.

to eliminate all risks of contamination, including cross-contamination. Special attention should be paid to line clearance in order to avoid mix-ups. Validated cleaning procedures should be followed to prevent cross-contamination.

For the production of the particular products referred to in section 11.20 of the guide on GMP (2, page 38), 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 excipients in various cleaning agents.

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 so as to make it possible to recognize and, as necessary, allow for any variation in production.

Chemical and biological reference standards for analytical purposes

Reference standards from reputable sources (WHO or national standards) should be used, if available; otherwise the reference substance(s) for the active ingredient(s) should be prepared, tested and released 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.

Principles applicable to reference products for clinical trials

In studies in which an investigational product is compared with a marketed product, steps should be taken 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 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. 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 include a reference 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 2 years after the 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), precise enough to avoid any ambiguity and formally authorized, and refer to the approved product specification file (see below).

Product specification file(s)

A product specification file (or files) should contain the 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 has been designated or trained as the authorized person responsible for the release of batches (see reference 2, page 18). It should be continuously updated while at the same time ensuring appropriate traceability to the previous versions.

Specifications

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

- The accuracy of the therapeutic or unitary dose: homogeneity, content uniformity.
- The release of active ingredients from the dosage form: dissolution time, etc.
- The estimated stability, if necessary, under accelerated conditions, the preliminary storage conditions and the shelf-life of the product.[1]

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[1] See *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 1.* Geneva, World Health Organization, 1997:46–61.

In addition, the package size should be suitable for the requirements of the trial.

Specifications may be subject to change as the development of the product progresses. Changes should, however, be made in accordance with 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, and the regulatory and pharmacopoeial requirements.

Master formulae and processing instructions

These 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 made in accordance with a written procedure, authorized by a responsible person and clearly recorded.

It may sometimes not be necessary to produce master formulae 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 be packaged should be specified before the start of the packaging operations. Account should be taken of the number of units necessary for carrying out quality controls and of the number of samples from each batch used in the clinical trial to be kept as a reference for further rechecking and control. A reconciliation should be carried out at the end of the packaging and labelling process.

Labelling instructions

The information presented on 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.[1]
- The storage conditions.
- The expiry date (month/year) or a retest date.

[1] This is not necessarily inserted at the manufacturing facility but may be added at a later stage.

Additional information may be displayed in accordance with the order (e.g. dosing instructions, treatment period, standard warnings). When necessary for blinding purposes, the batch number may be provided separately (see also "Blinding operations" on p. 123). 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. They should contain any relevant remarks which increase existing knowledge of the product, allow improvements in the manufacturing operations, and justify the procedures used.

Coding (or randomization) systems

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

A coding system should be introduced to permit the proper identification of "blinded" products. The code, together with the randomization list, must permit 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 permit determination without delay in an emergency situation of the identity of the actual treatment product received by individual subjects.

12. Production

Products intended for use in clinical trials (late Phase II and Phase III studies) should as far as possible be manufactured at a licensed facility, e.g.:

- A pilot plant, primarily designed and used for process development.
- A small-scale facility (sometimes called a "pharmacy")[1] separate both from the company's pilot plant and from routine production.
- A larger-scale production line assembled to manufacture materials in larger batches, e.g. for late Phase III trials and first commercial batches.
- The normal production line used for licensed commercial batches, and sometimes for the production of investigational pharmaceutical products if the number, e.g. of ordered ampoules, tablets or other dosage forms, is large enough.

The relation between the batch size for investigational pharmaceutical products manufactured in a pilot plant or small-scale facility and the planned full-size

[1] Some manufacturers use the term "pharmacy" to designate other types of premises, e.g. areas where starting materials are dispensed and batches compounded.

batches may vary widely depending on the pilot plant or "pharmacy" batch size demanded and the capacity available in full-size production.

The present guidelines are applicable to licensed facilities of the first and second types. It is easier to assure compliance with GMP in facilities of the second type, since processes are kept constant in the course of production and are not normally changed for the purpose of process development. Facilities of the remaining types should be subject to all GMP rules for pharmaceutical products.

Administratively, the manufacturer has yet another possibility, namely to contract out the preparation of investigational products. Technically, however, the licensed facility will be of one of the above-mentioned types. The contract must then clearly state, inter alia, the use of the pharmaceutical product(s) in clinical trials. Close cooperation between the contracting parties is essential.

