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Research on Current Quality System of Drug Products

Research Report

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Guideline for Technology Transfer (Final Draft)

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Introduction

This research is intended to provide appropriate guidance for technology transfer of which importance is expected to increase under the new manufacturing and marketing approval system to be implemented by the revised Japanese Pharmaceutical Affairs Law, and supplement the GMP regulations to be revised soon. The research is also intended to propose some regulations to realize technology transfer necessary for high quality and stable manufacturing of new drugs and existing products by reviewing technology transfer based on the following principles.

In this research, draft guideline has been established on the basis of the following principles.

- The technology transfer means actions to transfer information and technologies necessary to realize quality of design of drugs during manufacturing.
- Appropriate technology transfer is important to upgrade the quality of design to be the quality of product, and ensure stable and high quality of the product.
- It should be noted that drugs may have a great impact on human lives and health, and their raw materials, compositions and manufacturing methods are subject to various changes during their long term manufacturing and marketing.
- To assure the drug quality, it is required to make sure 5 W's and 1 H, that is what, when and why information should be transferred to where and by whom and how to transfer, then share knowledge and information of the drug product between transferring and transferred parties.
- The technology transfer does not mean transient actions taken by the transferring party toward the transferred party, but means continuous information exchange between the both parties to maintain the product manufacturing.

Basic Policies on the Establishment of the Guideline for the Technology Transfer

The basic policies on the establishment of the guideline are shown as follows.

1) Assurance of consistency of new drug from development through manufacturing

- When a drug is launched into the market, the quality of design of the drug should be reproducible as the quality objectives so that the drug can have indications as confirmed in clinical studies conducted at the development phase.
- The transferring party in charge of development should fully understand what kind of technical information is required for the technology transfer, and should establish an appropriate evaluation method to determine whether a drug to be manufactured meets the quality of design.
- It is important to fully refer to product information of the past, while understanding that technical information of new drugs are generated from data of a limited amount of batches, various standards have been established within a narrow range, and quality evaluation method established in the development phase is not always sufficient in the manufacturing phase.

2) Consistency Between Quality and Specification

- It is required to verify that the product specification adequately specifies the product properties and quality.
- The product specification should ensure that the quality of design specified in the development is assured as the quality objectives, and the product satisfies the quality of design.
- It should be fully understood that quality assurance in the manufacturing is based on the product specification. Relations between upper and lower limits of setting range of manufacturing formula (compositions and manufacturing methods) and upper and lower limits of specification values in the product specification should be fully understood, and appropriate specifications and the specification range should be established to maintain the consistency between the quality objectives and product specification.
- For specifications of raw materials, labeling and packaging material, intermediates, semimanufactured products, and in-process test, consistency between test items, specification range, and product specifications should be maintained.
- Since initial manufacturing formula and product specification are established based on limited information, the consistency between the quality and specification after the start of manufacturing should be fully verified, and these should be improved through appropriate change controls, if necessary.

3) Documentation Management and Update of Technical Information

- Responsibility system should be established in view of responsibility for giving sufficient information (Accountability) and responsibility for consequences of actions (Responsibility). For this purpose, appropriate documentation management of technology transfer is required.
- In light of the fact that drugs have long product life, the documentation management should be performed assuming that the technology transfer would occur several decades after the completion of development.
- Since the control range of formula to realize planned quality objectives has been specified within a narrow range at the early phase of manufacturing, the control range might be revised due to information accumulation accompanied with repeated manufacturing, and the product quality is not fixed one but may be improved and involved in the revision of specification and test methods. Taking these into consideration, initial technical information should be reviewed at regular intervals on the basis of the quality of design, and then the information should be updated.

Table of Contents

The table of contents is shown as follows. The 1st chapter addresses background and the scope of the guideline. The 2nd to 4th chapters address items to be noted when the technology transfer is implemented as well as the process of technology transfer, while the 5th chapter shows detailed procedure and documentation of technology transfer. In addition, the 6th and latter chapters show considerations necessary for the implementation of technology transfer, and exemplify items to be listed in the technology transfer documentation.

Guideline for Technology Transfer

1. Preface

1.1 Background

In the drug approval system, the manufacturing approval was replaced with the manufacturing and marketing approval in April 2005, resulting in a big change in the Japanese pharmaceutical system and regulations. Under these circumstances, in order to continue providing effective and safe drugs to the public as in the past, it is required to restructure a quality assurance system of drugs at all stages through research and development (R&D), manufacturing and marketing in line with the trends by reviewing the current quality assurance system and its methods including existing Good Manufacturing Practice (GMP) to comply with the new system and adopting achievements of technological progress and international harmonization of pharmaceutical regulations.

In recent years, there is a growing awareness that an appropriate transfer of manufacturing technologies (technology transfer) is important to upgrade drug quality as designed during R&D to be a final product during manufacturing as well as assure stable quality transferred for many reasons between contract giver and contract acceptor during manufacture. Also, to assure the drug quality in the transferred party, it is required to make sure 5 W's and 1 H, that is what, when and why information should be transferred to where and by whom and how to transfer, then share knowledge and information of the technology transfer each other among parties related to drug manufacturing. Fur this purpose, it is required to establish an appropriate guideline for technology transfer and help to restructure the quality assurance system. This guideline categorizes information generated in the processes through pharmaceutical R&D and manufacturing as well as the information flows, discusses information necessary for the technology transfer and communication route, and proposes ideal technological transfer.

1.2 Objective

The objectives of this guideline are:

1) To elucidate information necessary to transfer technology from R&D phase to actual manufacturing phase by sorting out various technical information obtained during R&D of new drugs;
2) To elucidate information necessary for technology transfer occurring between different manufacturing plants when the manufacturing plants of existing products, etc. are changed; and
3) To exemplify specific procedures and points of concern for the two types of technology transfer in the above to contribute to smooth technology transfer.

