ならないこととされているが、複数の製造施設（例えば治験用原薬と治験薬（製剤）の製造施設）を自社で有し、基本的な部分の手順の内容が社内で共通化されている場合（例えば、バリデーションの考え方、回収処理の手順等）、当該手順を各々の製造施設で作成するのは合理的でないと思われる。そのような手順については、いずれかの製造施設で手順書等を作成、保管し、他方の製造施設には手順書等の写しを配布して保管することで差し支えないか。

写しを使用することは差し支えないが、必ず治験薬製造施設ごとに手順書等を承認し、その記録を保管すること。

２０．委託製造

（質問５１）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、製剤化工程については本項でいう委託製造にあたる。

２１．治験薬の製造施設の構造設備

（質問５２）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。なお、治験薬は、開発段階によっては、その毒性、薬理作用、感作性等について十分な知見が得られていない場合が想定されるため、他の医薬品への交叉汚染等、治験薬特有の事項に十分留意すること。

（質問５３）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を含め、治験薬ＧＭＰの各項目への遵守については治験依頼者の責任の下、適切に実施できる体制をとるとともに、他の医薬品等への交叉汚染等、治験薬特有の事項に十分留意すること。

その他

（質問５４）第一項に、「マイクロドーズ臨床試験など早期探索的段階を含む臨床試験に使用する治験薬の製造管理及び品質管理の基準」とあるが、早期探索的段階の臨床試験も本基準の適用対象となるか。

本基準の適用対象となる。ただし、マイクロドーズ臨床試験においては、その後の臨床試験に直接つながるものではないことから、通常の臨床開発で用いられる治験薬との一貫性を必ずしも求める必要はない。現実の作業を考慮するならば、使用する薬剤がごく微量であることに対応した製造管理及び品質管理が実施されることとなる。また、ポジトロン核種標識体は放射性半減期が極めて短いがゆえに、^{14}C 標識体や非標識体とは合成の手法や装置が全く異なり、品質保証の裏付け方法も同一の視点では論じられず、本基準を画一的に適用することが困難であることから、例えば、本Q&A における「５．治験薬製造部門及び治験薬品質部門」、「１０．治験薬の品質管理」の質問に

対する回答に示すように、柔軟に運用すべきである。

添付資料２－Ａ　治験薬ＧＭＰに関するＱ＆Ａ（案）
平成１９年１２月２８日パブリックコメント募集，研究班作成英語参考訳

Q&A concerning the GMP for Investigational Products (Draft)

Chapter 1　General Provisions

1. Purpose

(Q1) It is stated "to protect subjects from defective investigational products by ensuring the quality of investigational products." Specifically what can be considered?

The prevention of the occurrence of hazards attributable to manufacturing errors (e.g., mistakes in critical processes such as sterilization, contamination or cross-contamination, mix-up or mislabeling) or hazards caused by deteriorated products attributable to the inadequate quality of raw materials or ingredients that subjects may suffer.

(Q2) The term "consistency" is used. What does it specifically mean?

The term "consistency" used here refers to the insurance of the level of quality at which while there is a scientifically significant difference, common points and differences between the two products and the causal relationship to them are identified.

(Q3) The term "equivalency" is used. What does it specifically mean?

The term "equivalency" used here refers to the insurance of the level of quality at which there is no scientifically significant difference in safety or efficacy between the two products and they can be determined to be almost the same.

2. Scope of Application

(Q4) What kind of person does the sponsor refer to?

The sponsor refers to "the person who sponsors a clinical trial" specified in Article 2, Paragraph 16 of the GCP Ordinance.

The sponsor used in the Standards is not limited to special persons such as the president or a person responsible for the clinical trial notification.

(Q5) Is it acceptable to produce an investigational product at an authorized plant of a drug manufacturer?

Yes, it is acceptable.

A sufficient amount of evidence of an investigational product such as its toxicity, pharmacological actions and sensitization may not be obtained in some development phases; therefore, full attention should be paid to cross-contamination with other drugs, etc. and matters specific to the investigational product.

(Q6) How should investigational drug substances be handled?

As for the handling of drug substances based on the GMP for drugs, investigational drug substances shall be controlled in a stepwise manner from a starting material and intensively managed from the process having a major effect on the quality of the investigational drug substances in accordance with the GMP for

investigational products.

(Q7) Is it allowed to produce an investigational drug substance at more than two manufacturing plants?

Yes, it is allowed. However, the GMP for investigational products is applicable to each manufacturing plant.

(Q8) When a comparator or placebo is purchased from another company, are the Standards applicable to it?

Yes, the Standards are applicable. Article 2 of the Ministerial Ordinance on Good Clinical Practice (Ordinance No. 28 of the Ministry of Health and Welfare (MHW) in 1997; hereinafter referred to as the "GCP Ordinance") specifies that "the 'investigational product' refers to a test product and comparator (limited to those used in clinical trials", and the "'comparator' refers to a drug, medical substance or other substances used as a reference in clinical trials or postmarketing clinical studies for the purpose of comparison with a test product."

(Q9) A clinical trial is planned to be performed in a foreign country, but the investigational product (drug preparation) to be used is to be manufactured in Japan and exported from Japan. In this case, will the GMP certificate be issued in accordance with the GMP for investigational products?

A GMP certificate (letter format) can be issued for countries with which a bilateral arrangement (Memorandum of Understanding) is concluded.

3. Basic Concepts

(Q10) When the Standards are ignored, or major deviations from the Standards are made, is there any penalty?