Manufacturing operations

Validated procedures may not always be available during the development phase, which makes it difficult to know in advance what are the critical parameters and what in-process controls would help to control these parameters. Provisional production parameters and in-process controls may then 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.

For sterile investigational products, assurance of sterility 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.

Packaging and labelling

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 licensed products. Supervisory 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 of, or tampering with, 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 of the different products being compared.

13. Quality control

As processes may not be standardized or fully validated, end-product testing is more important in ensuring that each batch meets its specification.

Product release is often carried out in two stages, before and after final packaging:[1]

1. Bulk product assessment: this 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.
2. Finished product assessment: this 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.

When necessary, quality control should also be used to verify the similarity in appearance and other physical characteristics, odour, and 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 2 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, and destruction

The shipping, return and destruction of unused products should be carried out in accordance with the written procedures laid down in the protocol. All unused products sent outside the manufacturing plant should, as far as possible, either be returned to the manufacturer or destroyed in accordance with clearly defined instructions.

Shipping

Investigational products should be shipped in accordance with the orders given by the sponsor.

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[1] This practice also exists at certain large companies with regard to licensed products.

A shipment is sent to an investigator only after the following two-step release procedure: (i) the release of the product after quality control ("technical green light"); and (ii) 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 will be received and acknowledged by the correct addressee as stated in the protocol.

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

Returns

Investigational products should be returned under 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 returned medicinal products should be kept. The responsibilities of the investigator and the sponsor are dealt with in greater detail in the WHO guidelines on GCP (*3*).

Destruction

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

Destruction operations should be recorded in such a manner that all operations are documented. The records should be kept by the sponsor.

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

References

1. *Good manufacturing practice for medicinal products in the European Community*. Brussels, Commission of the European Communities, 1992.

2. Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992:14–79 (WHO Technical Report Series, No. 823).

3. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. In: *The use of essential drugs. Model List of Essential Drugs (Eighth List). Sixth report of the WHO Expert Committee*. Geneva, World Health Organization, 1995:97–137 (WHO Technical Report Series, No. 850).

19　臨床試験に使用する原薬

19.1　一般事項

19.10　開発段階における治験用新規原薬生産については、今まで述べた本ガイドラインの管理手法の全てが適切とはいえない。本章では、治験用原薬に特異的なガイドラインを示す。

19.11　臨床試験用に用いる原薬の製造過程で実施する管理は、当該原薬を配合する製剤の開発段階と整合性を持たせること。工程についての知見が蓄積され、製剤の試験が前臨床段階から臨床段階に進むに従い、工程及び試験手順は、変更に備えて、柔軟性を持たせること。開発が臨床試験を目的とする製剤用の製造段階に入った場合、製造業者は、原薬の品質を保証する適切な製造管理手順を用い、適正な設備で製造していることを保証すること。

19.2　品質

19.20　臨床試験に使用する原薬の製造には、適切なＧＭＰの考え方を適用し、また、各ロットの承認を行う体制を備えること。

19.21　臨床試験に使用する原薬の合否判定をするため、製造部門から独立した品質部門を設置すること。

19.22　通常品質部門において実施される試験の一部は、他の部門において実施する場合がある。

19.23　品質評価として、原料、包装材料、中間体及び原薬を試験する体制を有すること。

19.24　工程及び品質の問題について評価を行うこと。

19.25　臨床試験への使用を目的とする原薬の表示は適切に管理し、治験用であることを明記すること。

19.3　装置及び設備

19.30　臨床試験に使用する原薬を生産する小規模設備又は実験室の使用を含め、臨床開発の全過程を通じて、装置を校正し、清掃し、当該装置が使用目的に適合することを保証する手順を設けること。

19.31　設備使用に係る手順は、汚染及び交叉汚染のリスクを最小限にする方法で原材料等が取り扱われていることを保証するものであること。

19.4　原料の管理

19.40　臨床試験に使用する原薬製造用の原料は、試験により評価判定を行い、又は供給者の分析情報を受け、確認試験を行うこと。原料試験が危険と考えられる場合には、供給者の分析情報で十分である。