1.3 Scope

This guideline applies to the technology transfer through R&D and manufacturing of drugs (chemically synthesized drug substances and drug products) and the technology transfer related to changes in manufacturing plants of already marketed drugs. The both technologies include those of manufacturing and quality control (manufacturing methods and tests).

1.4 Organization

This guideline consists of the followings:

- Explanation of technology transfer process
- Explanation of considerations for technology transfer
- Explanation of procedures and necessary documents for technology transfer
- Examples of technical information to be transferred
- Points of concern for documenting technology transfer

2. Technology Transfer Process of New Drugs from Development Phase through Manufacturing Phase

The quality of design of drugs is designed based on basic data concerning efficacy, safety and stability of drugs (drug substances) obtained from various studies in preclinical phases and data concerning efficacy, safety and stability of drug products obtained from clinical studies. The quality of design will be almost completed in Phase II clinical

study. Various standards for manufacturing and tests will be established by reviewing pilot research during the period of Phase III study to realize the quality of design, and the quality of design will be verified in various validation studies, and will be upgraded to be the quality objectives, and the actual production will be started. The technology transfer consists of actions taken in these flows of development to realize the quality as designed during the manufacturing. Even if the manufacturing starts, the technology transfer will take place in processes such as changes in manufacturing plants. The processes are classified broadly into the following five categories.

2.1 Quality Design (Research Phase)

The quality design is to design properties and functions of drugs, and performed mainly in phases from late preclinical studies to Phase II clinical study. For drug products, the quality design corresponds to so-called pharmaceutical design to design properties and functions such as elimination of adverse reactions, improvement of efficacy, assurance of stability during distribution, and adding usefulness based on various data such as chemical and physical properties, efficacy, safety and stability obtained from preclinical studies. For drug substances, the quality design is to determine starting materials and their reaction paths, and basic specifications of the drug substances.

2.2 Scale-up by Pilot Research, and Detection of Quality Variability Factors (Development Phase)

To manufacture drugs with qualities as designed, it is required to establish appropriate quality control method and manufacturing method, after detecting variability factors to secure stable quality in the scale-up validation that is performed to realize pilot research of drugs designed on the basis of results from small-scale experiments. In general, this process is called the pilot research where the quality of design will be upgraded to be the quality objectives. Adequate data accumulation in the pilot research is important for successful technology transfer.

2.3 Technology Transfer from Development Phase to Manufacturing Phase

Transfer of technical information is necessary to realize that actual products are manufactured in manufacturing facilities using compositions and manufacturing methods established in the above. In the past, the technology transfer was mainly seen as standard transfer or as technology instruction from development department to manufacturing department within the same company. In future, since contract manufacturing is expected to increase under the revised Pharmaceutical Affairs Law, the technology transfer between companies will increase. In principle, how accurately transfer technical information from transferring party to transferred party is important, and it is essential to establish responsibility system and prepare documents clarifying 5 W's and 1 H, and have adequate technology exchange between the both parties for successful transfer.

When transfer technology of new products from research and development department to manufacturing department, it is recommended to compile technical information to be transferred as research and development report (hereinafter referred to as "the development report"), and use the development report as a part of technology transfer documentation.

2.4 Validation and Manufacturing (Manufacturing Phase)

Manufacturing is implemented after various validation studies verify that it is able to stably manufacture based on transferred manufacturing formula. While the manufacturing facility accepting technology is responsible for validation, the research and development department transferring technology should take responsibility for validations such as performance qualification (PQ), cleaning validation, and process validation (PV) unique to subject drugs. For validations such as installation qualification (IQ) and operational qualification (OQ), which are not unique to the subject drugs, it is possible to effectively use data of already implemented validations.

2.5 Feedback of Information Generated from Manufacturing Phase

As a result of technology transfer, products are manufactured and brought to the hands of consumers. Since manufacturing and quality evaluation methods established in the early phase of manufacturing is not always the best ones, it is required to accumulate various technical information obtained through repeated manufacturing. Also, it is important to appropriately modify various standards established before on the basis of these information. For this purpose, appropriate feedback system for technical information at transferred parties and documentation management

of technology transfer at transferring parties should be established. For drugs as they have long product life, documentation management should be performed assuming that the technology transfer would occur several decades after the completion of development. Also since product improvements and changes of specifications and methods are often implemented, the initial technical information should be reviewed and updated at regular intervals. For this kind of documentation management and information updating, it is desirable to establish product specification describing entire characteristics of the product in addition to the development report, which is to be revised and updated regularly.

3. Three Requirements to be Considered for Technology Transfer

It is important to satisfy the following three requirements in order to steadily implement the technology transfer through the processes described in the chapters 2.1 to 2.5.

3.1 Assurance of Consistency from Development through Manufacturing

To make developed new drugs have efficacy and safety as predetermined in clinical studies, the quality of design should be reproducible as the quality objectives (assurance of consistency). For this purpose, the transferring party in charge of development should fully understand what kind of technical information is required by the manufacturing plant which receives technology transfer, and should establish an appropriate evaluation method to determine whether a drug to be manufactured meets the quality of design. It should be recognized that technical information of new drugs at the early phase of manufacturing are generated from data of a limited amount of batches, various standards obtained from the limited data are established only within a narrow range, and quality evaluation method established in development phase is not always sufficient for latter phases including pilot research. For stable manufacturing of consistent products, it is fundamental to fully refer to and review information of research and manufacturing of existing products when the pilot research is implemented, and this is a key to successful technology transfer.

3.2 Consistency between Quality and Specification

When the product specification is established on the basis of the quality objectives determined in the above, it is required to verify that the specification adequately specifies the product quality (consistency between quality and specification). That is, it is required to ensure the quality predetermined in the quality design as the quality objectives, and assure in the product specification that the product satisfies the quality of design.
In reviewing pilot research, since manufacturing methods are established with limited amount of lots and limited resources of raw materials, the product specification should be established based on data from study results with limited lots; however, relations between upper and lower of control limits of compositions and manufacturing methods and upper and lower of control limits of the product specification should be fully understood, and the consistency between the quality objectives and specification should be maintained.
Also, since initial manufacturing formula and specification are established based on limited information, the consistency between the quality and specification should be fully verified after the start of manufacturing, and the consistency should be improved through appropriate change controls, if necessary.