The Standards specify standard methods and other relevant matters for the methods of manufacturing control and quality control, and buildings and facilities of investigational products used for clinical trials. The Standards do not prevent adaptation of other methods, etc. as long as they are equivalent to or better than those specified therein.

However, when the appropriate methods of manufacturing control and quality control and necessary buildings and facilities are not ensured by ignoring the Standards, and the provisions of Article 17, Paragraph 1 or Article 26-3 of the GCP Ordinance are found to be violated, the condition is handled as a violation to the GCP Ordinance. In such a case, a penalty pursuant to the provision of Article 87 of the Pharmaceutical Affairs Law (hereinafter referred to as "PAL") is applied to the sponsor. In addition, actions that the Minister of Health, Labour and Welfare can take against the sponsor, etc. such as provisions that the Minister of Health, Labour and Welfare can terminate clinical trials and give other necessary instructions are stipulated in each item of Article 80-2 of PAL pursuant to Article 80-2, Paragraph 9 of PAL. Furthermore, the results of the concerned clinical trial are deemed to be a violation of Article 14, Paragraph 3 of PAL; thus, they cannot be used as an approval review document for approval application.

(Q11) It is stated in Section 3.1 that "since the Standards are applied to a period important for drug development, they should be used as part of quality management focusing on product lifecycle." Is it necessary to comply with the ICH Q9 (Quality Risk Management) and ICH Q10 (Pharmaceutical Quality System)?

The ICH Q9 (Quality Risk Management) presents specific examples of principles and procedures for risk management that can be adopted to various aspects of the quality of drugs, and the GMP for investigational products does not necessarily require adherence to it. However, its concepts are important, and the application of ICH Q9 by the sponsor as necessary is likely to consolidate the quality of a future marketing product and its assurance. The starting point should be determined on judgment of a company. For instance, it can be specified at a stage after a phase where the investigational product is targeted as the development candidate, that is a phase where the assurance of consistency between the investigational product and the product after marketing is considered necessary.

If the ICH Q10 (Pharmaceutical Quality System) is agreed upon, a concept almost the same as the above idea may be applied.

(Q12) The phrase "rationales for establishment of the design quality and product quality of the investigational product" is mentioned in Section 3.3. The statement seems to be conscious of the ICH Q8 (Pharmaceutical Development). Is it necessary to comply with the ICH Q8?

The Q8 (Pharmaceutical Development) is intended to present a guide to drafting the "Pharmaceutical Development" section for drug preparations that are defined in the scope of application of CTD Module 3. The GMP for investigational products does not require to always comply with the Q8. Nevertheless, it is important to consider its principles from the perspective of accumulating technical information in new drug development. What is required in this section is not simply the necessity for adherence to the ICH Q8. The section describes how technical information of an investigational product in development phase should be passed on to the future marketing product when processing change control, as well as the importance of how the said information should be controlled.

4. Definitions

(Q13) The term "manufacturing plants for investigational products" is used in Section 4.7. How is it different from the "manufacturing site" used in the GMP for drugs?

In order to make clear the distinction from sites authorized for drug manufacturing pursuant to PAL, the term "manufacturing plant" was used.

(Q14) What factors can be considered for qualification? To what extent should qualification be performed in the development phase?

Qualification is classified into the following four stages according to its status: DQ (Design Qualification), IQ (Installation Qualification), OQ (Operational Qualification) and PQ (Performance Qualification). What type of and to what extent qualification needs to be performed for manufacturing control and quality control of an investigational product should be independently determined based on the quality and the level of data reliability required for the stepwise development phase of the investigational product.

5. Manufacturing Department and Quality Department of the Investigational Product

(Q15) It is specified that for each manufacturing plant for investigational products, an investigational product manufacturing department and an investigational product quality department shall be established. Is it acceptable to appoint one person each for such departments?

The number of staff for each department may vary according to the scale of the company and the number of items. Thus, it is acceptable to appoint one person each if there is no conflict in activities and the departments function well. However, even in such a case, quality department staff are required to be capable of objectively evaluating activities performed by a manufacturing department.

(Q16) Is it necessary to form a GMP system at each of the manufacturing plants if an investigational product manufacturing department and investigational product quality department are separately located at different manufacturing plants but belong to the same company?

In principle, a GMP system for an investigational product should be established at each manufacturing plant. However, this is not applicable to cases where manufacturing plants belong to the same company. If each department functions well without conflict, they can fully cooperate with each other, and there is a reasonable rationale for managing the departments at each manufacturing plant.

(Q17) When one item is manufactured by the same company but at more than one manufacturing department of manufacturing plants, is it acceptable to control them as one manufacturing plant for the investigational product?

In principle, a GMP system for an investigational product should be established at each manufacturing plant. In the questioned case, it can be interpreted that the manufacturing plant for the investigational product performing the pre-process is producing the product upon request from the manufacturing plant for the investigational product performing the post-process in the company; thus, a GMP system for the investigational product should be established in such a way that responsibilities in each process can be fulfilled.

(Q18) It is stated that an investigational product quality department should be established. Is it acceptable to consider it a synonym of "quality department" (quality assurance department + analysis and testing department) in the GMP for drugs? Or is it intended to use a different term from the original "quality control department?"

It is a synonym of the "quality department" (quality assurance department + analysis and testing department) in the GMP for drugs and does not refer only to the analysis and testing department as like the original "quality control department."

(Q19) Is it acceptable to take the form of separately establishing a quality assurance department and an analysis and testing department for the investigational product quality department as in the "Guidelines for GMP for drug substances" (Notification No. 1200 of the Pharmaceutical and Medical Safety Bureau

(PMSB) dated November 2, 2001)?

