Guideline for Technology Transfer

1. Preface

1.1 Background

According to the revised Japanese Pharmaceutical Affairs Law in July 2003, the manufacturing approval system has been replaced with the manufacturing and marketing approval system in April 2005, resulting in a big change in the Japanese pharmaceutical system and regulations. Under these circumstances, it is highly desired to improve 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 manufacture as well as assure stable quality transferred for many reasons between contract giver and contract acceptor during manufacture. Also, to assure the drug quality, it is desired 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 between stake holders related to drug manufacturing. Fur that purpose, it is necessary to establish an appropriate guideline for the technology transfer and upgrade 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 necessary information to transfer technology from R&D to actual manufacturing by sorting out various information obtained during R&D;
2) To elucidate necessary information to transfer technology of existing products between various manufacturing places; 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 production of drugs (chemically synthesized drug substances and drug products) and the technology transfer related to post-marketing changes in manufacturing places. 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 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

The drug quality is designed based on basic data concerning efficacy and safety 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 in process of reviewing factory production and 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 of product, 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 manufacture. Even if the production starts, the technology transfer will take place in processes such as changes in manufacturing places. 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 often performed in phases from late preclinical studies to Phase II 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 and Detection of Quality Variability Factors (Development Phase)

2.2.1 Research for Factory Production

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 factory production of drugs designed on the basis of results from small-scale experiments. In general, this process is called the research for factory production where the quality of design will be upgraded to be the quality of product.

2.2.2 Consistency between Quality and Specification

When the product specification is established on the basis of the quality of product determined in the above, it is required to verify that the specification adequately specifies the product quality. (Consistency between quality and specification)

In short, the consistency between quality and specification is to ensure in the product specification that the quality predetermined in the quality design is assured as the manufacturing quality, and the product satisfies the quality of design.

In reviewing factory production, 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 limits of manufacturing formula (compositions and manufacturing methods) and upper and lower of control limits of the product specification should be fully understood, and the consistency between the product quality 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 revised through appropriate change controls, if necessary.

2.2.3 Assurance of consistency through development and manufacturing

To make developed product have indications as predetermined in clinical phases, the quality of design should be reproducible as the quality of product (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 transferred party in charge of manufacturing, 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 developed product are generated from data of a limited amount of batches, various standards have been established from the limited data, and quality evaluation method established in development phase is not always sufficient for factory production. For stable production of consistent products, it is fundamental to fully refer to information of similar products of the past maintained by the manufacturer when research for factory production is implemented, and this is a key to successful technology transfer.

2.3 Technology Transfer from R&D to Production

Transfer of technical information is necessary to realize manufacturing formula established in the above in the actual production facility. In the past, the technology transfer was mainly seen as standard transfer or as technology instruction from technology department to production 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 (know-how) 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 production department, technical information to be transferred should be complied as research and development report (development report and recommend to use the development report as a part of technology transfer documentations).

2.4 Validation and Production (Production Phase)

Production is implemented after various validation studies verify that it is able to stably produce 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 Production Phase and Technology Transfer of Marketed Products

As a result of technology transfer, products are manufactured and brought to the hands of consumers. Since the technical information of developed products are obtained from data of a limited amount of batches, various standards have been established from the limited data, and quality evaluation method established in development phase is not always sufficient for factory production, it is highly desired to feed back and accumulate technical information obtained from repeated production, if necessary. Also, it is important to appropriately modify various standards established before on the basis of these information, and accountability (responsibility for giving sufficient explanation) and responsibility (responsibility for outcomes of actions) for design and manufacturing should be executed. For this purpose, appropriate feedback system for technical information and documentation management of technology transfer should be established. For drugs as they have long product shelf 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.

Since manufacturing places of marketed drugs are often changed for many reasons, already standardized test methods and manufacturing methods are sometimes transferred to other offices or other companies. In this case, subject drug should contain rigorous equivalency including bioequivalency rather than consistency needed for newly developed drugs. Although there are no significant differences between existing drugs and development drugs in terms of technology transfer, it is desirable that subject technical information of the existing drugs should be compiled in forms such as product specification. Also as in the case of technology transfer from research and development to production, 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.

3. 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 necessary. Procedures and documentation of technology transfer are indicated as follows. Items to be specified in the documentation will be referred in detail in the 5th chapter.

3.1 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.

It is desirable that this organization complies with GMP.

3.2 Research and Development Report

To realize quality assurance at all stages from drug development to manufacturing, transfer of technical documents concerning product development or corresponding documents should be considered. The research and development report (development report) is a file of technical information necessary for drug manufacturing, which is obtained from pharmaceutical development, and the research and development department is in charge of its documentation. This report is an important file to indicate rationale for the quality design of drug substances and drug products including information such as raw materials, components, manufacturing methods, specifications and test methods. The development report should also include the above rationales, and it is desirable to document the report before the approval inspection. 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. The following exemplifies information to be contained in the development report.