19.41　場合によっては、原料の適合性の判定は、分析試験だけでなく、むしろ使用前の小規模実験(即ち、使用試験)により行うことがある。

19.5　製造

19.50　臨床試験に使用する原薬の製造は、実験ノート、ロット記録又はその他の適切な方法で記録すること。これらの記録には、使用した原材料等、装置、処理方法及び科学的な観察記録を含めること。

19.51　期待収量は、実製造段階で設定する期待収量より変動が大きく、決定し難い。収量変動の原因調査は要求されない。

19.6　バリデーション

19.60　臨床試験に使用する原薬の製造に係るプロセスバリデーションは、単一の原薬ロットしか製造されない場合又は原薬開発中の工程変更によりロットの再現が困難又は不正確である場合には、通常、不適切である。この開発段階における原薬の品質保証は、管理、校正、及び必要な場合には装置の適格性評価の組み合わせにより行うものである。

19.61　販売用に製造するロットは、当該ロットがパイロットスケール又は小スケールであっても、第12章に従ってプロセスバリデーションを実施すること。

19.7　変更

19.70　開発中においては、知識が蓄積し、製造がスケールアップするに従って、種々の変更が予測される。製造手順、規格又は試験方法に係る全ての変更は適切に記録すること。

19.8　試験室の管理

19.80　臨床試験に使用する原薬のロットを評価するために実施される分析法に対しバリデーションが行われていない場合には、当該分析法は科学的に信頼できるものであること。

19.81　全てのロットの参考品を保管するシステムを有し、申請の承認、中止又は中断後の適切な期間、十分な量の参考品を保管すること。

19.82　第11.6章で規定した使用期限及びリテスト日は、臨床試験に使用する既存の原薬に適用される。新規の原薬については、通常、臨床試験の初期の段階では、第11.6章の規定は適用されない。

19.9　文書化

19.90　臨床試験に使用する原薬の開発及び生産中に得られた情報を文書化し、利用できることを保証する体制を持つこと。

19.91　臨床試験に使用する原薬の出荷判定に用いる分析法の開発及び実施については適切に記録すること。

19.92　製造・管理に係る記録及び文書を保管するためのシステムを有し、申請の承認、中止、又は中断後の適切な期間、当該記録及び文書が保管されることを保証すること。

治験薬GMPについて－ あるべき姿、現状と課題 －

要旨

（あるべき姿）

治験段階の品質管理（治験薬GMP）は治験段階の必要に応じて行うべきである

（現状）

治験薬GMP通知は前期治験に対し過剰な要求をする一方、後期治験に対しては不十分なところがある

（課題）

治験段階に応じた要件の整理をした上で指針を作成する

MD/eINDのための指針は治験薬GMPのAnnexとする（？）

国際調和を考慮すべき

治験薬GMPの改訂は早急に実施すべきである（別の作業班？）

治験薬GMPの一般原則

WHO-GMP／ヒト用治験薬ガイドライン(2.General Considerations

- 開発段階の製品のバッチ内およびバッチ間の一貫性を保証し、治験の信頼性を保証すること
- 開発段階の製品と将来の市販製品との一貫性を保証することにより、市販製品の有効性と安全性に対する治験の適切性を保証すること
- 製造上の過誤（滅菌などの重要工程の省略、汚染及び交叉汚染、混同、誤表示等）、或いは不充分な品質の原料や成分に起因する品質劣化製品から被験者を守ること
- 製造工程における全ての変更を文書化すること