3.3 Update of Documentation Management and Technical Information

For both of new drugs and existing products, concerned parties should make clear the responsibility system in order to fulfill the responsibility for giving sufficient information (Accountability) and responsibility for consequences of actions (Responsibility) in view of the quality of design and quality objectives of the product. For this purpose, appropriate documentation management of technology transfer is important and required. In light of the fact that drugs have long product life, it should be fully understood that it is essential to perform the documentation management assuming that the technology transfer would occur several decades after the completion of development.
In addition, appropriate documentation management of various technical information accompanied with technology transfer should be established, and storage period should be set up according to the importance of data.
Since the quality objectives have been stipulated within a narrow range at the early phase of manufacturing, the control range might be revised due to information accumulation accompanied with repeated manufacturing, and the

product quality is not fixed one but may be improved and involved in the revision of specification and test methods according to technology progress. Taking these into consideration, initial technical information should be reviewed at regular intervals on the basis of the quality of design, and then the information should be updated.

4. Technology Transfer of Existing Products

Since manufacturing plants of existing products are often changed for many reasons after the launch of a new drug, already standardized test methods and manufacturing methods of the existing products are sometimes transferred to other offices or other companies. In addition, for certain reasons, qualities of the existing products might be improved.

In case of the change in manufacturing plants of the existing products, no alteration of product quality before and after the change (assurance of uniformity) is required rather than assurance of consistency needed for new drugs. Products manufactured in a new manufacturing plant should satisfy the product specification, while it is required to confirm that there is no alteration of trends of each control value of manufacturing, test and inspection processes which may affect the product quality. Although there are no significant differences between existing products and new drugs in terms of implementation of technology transfer, many of existing products have already established standards of manufacturing, test and inspection processes. Therefore, transferring and reproducibility validation of established standards become actual technology transfer in case there is no significant alteration of these standards which may affect the product quality and no possibilities to affect the product quality due to technology transfer. However, in case where alterations of facilities or manufacturing scales often occurring due to technology transfer may possibly affect the product quality, it is required to confirm whether there is any influence on the quality, establish manufacturing standard not affecting the product quality as much as possible, and revise various specification, test methods and inspection standards if necessary. In these cases, it should be always noted that each standard has been established within a narrow range at the early stage of manufacturing after the technology transfer as in the case of new drugs, and revised quality evaluation method of specification, test methods, etc. are not always the most ones. When revising manufacturing standard, specification test, etc., close attention is required, since equivalence evaluation of quality objectives (including bioequivalence) may be required in terms of change control.

In case quality objectives of the product are improved, quality equivalence including bioequivalence should be assured. That is, since examinations similar to those of generic products are required, Guideline for Bioequivalence Studies of Generic Products should be fully referred. Technology transfer in this case should be handled as in the case of new drugs. Since items stated in the chapters 2.3 to 2.5 shall apply to both of developed and existing products, it is desirable that technical information to be transferred should be compiled in forms such as product specification. For this purpose, Drug Product Standard Code is an important document. Also as in the case of developed products, responsibilities for the technology transfer should be clearly defined, documentation of technology transfer should be prepared, and the technology transfer should be implemented through adequate exchanges of technical information.

4.1 Assurance of Consistency, Equivalency, and Uniformity between Quality and Specification of Existing Products

Unlike new drugs, the quality of existing product is considered being stable. However, the quality of product may possible change due to various revisions (such as places, operators, raw materials, labeling and packaging material, facilities, test methods, etc.) accompanied with technology transfer. If the product specification does not fully stipulate the quality of product, changes in quality may be overlooked. Therefore, for the technology transfer, it should be confirmed that the product specification fully stipulates the product quality as in the case of developed products (assurance of consistency between the quality and specification).

Essential difference between assurance of consistency of new drugs and assurance of uniformity and equivalency of marketed products is whether approval is necessary or not. Concerning new drugs, their qualities are officially authorized by the regulatory approval granted after the technology transfer, while the quality of existing products has been officially authorized since they have already been approved. Therefore, in case of the above changes, the quality of existing product should be improved or not be altered. As such, if the quality is improved in

the technology transfer, equivalence including bioequivalence of other qualities should be assured, and if the quality is not changed, the uniformity before and after the changes should be assured. For this purpose, results of changes accompanied with the technology transfer should be fully evaluated. If necessary, appropriate change control procedures should be taken after the processes of quality of design, pilot research, and validation, and required legal procedures should be taken as in the case of developed products.

5. Procedures and Documentation of Technology Transfer

To properly transfer technology according to the above processes, documentation of technology transfer including appropriate procedures and technical documents is required. Procedures and documentation of technology transfer are indicated as follows. Items to be specified in the documentation will be referred in detail in the 6th chapter.

5.1 Organization for Technology Transfer

One of the most significant elements for successful technology transfer is close communication between transferring and transferred parties. Therefore, organization for technology transfer should be established and composed of both party members, roles and scope of responsibilities of each party should be clarified, and adequate communication and feedback of information should be ensured.

If view of the fact that results of technology transfer is reflected to GMP conformity after the start of manufacturing, it is important to establish an organization of transferred parties with due consideration for transferring to final GMP system.

5.2 Development Report

To realize quality assurance of new drugs at all stages from drug development to manufacturing, transfer of technical documents concerning product development or corresponding documents should be considered. The development report is a file of technical information necessary for drug manufacturing, which is obtained through development process, and the research and development department is in charge of its documentation. This report is an important file to indicate rationale for the quality of design of drug substances and drug products including information such as raw materials, labeling and packaging material, manufacturing methods, specifications and test methods. The development report should also include the above rationales, and it is desirable to complete the documentation before the approval inspection if possible or before the pre-approval inspection at the latest. Although the development report is not prerequisite for the application for approval, it can be used at the pre-approval inspection as valid document for the quality design of new drug. Also, this report can be used as raw data in case of post-marketing technology transfer of existing products. The following exemplifies information to be contained in the development report.