The investigational product quality department can be formed with separate quality assurance, and analysis and testing departments as along as it functions independently from the Investigational Product Manufacturing Department. When radioactive substances with extremely short half-lives used for nuclear imaging by PET(Positron Emission Tomography) are used in clinical trials in the early exploratory phase, the form of the department can be flexibly managed based on their specificity.

(Q20) The entire manufacturing of an investigational product is contracted out so that the sponsor (company) does not perform production. In this case, is it required to establish an investigational product manufacturing department?

It is not necessary to build an investigational product manufacturing department. However, even in the case where all manufacturing processes of an investigational product are outsourced, and the sponsor does not carry out any manufacturing activities of the investigational product, the sponsor shall review whether or not manufacturing control and quality control are properly performed by the contractee of the investigational product, and then the investigational product should be released to the clinical department of the sponsor. Because of this, an investigational product quality department which assesses the releasability of an investigational product shall be established to perform proper control and management.

6. Control of Investigational Product Release

(Q21) Are requirements for qualification necessary for the person who decides the releasability?

No special qualification is required. However, the person should have adequate education and training and have knowledge and experience in clinical trials and in the manufacturing control and quality control of the investigational product because the said person needs to be familiar with overall manufacturing of investigational products, for example, a pharmacist or a person who has completed an advance course majoring in pharmacy, medicine, dentistry, veterinary medicine, agriculture, science or engineering at a university, a college or a professional college under the former education system, a university or a technical college under the School Education Law. These are not necessarily essential requirements nor limit appointment of persons with other qualifications.

7. Documents on the Investigational Product

(Q22) Is it acceptable to directly use the document originally titled "Investigational product master formula?" Is it also acceptable to specify the document with the title "Investigational product master formula?"

The development phase is a stage intended to "standardize" each matter concerning an investigational product; thus, "Investigational product 'master formula'" is not appropriate as the document title. It was referred to as "The document on the investigational product" to imply that it is a document organizing the quality information of an investigational product which has been collected to that point. Therefore, the document corresponds to the original investigational product master formula in terms of the contents, and it is acceptable to simply use the original title, namely "The investigational product master formula", in the

company.

(Q23) How should the scopes of manufacturing processes and manufacturing procedures that should be presented in the document on the investigational product by the sponsor be considered?

In principle, a series of manufacturing processes from the drug substance, drug preparation to packaging and their procedures should be presented. However, for example, when necessary information cannot be obtained from the supplier of the drug substance, etc., it is acceptable to present simplified texts based on limited available information by mentioning the source of the information and the reason for unavailability of data. When the drug substance is registered in the master file, manufacturing procedures can be provided by mentioning its registration number.

However, when the sponsor performs manufacturing processes or contracts out all or part of the manufacturing processes at his or her responsibility, the manufacturing procedures for the concerned processes should be presented. For the document on an investigational product that is not targeted as a development candidate in the early exploratory phase, it is acceptable to provide details appropriate for the purpose of the concerned clinical trial.

(Q24) When investigational products excluding comparators are manufactured, but the manufacturer does not serve as the sponsor, how should the scopes of manufacturing processes and manufacturing procedures that should be presented in the document on the investigational product be considered as the manufacturer of the investigational product?

It is acceptable to provide only matters concerning manufacturing processes that the investigational product manufacturer carries out regardless of the sponsor outsourcing manufacturing. For contract manufacturing, it is specified in Section 20.3 that "the contractee of the investigational product only needs to prepare the documents describing the matters concerned with the manufacturing process he or she is in charge of."

(Q25) What should be presented in the document on the investigational product for a comparator?

Information on ingredients, quantities, specifications and test methods, manufacturing procedures, and other necessary matter that can be obtained from the supplier, etc. should be presented in addition to the manufacturing procedures for packaging and labeling that he or she carries out.

(Q26) When a comparator is obtained from another company or from the market, it is difficult to provide ingredients, quantities, specifications and test methods. What should be done?

Even in the case where a comparator is obtained from another company or from the market, matters concerning specifications and test methods for receiving inspections should be presented.

(Q27) There are numerous matters to be presented in the document on the investigational product. Is it acceptable to publish it in separate volumes as long as data are searchable?

It can be controlled as separate volumes as long as, for example, an index or reference numbers are

presented in the document on the investigational product, and target items are easily searchable.

(Q28) Is it necessary to provide "a summary of the clinical trial" in the document on the investigational product?

The summary is not always required. However, it is preferable to provide the summary if possible because it can be used for reviewing in what clinical trial the investigational product is to be used. When preparing the said item, it is sufficient to briefly state the phase of the clinical trial, study design, target disease, dosage and administration, etc. and the purpose of use of the investigational product. The protocol or investigator's brochure specified in Articles 7 and 8 of the GCP Ordinance, respectively, can be also used.

(Q29) When manufacturing procedures, specifications or test methods mentioned in the document on the investigational product are slightly changed with the progress of the clinical trial, is it acceptable to collectively file the manufacturing procedures, specifications and test methods after ensuring correspondence with the product lot without making a revision each time?

When making changes in the manufacturing procedures, specifications or test methods, revisions need to be made beforehand. However, a few manufacturing procedures, which may be selected with a change of the manufacturing scale of the investigational product, can be prespecified in the document on the investigational product. In such a case, the actually adopted manufacturing procedure should be indicated in manufacturing records.

(Q30) When using an investigational product with different contents in one clinical trial, is it acceptable to control the document on the investigational product, etc. as one document?