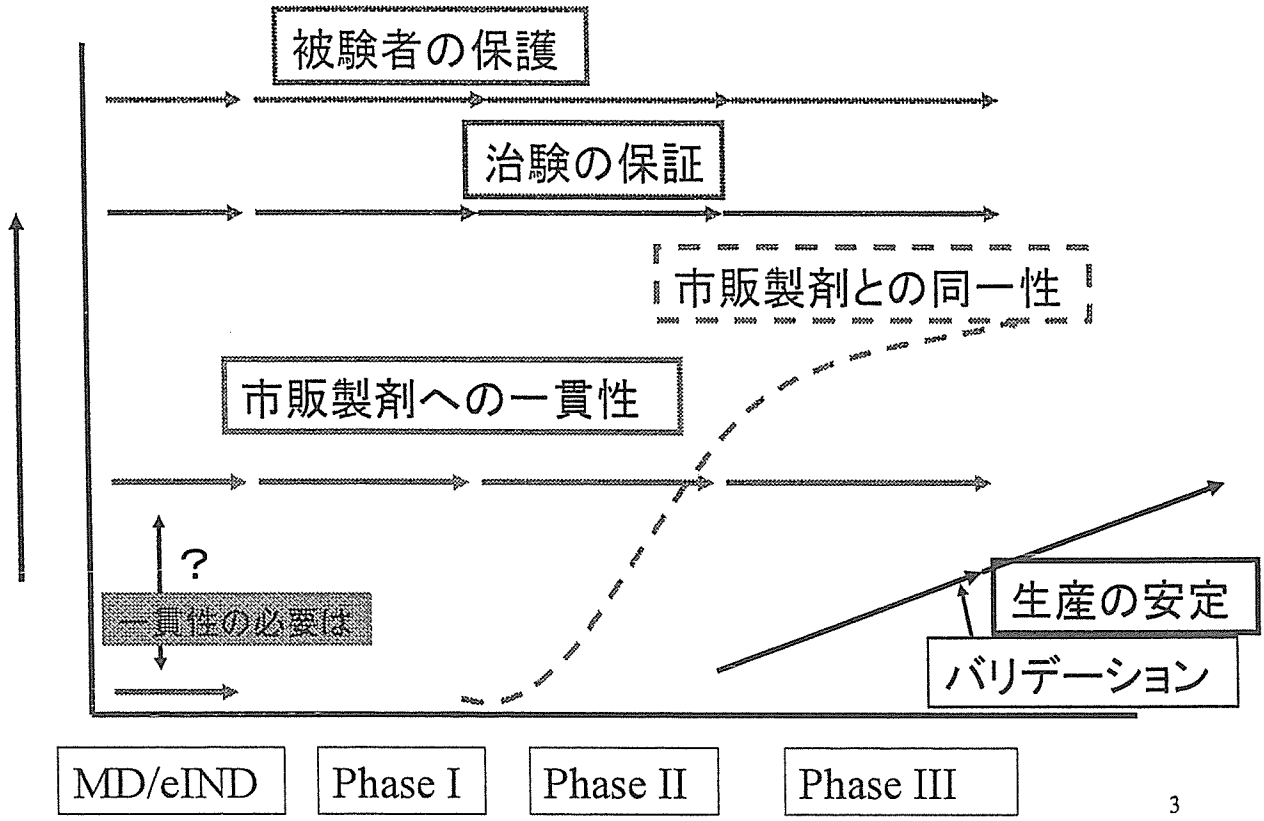
平成9年5月20日付 薬監第70号より

ア 治験薬の品質の均一性を保証することで、臨床試験の信頼性を確保すること

イ 治験薬と市販後製品の同一性を保証することで、製品の有効性と安全性を確保すること

ウ 治験薬の品質を保証することで、不良な治験薬から被験者を保護すること

開発段階に応じた各原則の適用レベル



3

“治験薬GMP”の3極現状

【日本】

治験薬が薬事法上の医薬品に該当しないこと、新GCP基準に謳われたことより、平成9年(1997年)の厚生省薬務局長通知「薬発第480号(治験薬GMP)」として発出、要件化

⇒治験段階すべて同じルール(eg バリデーションを要求)、改正医薬品GMP省令との不整合、国際調和の観点から陳腐化。初期治験には過剰である一方後期には不十分。

⇒改正治験薬GMP(業界案)が提出されている。

【EU】

EU-GMPのAnnex 13として治験薬GMPとしての要件を明記(EU-GMP本文に代替するものではなく、治験薬製造に関する特別な事項を上乗せ補完)

⇒Directive 2001/20/EC (GCP規則)の2004年施行に伴い、治験薬製造であっても製造許可と管理を義務付け

⇒第三国(日本を含む)からの輸入治験薬についてはQualified Personの保証が必要

【米国】

治験薬であっても、原則的に医薬品のcGMPをそのまま適用

⇒2006年1月に、Phase Iのみの治験薬製造であれば21 CFR 210 & 211(cGMPを記した法律)を適用免除としたFederal Registerを発出したが、反対意見も出たため検討中

⇒ Phase I 治験薬製造に対する21 CFR 210 & 211の適用免除の穴埋めとして、「Phase I用cGMPガイダンス(案)」を発表したが、まだファイナル版に至っていない