- Background of development of drug substances and drug products at stages from early development phase to final application of approval
- Rationale for the selection of raw materials, labeling and packaging material, and synthetic route
- Rationale for designs of dosage form, formula designs, and manufacturing methods
- Rational and change histories of important processes and control parameters
- Quality characteristics of manufactured batches (including stability data)
- Specifications and test methods of drug substances, intermediates, drug products, raw materials, and labeling and packaging material, and their rationale (validity of specification range of important tests such as contents, impurities and dissolution, rationale for the selection of test methods, regents, and columns, and traceability of raw data of those information)

5.3 Technology Transfer Documentation

Technology transfer documentation is generally interpreted as documents indicating contents of technology transfer for transferring and transferred parties. The raw data of the documents (such as development report) should be prepared and compiled according to purposes, and should be appropriately managed so that the data can be referred any time. For successful technology transfer, task assignments and responsibilities should be clarified, and acceptance criteria for the completion of technology transfer concerning individual technology to be transferred should be established beforehand.

In principle, it is desirable to prepare product specification with detailed information of product (drug substances or

drug products) subject to transfer, then proceed with the technology transfer according to the technology transfer plan established on the basis of this specification, and document the results as the technology transfer report.

5.3.1 Product Specification (Product Specification File)

The product specification is to compile information which enables the manufacture of the product, and to define specification, manufacturing and evaluation methods of the product and its quality, and the transferring party is responsible for documenting the file.

For new products, the development report can be used as a part of product specification file.

The product specification file should be reviewed at regular intervals, and revised as appropriate incorporating various information obtained after the start of manufacturing of the product.

The product specification file should contain the following.

- Information necessary for the start and continuation of product manufactuirng
- Information necessary for quality assurance of the product
- Information necessary for assurance of operation safety
- Information necessary for environmental impact assessment
- Information of costs
- Other specific information of the product

} Including the contents of the development report

5.3.2 Technology Transfer Plan

The technology transfer plan is to describe items and contents of technology to be transferred and detailed procedures of individual transfer and transfer schedule, and establish judgment criteria for the completion of the transfer. The transferring party should prepare the plan before the implementation of the transfer, and reach an agreement on its contents with the transferred party.

5.3.3 Technology Transfer Report

The technology transfer report is to report the completion of technology transfer after data of actions taken according to the technology plan is evaluated and the data is confirmed pursuant to the predetermined judgment criteria. Both transferring and transferred parties can document the technology transfer report; however, they should reach an agreement on its contents, since this report means the completion of technology transfer.

5.3.4 Check and Approval by Quality Department

It is desirable that the quality departments of transferring and transferred parties should establish confirmation process for all kinds of technology transfer documentation, and should check and approve the documentation.

5.4 Implementation of Technology Transfer

Avoid as much as possible the technology transfer from transferring to transferred party only by handing over the technology transfer documentation.

It is recommended that the both parties should cooperate to implement technology education, training and validations at facilities where the transferred technology is actually used.

5.5 Manufacturing Related Documents Including Drug Product Standard Code

The transferred party should compile documents such as Drug Product Standard Code necessary for manufacturing, various standards and validation plans/reports after the completion of technology transfer. While the transferred party is responsible for compiling these documents, the transferred party should obtain conformation by the transferring party as appropriate.

5.6 Verification of Results of Technology Transfer

After the completion of technology transfer and before the start of manufacturing of the product, the transferring party should verify with appropriate methods such as product testing and audit that the product manufactured after the technology transfer meets the predetermined quality, and should maintain records of the results.

6. Examples of Technical Information to be Contained in Technology Transfer Documentation

The 1st to 5th chapters indicate basic concept of technology transfer, related items, and transfer procedures. This chapter exemplifies detailed understanding and contents of technical information to be contained in the technology transfer documentation. This chapter is classified into four sections, that is, facilities and equipments, test methods, drug substances, and drug products, for the sake of convenience; however, it is not recommended to use this classification in case of actual technology transfer.

6.1 Technical Information of Facilities and Equipments

For technology transfer, technical information of products as well as those of manufacturing facilities and equipments are important. To establish facilities and equipments conforming to GMP, it is essential to obtain and understand information from R&D process so that quality assurance of subject drugs can be secured and the facilities and equipments can comply with required conditions for manufacturing. For this purpose, the following technical information should be transferred.

- A person in charge of research and development should clarify considerations of GMP compliance specific to manufacturing methods (manufacturing processes) of the drug, and present them to a facility and equipment department.
- A person in charge of facility and equipment should establish facilities and equipments reflecting the above considerations, clarify details of the establishment and operational considerations of those facilities and equipments, and present them to a manufacturing department.
- A manufacturer should fully understand the above information, implement validations, perform appropriate operations and controls in conformity to the established facilities and equipments, and records results of operations and controls.

6.1.1 Technical Information to Establish New Facilities and Equipments

To establish new facilities and equipments in conformity to manufacturing of the drug, the facility and equipment department should set up required specifications (so called objectives) based on considerations presented by the R&D department, and realize functions in view of considerations specific to the facilities and equipments. In this regard, some functions may be combined, and it is required to prepare definite rationale for establishing functions. To comply with GMP, it is prerequisite to prepare documents of processes through specification decision and realization of functions as well as qualification evaluation, which can be explained to the third party (so called design qualification) as technical information.

Information Necessary for the Establishment of Facilities and Equipments

Information necessary for the establishment of facilities and equipments in conformity to GMP are classified into the following three categories.

1) Required Functions of facilities and equipments necessary for quality assurance of the drug
2) Required functions of facilities and equipments specific to manufacturing methods (manufacturing processes)
3) Basic required functions necessary for GMP compliance such as prevention of contamination, and human failures, etc.