It is acceptable as long as necessary matters are properly presented, and it does not disturb activities such as amendments.

8. Operating Procedures

(Q31) Is it acceptable to present processes or test procedures carried out in foreign countries in separate documents, and retain them at the overseas manufacturing plant?

The document can be controlled in separate volumes. However, a system enabling prompt access and revision of the volumes should be adopted when necessary.

9. Manufacturing Control of Investigational Products

(Q32) It is specified in Section 9.1.6 "to confirm cleanliness of the buildings and facilities." Is it acceptable to use the criteria determined in each company?

Yes, it is acceptable. However, verification of cleaning must be performed, and validation should be carried out as necessary. Particularly for drug substances, full attention should be paid to the possibility that safety is not ensured or to the possibility they may have high activity.

10. Quality Control of Investigational Products

(Q33) It is specified in Section 10.1.1 to conduct analysis and testing of raw materials and investigational products by lot or those of labeling and packaging materials by control unit. For receiving inspections of raw materials, and labeling and packaging materials specified in the compendia by the Japanese Pharmacopoeia, is it acceptable to only perform "visual inspection and review of the certification issued by the manufacturer?"

All items specified in the document on the investigational product, etc. need to be performed for the analysis and testing of not only compendial items but also raw materials, and labeling and packaging materials. However, the GMP for drugs stipulates that some items of analysis and testing for raw materials, and labeling and packaging materials can be omitted or simplified when there are reasonable rationales demonstrating that such omission or simplification does not affect the quality assurance of the concerned drug, and such a fact is specified in the document on the investigational product, etc. It is acceptable to handle this matter in the same manner in the GMP for investigational products.

(Q34) It is specified in Section 10.1.5 "to check and confirm that the manufacturing control and quality control at the manufacturing plant of the concerned contractee of the investigational product are properly carried out" when all or part of the manufacturing processes of the investigational product is contracted out to another party. Does this review have to be performed by visiting the site?

Concerning the review method, it can be examined by not only visiting the site but also other feasible and appropriate methods such as obtaining necessary records from the investigational product quality department of the contractee. However, the contractor should bear responsibility for the review results.

(Q35) With regard to Section 10.1.2, when it is contract manufacture, is it acceptable to perform the receiving inspection of an intermediate product that the contractee produced by reviewing the certificate of analysis and testing issued by the contractee?

The contractor is required to implement all items of analysis and testing specified in the document on the investigational product, etc. for an intermediate product. However, the contractor can use, on his or her own responsibility, the results of analysis and testing conducted by the contract manufacturer as part of the analysis and testing of quality control of manufacturing carried out by the contractor as long as there are reasonable rationales demonstrating that such application does not affect the quality assurance of the investigational drug that the contractor manufactures, and such a fact is specified in the document on the investigational product, etc.

(Q36) How can compliance with the Japanese GMP for investigational products by overseas manufacturing plants for investigational products be confirmed?

Compliance should be confirmed by on-site inspection or from records or documents under the responsibility of the sponsor.

(Q37) It is mentioned in Section 10.1.7 "investigational products with very poor stability." Specifically what items are included?

Such items include substances with extremely short radioactive half-live such as positron nuclide labeled substances can be included. The quality assurance of these radioactive investigational products used for microdose clinical trials should be carried out scientifically according to their characteristics.

(Q38) What conditions should be selected for the storage of the reserve sample specified in Section 10.1.8?

In principle, the reserve sample can be stored in the form of shipping and under the same conditions as those for usual storage and use.

(Q39) Concerning "the investigational products whose preservation is extremely difficult due to their properties" specified in relation to the storage of the reserve sample specified in Section 10.1.8, is it acceptable to consider them as those which cannot be used for analysis and testing due to changes over time such as decomposition and degradation?

Yes, it is acceptable.

(Q40) When producing an investigational product at an overseas manufacturing plant, is it acceptable to store the reserve sample at the manufacturing plant?

Yes, it is acceptable. However, it should be confirmed that the reserve sample is properly stored at the overseas manufacturing plant and can be promptly used for analysis and testing, etc. when necessary.

(Q41) The phrase "when analysis and testing are conducted using other testing facilities or testing institutions (hereinafter referred to as the "external testing institution, etc.")" is mentioned in Section 10.1.11. Does it refer to having company personnel perform analysis and testing by using an external testing institution, etc.?

That's correct. In addition, it should be confirmed that preparation and retention of records and analysis and testing are properly conducted in accordance with the provision of Section 11 when analysis and testing are performed by company personnel as well as staff of an external testing institution, etc.

12. Validation and Verification

(Q42) When validation is found necessary for the manufacturing of an investigational product, is it necessary to perform a review using three lots of an active drug?

Since it is in the development phase, the quantity of manufacturing lots may be small or the manufacturing procedure may not be established. In such a case, it is generally considered appropriate to conduct verification to scientifically review the concerned lot. In the case where validation should be implemented, it is also acceptable to not always include an active drug or repeat the review using three lots in consideration of the actual manufacturing condition and other relevant matters, as long as validation is carried out using a method enabling to scientifically ensure quality. In such a case, necessary review should also be performed so that consistency in the manufacturing processes can be secured.

(Q43) What are items that should be included for validation and verification of an investigational product?

Validation items may include analytical methods, computer system and sterility assurance. Verification items may include cleaning for the prevention of cross-contamination and a test to confirm the absence of infectious factors for materials to be used.

13. Change Control

(Q44) Is it necessary to evaluate safety or efficacy for control of changes in the investigational product?