Regarding 1) and 2), the person in charge of research and development should extract information affecting facilities and equipments from results of quality design during drug development (information on composition, manufacturing methods and specification), review results of scale-up and quality variability factors during possible pilot research, fully understand them and present documents containing clarified considerations of GMP compliance specific to subject drugs and manufacturing methods (manufacturing processes) to the person in charge of facility and equipment.

The person in charge of facility and equipment should document interpretations of the above information in forms such as "quality requirement specification" and present the documentation to the parson in charge of research and development to confirm each other. The both persons should clarify differences of each thought by conforming

documents prepared from their own perspectives, and establish certain input data of facility and equipment establishment by obtaining necessary or insufficient evidence data, extracting insufficient data, and feeding back them to the R&D department.
Concerning 3), information can be collected by sorting out and reviewing GMP requirements for properties of the drug and manufacturing methods and organization of facilities and equipments. Degree of contamination and acceptable contamination level of the subject drugs and acceptable limit of residues are important to determine prevention level of contamination and cleaning methods at the facilities and equipments. Since policies on facilities and equipments such as multi-item production level and automatic production level may have a great impact on granting levels to facilities and equipments regarding prevention for human failures such as cross-contamination or mix-up, measures should be taken in view of properties of drugs and manufacturing methods which are to be used at the facilities and equipments to be established.

Information on the Establishment of Facilities and Equipments

Establishing facilities and equipments includes actions to upgrade facilities and equipments to be functions for achieving established objectives (required specifications), plan and design details while reflecting considerations specific to the facilities and equipments, construct them in time for the start of manufacturing, and perform qualification evaluation upon the trial operation, while it is important to transfer results of the establishment of facilities and equipments to the drug manufacturer so that the manufacturer can implement validations and manufacturing.
It is important for GMP compliance to shape into documents the achievements of series of activities (design, procurement, building, construction, trial operation, etc.) from initial stages of establishment (plan and design), the trial operation through qualification evaluation, and present them to the third party.

6.1.2 Technical Information When Applied to Established Facilities and Equipments

The drug is often manufactured in existing facilities and equipments. Although there are limitations attributable to the characteristics of the existing facilities and equipments, technical documents should be prepared to demonstrate that those facilities and equipments meet required specifications for quality assurance. Basic contents of the technical documents are similar to those of new facilities and equipments, while only difference is documentation method.

Information necessary for the establishment of existing facilities and equipments are classified into the following three categories as in the case of the new facilities and equipments.

1) Required functions of facilities and equipments necessary for quality assurance of the drug
2) Required functions of facilities and equipments specific to manufacturing methods (manufacturing processes)
3) Basic required functions necessary for GMP compliance such as prevention of contamination, and human failures, etc.

Concerning considerations of applications to existing facilities and equipments in 1) and 2), existing functions should be clarified, and it should be verified that the functions are maintained by maintenance and inspection including routine monitoring. Then, activities are required to compare documents such as "quality requirement specification" prepared as in the case of input information of new facilities and equipments with existing functions and maintenance conditions in the existing facilities and equipments, and identify differences between them. If there are any differences, input information should be realigned by feedback of necessary and insufficient evidence data and other required information to the R&D department.
Regarding 3), activities are required to compare properties of facilities and equipments such as multi-item production level and automatic production level of the existing facilities and equipments as well as granting levels to facilities and equipments regarding prevention for human failures such as cross-contamination or mix-up with conditions for quality assurance attributable to properties of subject drugs and manufacturing methods, and to clarify differences between them. If there are any differences, measures should be taken as in the cases of 1) and 2).

6.2 Technology Transfer of Test Methods

This chapter exemplifies items to be included in the development report and the technology transfer plan both of

which are important to technology transfer of test methods, and describe general concepts.

6.2.1 Development Report of Test Methods

The main objective of documenting development report of test methods is to make quality assurance of drugs more secured one by appropriately transferring technical information accumulated at each stage from design of test methods through those implementation between various departments (organizations).
Therefore, it is desirable that the development report should include details of test methods, information related to drug properties such as physicochemical properties, biological properties, and safety information, background of development of the test methods and rationale for the establishment, and validity and rationale for specifications from early research and development phase to manufacturing.

Specifications and Test Methods

Test methods subject to technology transfer include the following.

- Test methods for drug substances
- Test methods for drug products
- Test methods for raw materials and labeling and packaging material
- Test methods for in-process tests
- Test methods for drug residue tests
- Test methods of various tests concerning environmental load (waste and wastewater treatment, etc.)

Rational for Specifications and Background

Especially for historic records of specifications of contents, impurities, and degradation products, rationales for their establishment and changes should be included.

Results of Validations

Results of analytical validations for established test methods should be described.

Development History of Important Test Methods (Development Report on Test Methods)

Concerning test methods necessary for the evaluation of product quality and important attributes, development and change histories including their rationales should be described. The test methods include the followings.

- Test methods to measure contents and organic impurities
- Test methods to measure residual solvents and volatile compounds
- Dissolution tests for oral solid drug products
- Test methods to measure residual and mixed minerals in drug substances such as metals
- Test methods to evaluate physicochemical properties of drug substances and drug products such as polymorphism and hygroscopicity

It is especially useful to describe in detail significant operating conditions considered to affect test results (including items concerning test equipments, reagents and test solutions, and reference standards) in relation to developmental history of tests so that transferred party can effectively understand transferred information and attain its technology as well as the description may contribute to future modification of test methods.
Developmental history of already established test methods specified in pharmacopoeia, etc. need not to be described; however, it is required to indicate rationale for adopting the test methods as well as that the test methods may apply to the samples to be analyzed.

Summary of Test Results (Summary of Batch Analysis)

Summary of test results of batches used to develop test methods described in the development report should be described as chart including references to raw data.

Reference Standards

Reference standards to be used in tests of subject substances (drug substances, chemically related substances, etc.) should be described. The description should include methods of manufacturing, purification, evaluation for the purity and quality, and storage.

Other information

Items other than the above such as information of drug substances and drug products (properties, stability, manufacturing methods, and formula, background of drug development, containers, etc.) should be described if necessary. If those information are described in the Common Technical Document (CTD), references to raw data should be included.

6.2.2 Technology Transfer Plan of Test Methods

For technology transfer of test methods, it is required to clarify validation range and acceptance criteria of conformity of technology transfer regarding individual test methods to be transferred. The validation range (e.g. full validations, reproducibility, etc.) should be judged on the basis of results of evaluation of technologies, facilities and equipments of transferred party, and the range may be influenced by information to be contained in the technology transfer documentation.

For comparative evaluation of test results, samples (including dose range, number of batches, etc.), specific test methods and evaluation methods to be used in the transferring and transferred parties should be specified. Acceptance criteria should be established for each test method of subject items on the basis of accumulated test results of the past and analytical validation data, and rationales for the acceptance criteria should be clearly described.

Technical information to be described in or attached to the technology transfer plan (including references to the development report) are shown as follows.

Information of Raw Materials

- Summary including physical and chemical properties and stability
  - Name and structural formula
  - Stability data
- Specifications and test methods
  - Specific test methods and specifications
  - Change history of specifications and test methods and its rationale
  - Results of analytical validation
- List of reference standards (Test results should be attached.)
- Information of toxicity and safety for laboratory use
- List of subject samples for comparative evaluation and their test results

Information of Drug Substances

- Summary including physicochemical properties and stability
  - Name and structural formula
  - Elucidation of chemical structure
  - Possible isomers
  - Stability data (including severe test data)
- Batch records
  - Chemical synthesis methods of subject batches
  - Analytical data of batches
  - Impurity profile of representative batch
- Specifications and test methods
  - Specific test methods and specifications (including items related to efficacy such as particle size distribution, polymorphism, crystallinity, and hygroscopicity)
  - Change history of specifications and test methods and their rationales
  - Results of analytical method validation
- List of reference standards (Test results should be attached.)
- Development report on test methods (Interim report is acceptable depending on development phases.)
- Information of toxicity and stability for laboratory use
- List of subject samples for comparative evaluation and their test results

Information of Drug Products

- Summary including formula and stability
  - Active ingredients and contents

- Elucidation of decomposition mechanism and products
- Stability data (including severe test data)
- Storage conditions and expiry date (if established)

- Analytical data of batches
- Specifications and test methods
  - Specific test methods and specifications (including items related to efficacy such as particle size distribution, dissolution)
  - Change history of specifications and test methods and its rationale
  - Results of analytical method validation
  - List of reference standards (Test results should be attached.)
  - Development report on test methods (Interim report is acceptable depending on development phases.)
  - Information of safety for laboratory use
  - List of subject samples for comparative evaluation and their test results

Information on Implementation of Technology Transfer

- Persons in charge of planning, checking and settlement of technology transfer
- Test methods
- Objectives
- Persons in charge of transferring and transferred parties
- Training plan (including explanation of test methods and demonstration)
- Plan of comparative evaluation study
  - Samples: Lot No. (including rationale for the number of lots), storage condition during test, and handling after the completion of the test (disposal or return to the transferred party, etc.)
  - Test period
  - Number of repeated tests
  - Handling of data (Handling method)
  - Retest and handling of outlier
  - Acceptance criteria
  - Storage of raw data (storage department, storage place, and duration, etc.)
  - Judge (person in charge of judgment in the transferring party)

6.3 Technology Transfer of Drug Substances

During R&D processes prior to technology transfer of drug substances, information indicated in 6.3.1 to 6.3.3 should be collected, and based on these information, technology transfer documentation including those indicated from 6.3.4 onward should be prepared.

6.3.1 Information to be Collected During Quality Design (Research Phase)

Items Concerning Raw Materials, Intermediates and Drug Substances

Items Concerning Raw Materials, Intermediates and Drug Substances

- Impurity profile and information on residual solvents (structure of impurities and route of synthesis)
- Information on descriptions of crystals of drug substances (crystallization, salt and properties of powders)
- Information on stability and description (raw materials, drug substances (including packaged drug substances), intermediates, solutions, crystallized solution, and humid crystals)
- Information on safety of drug substances, intermediates, and raw materials (Material Safety Data Sheet (MSDS))
- Information on animal origins of raw materials, etc.
- Information on packaging materials and storage methods (quality of packaging materials, storage temperature, and humidity)
- Expiry and retest dating
- Information on reference standards and seed crystals (method of dispensing, specifications and test methods, and storage methods)

Items Concerning Manufacturing Methods

- Information on manufacturing methods (synthetic routes and purification methods)
- Information on operating conditions (control parameters and acceptable range)
- Information on important processes and parameters (identification of processes and parameters which will

affect quality)
- Information on in-process test
- Information on rework and reprocessing (processes and methods)
- Basic data concerning manufacture (properties, heat release rate, reaction rate, and solubility, etc.)
- Data concerning environment and safety (environmental load and process safety)

Items Concerning Facilities and Equipments
- Information on equipment cleaning (cleaning methods, cleaning solvents, and sampling methods)
- Information on facilities (selection of materials, capacity, and equipment types, and necessity of special equipments)

Items Concerning Test Methods and Specifications
- Information on specifications and test methods of drug substances, intermediates, and raw materials (physicochemical, microbiological, pyrogenic substances and physicochemical properties, etc.)
- Validations for test methods of drug substances and intermediates

6.3.2 Items to be Checked in the Review of Scale-up

Manufacturing processes of drug substances often involve handling of unstable chemical substances, and they have characteristics accompanied with chemical changes. Therefore, scale-up should be considered with much attention to prediction of handling period for each operational unit and stability of subject compounds during operation, and conditions of scale-up should be established.

Also, since factors of equipments may have significant influence on qualities regarding scale dependent parameters of operational parameters, considerations should be given in this regard.