When unknown impurities are produced as a result of changes in the manufacturing procedures, or when there is concern for a residual solvent or crystalline form due to changes of solvent, for example, not only equivalence of the quality before and after the changes but also their effect on safety and efficacy needs to be evaluated.

14. Deviation Control

(Q45) Is the deviation control of investigational products different from that of approved drugs? To what extent should deviations be controlled?

Basically there is no difference. However, investigational products are only in the development phase so that reliable conditions or specifications may not be established or always validated. In addition, because of a lack of established criteria, evaluation of the effect of deviations on quality may be difficult in some cases. Therefore, in principle for all deviations, the quality of the concerned lot must be evaluated to the extent possible based on quality information accumulated to that point by investigating the causes and taking account of the possibility of the effect of deviations on quality. In addition, it is important to document a series of all facts on these deviations and to associate related safety studies with clinical trials. It is also critical to properly link improvement and modification through deviation control with the establishment of design quality and product quality.

16. Recall Handling

(Q46) It is stated in Section 16.1.2 "to store the investigational product by separation for a fixed time, and to dispose the recalled investigational product properly." Does the term "store for a fixed time" here mean to preserve the investigational product until the date of approval as like recall records?

It signifies to store the investigational product for the same period as that for recall action records unless the recalled investigational product obviously has no effect on the clinical trial results.

17. Self-inspection

(Q47) It is stated in Section 17.1.1 "to conduct proper self-inspection." Does the term "proper" here also have a connotation of "as necessary?"

Manufacturing of investigational products should not be periodic but be timely in association with safety studies or clinical trials. Because of this, a plan coupled with the progress of development should be drawn up beforehand and implemented, and self-inspection should be properly performed according to the progress

of development, when necessary.

(Q48) What should be performed for self-inspection of investigational products?

For example, review of the plans, reports, records and other relevant documents on manufacturing from materials to the final product and their analysis and testing as well as on facilities, devices, the environment and other relevant matters for each manufacturing lot. It is important to perform effective self-inspections and avoid carrying out formal inspections.

18. Education and Training

(Q49) It is stated in Section 18.1.1 "to systematically give education and training." Does the term "systematically" here mean "regularly?"

Unlike the manufacturing of drugs, consistency is not required for that of investigational products, and it is not a programmed operation; thus, regular education and training is not quite adequate. The term "systematically" used here should be understood as properly performing organized education and training in a timely manner in the situation where effectiveness must be enhanced such as before the start of operations or at making changes in activities. It is also preferable to conduct general education on the GMP for investigational products at a certain regular interval because it has purposes such as thorough recognition and communization.

19. Document and Record Control

(Q50) It is specified in Section 8 that operating procedures should be prepared and retained at each manufacturing plant for an investigational product. When a company has more than one manufacturing plant (e.g., manufacturing plants of drug substances and investigational products (drug preparations) for clinical trials) and the contents of basic procedures are commonly used in the company (e.g., concepts of validation and procedure for recall handling), it seems to be unreasonable to prepare the concerned procedure at each manufacturing plant. Is it acceptable to prepare and retain operating procedures at one of the manufacturing plants, distribute their copies to the other manufacturing plants and retain the copies at the other plants for the concerned procedure?

Copies can be used, but the operating procedures must be approved at each manufacturing plant for the investigational product and such a record must be retained.

20. Contract manufacture

(Q51) Is it acceptable to consider that the manufacturer of an investigational drug substance corresponds to a contractee when the manufacturer does not serve as the sponsor?

Yes, it is acceptable. When the manufacturer of an investigational drug substance sponsors a clinical trial by requesting another company to manufacture the drug preparation from the investigational drug substance that the manufacturer produces, the said manufacturer of the drug substance will be the sponsor, and the manufacturing process of the drug preparation will be the contract manufacture used in the Section.

21. Buildings and Facilities of the Manufacturing Plant for the Investigational Product

(Q52) It is specified that investigational products can be produced at authorized plants of drug manufacturers. In this case, is it acceptable to produce investigational products using manufacturing facilities for drugs?

Yes, it is acceptable. A sufficient amount of evidence of an investigational product such as its toxicity, pharmacological actions and sensitization may not be obtained in some development phases; therefore, full attention should be paid to cross-contamination with other drugs and matters specific to the investigational product.

(Q53) Is it permitted to manufacture investigational products by using other companies' manufacturing plants?

Yes, it is permitted. However, a system enabling proper compliance with the items of the GMP for investigational products including the control of the manufacturing plant during the manufacturing period should be formed under the responsibility of the sponsor, and full attention should be paid to cross-contamination with other drugs, etc. and matters specific to the investigational product.

Others

(Q54) "The standards for manufacturing control and quality control of investigational products used for clinical trials including the early exploratory phase such as microdosing clinical trials" is mentioned in Chapter 1. Are such standards also applicable to clinical trials in the early exploratory phase?

The Standards are applicable. However, consistency with an investigational product used in usual clinical development is not always required for that used for microdosing clinical trials because they are not directly connected with subsequent clinical trials. If considering the actual operations, manufacturing control and quality control appropriate for drugs used at microdose should be performed. In addition, radioactive substances used for nuclear imaging by PET have an extremely short radioactive half-life so that methods and equipment of synthesis are completely different from those for ^{14}C-labeled and non-labeled substances, and methods for supporting quality assurance cannot be discussed from the same perspective. Therefore, it is difficult to uniformly apply the Standards; they should be flexibly put into practice as mentioned in answers to questions concerning Sections "5. Manufacturing Department and Quality Department of the Investigational Product" and "10. Quality Control of Investigational Product" in this Q&A.