Items to be confirmed in reviewing scale-up of reaction and crystallization processes are shown as follows:

Items to be Confirmed in Reviewing Scale-Up of Reaction Processes
- Reproducibility of temperature changes and its effects (effects of delay in temperature up and down on quality)
- Effects of churning in heterogeneous and semi-batch reactions (formations of concentration distribution and diffusion-controlled zone)
- Prediction and effect of operation period of consecutive reaction or exothermic reaction in semi-batch reactors (extension of operation period due to insufficient capacity of facilities and its effects on quality)
- Balance between heat release rate and heat dissipation capacity (temperature changes of exothermic reaction and its effects)
- Effects of facilities (validity of required capacity of utility, temperature distribution, and effects of overheating of laminar film, etc.)
- Confirmation of fluctuations due to scale-up (phenomenon which did not appear in the laboratory and small-scale manufacturing)

Items to be Confirmed in Reviewing Scale-up of Crystallization Processes
- Effects of churning (effects on particle size and polymorphism, and selection of scale-up factors)
- Reproducibility of temperature changes (reproducibility of established temperature changes and effects on quality)
- Effects on facilities (temperature distribution, changes in flow condition, effects of local concentration distribution and temperature distribution, and supercooling of laminar film)
- Prediction of time for solid-liquid separation and its effects (stability of crystallized solution waiting for filtration)
- Confirmation of operability (problems at actual equipment levels such as crystallized solution emission, transfer, and churn load)

6.3.3 Elucidation of Quality Variability Factors

To elucidate quality variability factors, the following items should be reviewed during quality design through scale-up review.

Processes Affecting Quality

To identify processes which may affect quality of final drug substances, such as processes to generate final substances, structures with pharmacological activities, and processes that can remove residual impurities in drug

substances and processes where impurities unremoval in purification are generated.

Establishment of Important Parameters Affecting Quality

Among parameters controlling the above processes, those which may affect the quality of final drugs such as generation and elimination of impurities, and physiochemical properties of the final drug substances should be investigated as subjects to change control, and control ranges of parameters which affect the quality should be established as important parameters. The important parameters are subject to validation. Parameters not affecting the quality are not subject to validation, but their change histories should be recorded.

6.3.4 Development Report on Drug Substances

The development report should include the followings:

- Development history including different synthetic methods used to manufacture investigational drugs
- Finally determined chemical synthetic route
- Change history of processes
- Quality characteristics of manufactured batches
- Specifications and test methods of intermediates and final drug substances
- Rationale for establishment of important processes
- Important parameters and control range
- References to existing reports and literatures, etc.

6.3.5 Technology Transfer Information of Drug Substances

Technology transfer information which transferring party should compile are shown as follows.

- **Information on Manufacturing Methods**
  - Development report on synthetic drug substances or those corresponding to the report
  - Plan and report of process validations
  - Items of in-process control: in-process test (test methods and specifications)
  - Investigation report on causes of abnormalities (if occurred)

- **Information on Cleaning Procedures**
  - Cleansing instructions
  - Record of cleaning
  - Plan and report of cleaning validation
  - Test methods and specifications
  - Validation report on analytical methods used for cleaning validations

- **Information on Analytical Methods**
  - Development report on analytical methods or those corresponding to the report
  - Test methods and specifications (raw materials, intermediates, final drug substances, and container/closure)
  - Validation report on release test methods
  - Stability test (validation report on analytical method, plan/report of stability test, container form, reference standard, and relevant reports)
  - Investigation report on causes of out-of-specification (OOS) test results (if occurred)

- **Information on Methods of Storage/Transportation**
  - Container/closure system
  - Expiry and retest dating
  - Conditions of transportation
  - Information on sensitivity to temperature, humidity, light, and oxygen
  - Instructions of temperature monitoring for drug substances which need cold storage

- **Information on Facilities**
  - Structural materials

- Category and type of main facility
- Important facilities for final processing that may affect physicochemical properties (particle size and surface conditions, etc.)

- **Information on Environmental Management (Drug Substances for Injection and Highly Active Substances, etc.)**
  - Clean area (temperature, humidity, microorganism monitoring, airborne particles, and control of differential pressure)
  - Information on safety
    - Safety information of raw materials, intermediates, and final drug substances
    - Information on degradability
    - Information on dust explosion
    - Information on deflagration

- **Information on Industrial Hygiene/Occupational Health**
  - Protection for operators
  - Protection for products

6.4 Technology Transfer of Drug Products

During R&D processes prior to technology transfer of drug products, information indicated in 6.4.1 to 6.4.3 should be collected, and based on these information, technology transfer documentation including those indicated from 6.4.4 onward should be prepared.

6.4.1 Information to be Collected During Quality Design (Research Phase)

(Oral solid formulation)

Items Concerning Compositions

- Physicochemical properties of drug substances (crystallinity, melting point, dissolution, distribution coefficient, hygroscopicity, degradant, impurities, particle size, wettability, moisture, handling, etc.)
- Biopharmaceutical properties of drug substances (hygroscopicity and dose dependency, etc.)
- Stability of drug substances (temperature, humidity, and light)
- Compatibility of drug substances with inactive ingredients
- Formula design of drug products in clinical phases and its rationale (hygroscopicity, dose dependency, etc.)
- Formula design of final drug products and its rationale (reasons for combining individual inactive ingredients and validities)
- Change histories of formula during development and relations with final drug products
- Packaging design
- Stability of drug products (temperature, humidity, and light)
- Information on drug substances, inactive ingredients, and packaging materials (specifications, manufacturers, Drug Master File, MSDS, etc.)
- Information on origins of drug substances and inactive ingredients (raw materials of animal origins, etc.)

Items Concerning Manufacturing Methods

- Information on selection of dosage forms (direct compressed tablets, dry and wet granulation, agitation fluidized bed granulation, uncoated tablets, coated tablets, properties of inactive ingredients, etc.)
- Information on manufacturing methods of drug products in clinical phases (manufacturing flows, manufacturing conditions, in-process control, etc.)
- Manufacturing methods of final prescribed drug products (manufacturing flows, manufacturing conditions, in-process control, scale-up, validation, etc.)
- Information on other important processes and manufacturing procedures (determination of granulation end-point, determination of mixing time with lubricants, cleaning methods, cleaning validation, etc.)