治験薬の製造管理及び品質管理に関する基準（治験薬ＧＭＰ）について（案）

治験薬を製造する際に遵守すべき適切な製造管理及び品質管理の方法並びに必要な構造設備に関する事項については、「医薬品の臨床試験の実施の基準に関する省令」（平成 9 年厚生省令第 28 号）第 17 条第１項及び第 26 条の３の規定を踏まえ、「治験薬の製造管理及び品質管理基準及び治験薬の製造施設の構造設備基準（治験薬ＧＭＰ）について」（平成９年３月 31 日薬発第 480 号）により定められている。また、併せて、治験薬 GMP の運用については、「「治験薬の製造管理及び品質管理基準」及び「治験薬の製造施設の構造設備基準」（治験薬ＧＭＰ）の運用について」（平成９年５月 20 日薬監第 70 号）により具体的事項が示されているところである。

今般、マイクロドーズ臨床試験など早期探索的段階を含め、治験の特性を考慮し、治験の段階に応じた治験薬の品質保証が可能となるよう、治験薬 GMP について、より実効性のあるものとして見直しを行うものである。

⇒今般の改正にあたっての趣旨を総括して述べている。

⇒Q&A 質問 54

治験薬の製造管理及び品質管理に関する基準（治験薬ＧＭＰ）

第１　総則

１．目的

本基準は、「医薬品の臨床試験の実施の基準に関する省令」（平成９年厚生省令第 28 号。以下「ＧＣＰ省令」という。）第 17 条第１項及び第 26 条の３に規定される治験薬を製造する際に遵守すべき適切な製造管理及び品質管理の方法並びに必要な構造設備に係る事項を定めるものであり、その目的は次に掲げるものである。

1.1　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。

⇒ 全てにおいて最優先されるべきことである。なお、具体的な例を、Q&A の質問 1 で説明している。

⇒Q&A 質問 1

1.2　治験薬のロット内及びロット間の均質性を保証することで、臨床試験の信頼性を確保すること。

⇒同一の治験段階において、ロット内及び複数ロット間で品質のバラツキがあれば、それを使用して得られる治験データの信頼性に疑義が持たれる。それに対する注意の喚起である。

1.3　治験薬が開発候補として絞り込まれた段階においては、当該治験薬と市販後製品の一貫性を、治験薬の製造方法及び試験方法が確立した段階においては、当該治験薬と市販後製品の同等性を保証することで、市販後製品の有効性及び安全性並びに臨床試験の適切性を確保すること。

⇒早期探索的臨床試験による開発候補の絞り込みの段階も含めると、実際には３段階に区分した内容となっている。すなわち、治験薬が開発候補として絞り込まれる以前の段階においては、一貫性も同等性も不問としている。趣旨としては、治験薬製造も新薬開発の一端に過ぎず、そ

の目的及び目標は、承認を得て市販製品に繋ぐことにあり、そのためには、安全性や有効性を考慮した品質の一貫性と同等性が求められることを意図している。なお、一貫性及び同等性については、Q&Aの質問２と質問３で解説している。

⇒Q&A 質問２、質問３

2. 適用範囲

2.1　本基準は、ＧＣＰ省令第17条第１項及び第26条の３の規定に基づき治験依頼者又は自ら治験を実施する者が実施すべき事項を定めたものであり、ＧＣＰ省令に基づき実施される治験に用いる治験薬に適用されること。

⇒基本的には、現行「治験薬（GMP）」と同様、GCP省令の規定に基づくものであることを明示している。

⇒Q&A 質問４

2.2　本基準は、治験薬製造施設が海外にある場合においても適用されるものであること。

⇒海外への輸出用治験薬においては、輸出先国におけるGMPが要求されるのと同様、逆の立場（輸入）においては、本基準が適用されることを述べている。

⇒Q&A 質問９

2.3　本基準は、ＧＣＰ省令第17条第１項または第26条の３が適用となる治験に用いる治験薬の製造について適用されるものであり、当該治験薬が承認された後に「医薬品及び医薬部外品の製造管理及び品質管理の基準に関する省令」（平成16年２月24日厚生省令第179号。以下「ＧＭＰ省令」という。）が適用されるかどうかによるものではないこと。

⇒基本的には、現行「治験薬GMP」と同様の記述であるが、例えば対照薬などが、これに該当することになる。

⇒Q&A 質問５～質問８

2.4　ＧＣＰ省令に規定する自らが治験を実施する場合については、本基準の「治験依頼者」を「自ら治験を実施する者」に、「第24条第３項」を「第26条の10第３項」に読み替えて適用する。

⇒「医師主導の治験」に対するものである。

3. 基本的考え方

⇒今般の改正治験薬GMPの運用における重要な基本コンセプトを特記項目としている。なお、本基準の遵守を無視或いは不履行の場合には、ペナルティが科せられることをQ&Aの質問10に示している。

⇒Q&A 質問10

3.1　治験薬の製造管理及び品質管理に求められる要件は、開発の進展に連動すべきものであり、また、同一の臨床段階においても、多岐に渡る臨床試験の目的や方法により求められる事項の程度に差異がありうる場合が想定されることから、一律的に規定することは困難である。本基準は、臨床試験の各段階における要件を区別して規定するものではないが、臨床試験を有効かつ適正に実施するためにも、開発に伴う段階的な状況やリスクを考慮して、適切だと判断され

る要件については柔軟に運用すること。また、本基準が医薬品開発の重要な期間に対して適用されることから、製品ライフサイクルを見据えた品質マネジメントの一環として活用することが望ましい。

⇒*治験の初期段階から承認申請直前までの一律的な規定は非現実的として、企業のリスクマネジメントによる主体的かつ柔軟な対応を許容している。また、治験段階のデータが承認申請に結び付き、その後の市販製品に繋がることを十分に認識して対応することの重要性を述べている。なお、本項目は、ICH Q9（品質リスクマネジメント）やICH Q10（医薬品品質システム）の遵守を求めているのではなく、あくまでそれらの考え方の重要性を謳っているに過ぎない。そのことについては、Q&A の質問 11 で説明している。*

⇒*Q&A 質問 11*

3.2　被験者の保護及び臨床試験の信頼性の確保のために、治験薬の製造管理及び品質管理に係る全ての記録について、後日の確認が取れるように保存すること。

⇒*本項目は、トレーサビリティの必要性を謳っている。*

3.3　治験薬が開発候補として絞り込まれた段階においては、被験者の保護及び臨床試験の信頼性の確保に加えて、治験薬と市販後製品との一貫性・同等性を示す根拠として、また、治験薬の設計品質及び製品品質の確立の根拠として、開発段階における全ての変更を管理し、文書化し、記録として保存すること。

⇒*本項目は、将来の承認申請の根拠としての変更管理の重要性を謳っている。合せて、「WHO-GMP／ヒト用治験薬ガイドライン」記載の第４番目の原則である「製造工程における全ての変更を文書化すること」に相当する内容をカバーしている。また、ICH Q8（製剤開発）の考え方を盛り込むことで、"承認申請書との関係"についても触れ、承認申請書の質の向上を期待している。*なお、ICH Q8 を要件として求めているものではないことを、Q&A の質問 12 において説明している。

⇒*Q&A 質問 12*

3.4　治験薬の製造施設の構造設備については、治験薬の製造スケール等、開発と共に大きく変更されることが必然である一方、開発に伴って製造方法や試験方法等のデータが蓄積されていくことから、開発段階に応じたより適切な管理が求められる。その観点から、治験薬の製造施設の構造設備として、開発段階を考慮しない一律的な要件は不適切であると考えられることから、開発の最終段階に相当する医薬品の製造販売承認の要件及び医薬品の製造業許可の要件として求められる製造所の構造設備を認識した上で、必要な対応を図ること。

⇒*現行「治験薬 GMP」で言えば、ハード部分に相当する"治験薬の製造施設の構造設備基準"に関するものである。3.1 項におけるソフト部分以上に、ハード部分についての一律的な規定は非現実的として、当該治験薬の物性・特性を最も把握している企業の主体的かつ柔軟な対応を許容している。後段の記述は、従前の詳細要件の削除に伴って、参考とすべきハード要件（承認要件である医薬品 GMP 及び許可要件である薬局等構造設備規則）を挙げている。*

4. 定義

4.1　この基準で「被験薬」とは、ＧＣＰ省令第２条第５項に定める被験薬をいう。

4.2　この基準で「治験薬」とは、ＧＣＰ省令第２条第７項に定める治験薬をいう。

4.3　この基準で「治験薬の品目」とは、一つの承認申請のために行われる治験に使用される治験薬の品目をいう。

4.4　この基準で「資材」とは、治験薬の容器、被包並びに容器及び被包に貼付するラベルをいう。

4.5　この基準で「ロット」とは、一の製造期間内に一連の製造工程により均質性を有するように製造された治験薬（製造の中間工程で造られたものであって、以後の製造工程を経ることによって治験薬となるものを含む。以下、9.1.5、10.1.1、10.1.7 及び 10.1.8 において同じ。）及び原料の一群をいう。

4.6　この基準で「管理単位」とは、同一性が確認された資材の一群をいう。

4.7　この基準で「バリデーション」とは、治験薬を製造する施設（以下「治験薬製造施設」という。）の製造設備並びに手順、工程その他の治験薬の製造管理及び品質管理の方法（以下「製造手順等」という。）が期待される結果を与えることを検証し、これを文書とすることをいう。通常、製造方法や試験方法が確立し、再現性も考慮した繰り返しが必要な場合に行う。

⇒*今般、下記「ベリフィケーション」を新規に定義したことに伴い、治験薬 GMP における「バリデーション」を明確にするため、追記している。*

⇒*Q&A 質問 13*

4.8　この基準で「ベリフィケーション」とは、当該治験薬に期待される品質が得られたことを手順書、計画書、記録、報告書等から確認することをいう。通常、限定された状況、限定されたロットに対して、その妥当性や適切性の評価確認のために行う。

⇒*１回ぽっきりということが多い治験薬製造においては、バリデーションが必ずしも相応しい対応ということでもなく、非現実的であることから、"事後の評価・確認"ということの必要性と重要性の観点から、「ベリフィケーション」の概念を導入し、定義として追加している。*

4.9　この基準で「クオリフィケーション」とは、構造設備（例えば、設備・装置・機器・ユーティリティ等）について、計画・仕様・設計どおり適格であることを評価確認し、これを文書とすることをいう。

⇒ *クオリフィケーションは、バリデーションであれ、ベリフィケーションであれ、その前提条件として必要になることから、新規に追加している。なお、医薬品 GMP のバリデーション基準でいうところの定義をそのまま治験薬に適用することへの誤解を避けるため、本基準においては、「クオリフィケーション」としている。なお、クオリフィケーションの種類と運用については、*Q&A の質問 14 において解説している。