Items Concerning Facilities and Equipments

- Information on equipment cleaning (cleaning methods, cleaning solvents, sampling methods, etc.)
- Information on equipments (selection of materials, capacity and equipment types, necessity of special equipments, etc.)

Items Concerning Test Methods and Specifications

- Specifications and test methods of drug substances (physicochemical test, microbial test, etc.)
- Specifications and test methods of inactive ingredients (grade, physicochemical test, microbial test, etc.)
- Specifications and test methods of packaging materials (specifications, physicochemical test, microbial test, etc.)
- Acceptance criteria for product assessment (internal control specification based on stability, etc.) and specifications for application (approved specifications to ensure expiry date)
- Validation for test methods of drug substances and products

(Injectable Solutions (sterile drug products))

Items Concerning Compositions

- Information on formula design (reasons for combining individual inactive ingredients and validities; pH, relations between inactive ingredients and stability, overages, etc.)
- Information on stability of drug substances (heat, light and oxygen)
- Information on safety of drug substances and raw materials (MSDS)
- Information on origins of drug substances and raw materials (raw materials of animal origins, etc.)
- Formula design of drug products in clinical phases and its rationale (dissolution, change histories of dosage forms, etc.)
- Formula design of final drug products and its rationale (reasons for combining individual inactive ingredients and validities)
- Disparities in quality between different lots of drug substances and raw materials, stability of lots of raw materials, and effects on impurities
- Basic documents to ensure sterilization and cleaning in view of composition
- Information on stability of drug products (heat, light, oscillation, and oxygen)
- Change histories of formula in the process of development and rationale to ensure equivalence

Items Concerning Manufacturing Methods

- Information on selection of dosage forms (solution, freeze dry or powder preparations; relations with stability)
- Information concerning rationale for container/closure system and its validity (effects on stability such as eluate from containers or closures, interactions between drug products and containers (absorbability), and sealing performance, etc.)
- Information on initial design of manufacturing methods (aseptic manipulation or final sterilization method; effects of heat sterilization on stability)
- Information on selection of process filters (absorbability, etc.)
- Process design and important processes (test items in important processes and specifications)
- Rationale for design to ensure sterilization and cleaning in view of manufacturing methods

Items Concerning Facilities and Equipments

- Information on equipment cleaning (cleaning methods, cleaning solvents, and sampling methods)
- Information on facilities (selection of materials, capacity, and equipment types, and necessity of special equipments)

Items Concerning Test Methods and Specifications

- Specifications and test methods of drug substances (physicochemical test, microbial test, pyrogenic substances, etc.)
- Specifications and test methods of inactive ingredients (physicochemical test, microbial test, pyrogenic substances, etc.)
- Specifications and test methods of container/closure system (physicochemical test, microbial test, pyrogenic substances, etc.)
- Specifications and test methods of packaging materials (specifications, etc.)
- Specifications and test methods of products (physicochemical test, microbial test, pyrogenic substances,

etc.)

- Specifications of shipment (internal control specifications in view of stability, etc.) and specifications of products (approval specifications to ensure expiry date)
- Validation of test methods of drug substances and products
- Reference standard and reference substance (dispensing methods, specifications and test methods, and storage methods and stability, etc.)

6.4.2 Scale-up Validation and Detection of Quality Variability Factors (Development Phase)

(Oral solid formulation)

- Mixing conditions in mixing process of raw materials (uniformity of contents)
- Granulation conditions in granulation process (determination of granulation end-point, tablet hardness, and dissolution)
- Drying end-point in drying process (tablet hardness, compression problems, and stability)
- Mixing conditions in granulation mixing process (uniformity of contents)
- Mixing conditions in lubricant mixing process (tablet hardness, and dissolution)
- Time series fluctuations in tablet compressing process or filling process (tablet weight, tablet hardness, and uniformity of contents)
- Fluctuations due to raw materials (processes in manufacturers of raw materials and changes in material qualities, etc.)
- Fluctuations due to facilities (exchange of consumable parts, changes of equipments, and changes in manufacturing processes including automated processes, etc.)

(Injectable Solutions (Sterile Drug Products))

- Dispersion of final moisture and contents between different shelves and/or within the same shelf in freeze drying process
- Changes and dispersion in water content in rubber closures of vials
- Dispersion of contents and impurities, etc. after the final sterilization
- Concerning fluctuations of raw materials, dispersion in particle size which may affect solubility, peroxide which affect stability, and viable cell counts which affect abacterial situations should be evaluated.
- Concerning facilities, effects of temperature distribution within facilities and effects of changes in important parameters on product quality should be evaluated. Especially for drugs that are highly sensitive to oxygen, water and light as well as preparations with minute content such as protein, relations between conditions of facility operations and stability should be fully understood.
- Validity of solution preparation process (uniformity of contents of all raw materials and stability in solution conditions, etc.)
- Validity of sterile filtration processes (completeness, conformity of filtration process and drug solution, stability of filtrated drug solution, and initial disposal rate, etc.)
- Microorganism capture efficiency of barrier filter (validation data)
- Rationale for cleaning conditions in the container/closure system (cleaning validation, drying and residual moisture, etc.)
- Rationale for sterilization conditions in the container/closure system (validations of sterilization and pyrogenic substances removal, residual moisture of closures, etc.)
- Validity of filling processes (accuracy of filling, conformity of filling system and drug solution, stability of filled drug solution, and initial disposal rate, etc.)
- Validity of freeze-dry process (freeze-dry conditions, uniformity of inside of freeze-dry equipment, water contents and stability, etc.)
- Validity of capping and metal sealing (replacement rate of inactive gas in a head space and stability of the inactive gas)
- Validity of final sterilization process (validation of sterilization)
- Validity of test process (development of test process, types of foreign substances, and accuracy of test)
- Development of cleaning methods of facilities and validation of cleaning