⇒*Q&A 質問 14*

第２　治験薬の製造管理及び品質管理

５．治験薬製造部門及び治験薬品質部門

5.1　治験依頼者は、治験薬製造施設ごとに、治験薬の製造管理に係る部門（以下単に「治験薬製造部門」という。）、治験薬の品質管理に係る部門（以下単に「治験薬品質部門」という。）をおかなければならない。

なお、治験依頼者は、**治験薬の製造工程の全部を委託する場合でも、必要な部門をおかなければならない。**

⇒*現行「治験薬 GMP」の三役による個人の管理・責任から、部門による管理・責任の体制に変更している。後段は、臨床試験部門への治験薬の出荷に際しては、最低限度、照査・承認を行う必要性から、治験薬品質部門の設置を求めている。*

5.2　**治験薬品質部門は、治験薬製造部門から独立していなければならない。**

⇒ *国内外、医薬品を含めた GMP の基本要件であり、明文化している。なお、組織運営に関する Q&A については、実態の中で比較的多いと想定されるケースを挙げ、解説している。*

⇒*Q&A 質問 15～質問 20*

６．**治験薬の出荷の管理**

6.1　治験依頼者は、**治験薬の品目ごと**に、**治験薬品質部門のあらかじめ指定した者**に、製造管理及び品質管理の結果を適正に評価させ、治験薬の製造施設からの出荷の可否を決定させなければならない。

⇒*今般の改正治験薬 GMP における最重要業務ということで、１つの項目として別立てにして、明記している。内容的には、医薬品 GMP 及び ICH Q7（原薬 GMP のガイドライン）に同じ。*

6.2　治験薬の出荷の可否を決定する治験薬品質部門のあらかじめ指定した者は、**当該治験及び治験薬の製造管理及び品質管理について*充分な教育訓練を受け、知識経験を有する者***でなければならない。

⇒*出荷が最重要業務であることを踏まえ、その出荷判定者についての資格要件を明記している。なお、具体的な資格要件については、Q&A の質問 21 において説明している。*

⇒*Q&A 質問 21*

７．治験薬に関する文書

7.1　治験依頼者は、**治験薬の品目ごと**に、成分、分量、規格及び試験方法、製造手順、治験の概要その他必要な事項について記載した**治験薬に関する文書**を作成し、治験薬品質部門の承認を受けるとともに、これを保管しなければならない。

⇒*従前の「治験薬製品標準書」に相当する。開発段階は、"標準化"することが目的であり、先に「標準書」が在るというのは不可思議な状態となることを踏まえ、文書名称に拘らず、内容重視を尊重している。なお、従前から運用について疑問が持たれていた対照薬に関する事項、分冊管理に関する事項等については、Q&A の中で解説している。*

⇒*Q&A 質問 22～質問 30*

7.2　7.1 に規定する治験薬に関する文書は、当該治験薬の開発の進捗や新たに得られた知見等を踏まえ、適時適切に改訂されなければならない。

⇒*本項目でいう「治験薬に関する文書」は、その時点における当該治験薬の情報集であることから、開発の進捗に応じて内容の充実化が図られるはずであり、適時、適切な内容に改訂されることが期待されている。*

８．手順書等

8.1　治験依頼者は、治験薬製造施設ごとに、構造設備の衛生管理、職員の衛生管理その他必要な事項について記載した治験薬の衛生管理の手順に関する文書を作成し、これを保管しなければならない。

⇒従前の「治験薬製造衛生管理基準書」に相当する。

8.2　治験依頼者は、治験薬製造施設ごとに、治験薬等の保管、製造工程の管理その他必要な事項について記載した治験薬の製造管理の手順に関する文書を作成し、これを保管しなければならない。

⇒従前の「治験薬製造管理基準書」に相当する。

8.3　治験依頼者は、治験薬製造施設ごとに、検体の採取方法、試験検査結果の判定方法その他必要な事項を記載した治験薬の品質管理の手順に関する文書を作成し、これを保管しなければならない。

⇒従前の「治験薬品質管理基準書」に相当する。

8.4　治験依頼者は、8.1から8.3に定めるもののほか、治験薬の製造管理及び品質管理を適正かつ円滑に実施するため、次に掲げる手順に関する文書（以下「手順書」という。）を治験薬製造施設ごとに作成し、これを保管しなければならない。

8.4.1　治験薬製造施設からの出荷の管理に関する手順

8.4.2　バリデーション及びベリフィケーションに関する手順

⇒従前の「バリデーションに関する手順」に相当する。

8.4.3　変更の管理に関する手順

8.4.4　逸脱の管理に関する手順

8.4.5　品質等に関する情報及び品質不良等の処理に関する手順

⇒従前の「苦情処理に関する手順」に相当する。

8.4.6　回収処理に関する手順

8.4.7　自己点検に関する手順

8.4.8　教育訓練に関する手順

8.4.9　文書及び記録の管理に関する手順

8.4.10　その他製造管理及び品質管理を適正かつ円滑に実施するために必要な手順

8.5　治験依頼者は、治験薬に関する文書、治験薬の衛生管理の手順に関する文書、治験薬の製造管理の手順に関する文書、治験薬の品質管理の手順に関する文書及び手順書（以下「手順書等」と総称する。）を治験薬製造施設に備え付けなければならない。

⇒従前の３基準書及び手順書に関するものである。今般の改正治験薬GMPで期待していることは、表面的なタイトルでなく、あくまで内容を重視し、実効性を高めることである。その意図から、「治験薬のoo管理の手順に関する文書」としている。

⇒Q&A 質問31

９．治験薬の製造管理

9.1　治験依頼者は、治験薬製造部門に、手順書等に基づき次に掲げる治験薬の製造管理に係る