Historical data of pharmaceutical development of new drug substances and drug products at stages from early development phase to final application of approval

Raw materials and components

Synthetic route

Rationale for dosage form and formula designs

Rationale for design of manufacturing methods

Rational and change histories of important processes and control parameters

Quality profiles of manufacturing batches (including stability data)

Specifications and test methods of drug substances, intermediates, drug products, raw materials, and components, and their rationale (validity of specification range of important tests such as contents,

impurities and dissolution, rationale for selection of test methods, regents, and columns, and traceability of raw data of those information)

3.3 Technology Transfer Documentation

Technology transfer documentation are 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 always readily available and traceable. 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. 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.

3.3.1 Product Specification (Product Specification File)

The product specification is to compile information which enable 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 incorporate various information obtained after the start of production of the product, and be revised as appropriate.
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

} Development Report

3.3.2 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.

3.3.3 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.

3.3.4 Check and Approval by Quality Assurance Department

It is desirable that the quality assurance department should establish confirmation process for all kinds of technology transfer documentation, and should check and approve the documentation.

3.4 For 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.

3.5 Manufacturing Related Documents Including Drug Product Standards

The transferred party should compile documents such as drug product standards 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 transferring party should make necessary confirmation for these documents.

3.6 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.

3.7 Points of Concern for Post-Marketing Technology Transfer

While there are no fundamental differences in technology transfer between new development product and marketed product, some marketed products do not have development report which can be used as raw data. In this case, a development report needs not to be newly documented; however, it is strongly recommended that the file should be prepared including information of specified items. This file can be used as reference file in case of regular inspection.

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

The1st to 3rd chapters indicate technology transfer processes and procedures. This chapter describes practical concept and contents of technical information to be included in the technology transfer documentation.

4.1 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 that purpose, the following technical information should be transferred.

- The R&D department should clarify considerations of GMP compliance specific to subject drugs and manufacturing methods (manufacturing processes), and present them to a facility and equipment department.
- The facility and equipment department should establish facilities and equipments reflecting the above considerations, clearly details of the establishment and operational considerations of those facilities and equipments, and present them to a drug manufacturing department.
- The drug manufacturing department 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.

4.1.1 Technical Information to Establish New Facilities and Equipments

To establish new facilities and equipments in conformity to manufacture of subject drugs, 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 qualifications, which can be explained to the third party (so called design qualification (DQ)) as technical information.

Information Necessary for the Establishment of Facilities and Equipments (Input Information)

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 subject drugs
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 drug manufacturing department should extract information affecting facilities and equipments from results of quality design during drug development (information on composition, manufacturing and specification), review results of scale-up and quality variability factors during possible factory production, fully understand them and present documents containing

clarified considerations of GMP compliance specific to subject drugs and manufacturing methods (manufacturing processes) to the facility and equipment department.
The facility and equipment department should document interpretations of the above information in forms such as “quality requirement specification” and present the documentation to the R&D department to confirm each other. The both departments 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 unnecessary evidence data, extracting unnecessary 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 subject drugs 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 all properties of drugs and manufacturing methods which are to be used at the facilities and equipments to be established.

Information of Results of the Establishment of Facilities and Equipments (Output Information)

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 qualifications upon the trial operation, while it is important to transfer results of the establishment of facilities and equipments to the drug manufacturing department so that the department can implement validations and production.
It is important for GMP compliance to prepare documents including series of activities from initial stages of establishment (plan and design), the trial operation through qualifications and present them to the third party. In short, output information should be documented by extracting facility and equipment related information from documents compiled during the establishment of facilities and equipments (design, procurement, construction, and trial operation, etc.) to assure the quality of the subject drugs. Cross checking of input and output information are equal to series of qualifications such as DQ, IQ and OQ, while results of qualifications are integrations of output information.

4.1.2 Technical Information When Applied to Established Facilities and Equipments

Subject drugs are 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 (so called objectives) for quality assurance of drugs, and this kind of preparation can be equal to the establishment of facilities and equipments in conformity to the subject drug manufacturing. Basic contents of necessary 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 subject drugs
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 unnecessary 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).

4.2 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.

4.2.1 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 production.

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 components
- Test methods for in-process tests
- Test methods for drug residue tests
- Test methods for environmental tests

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 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 important to describe in detail significant operating conditions (including test equipments, reagents and test solutions, and items concerning 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. Also, failure mode factors for the test methods identified during reviewing process may be a part of important information.
Developmental history of already established test methods specified in pharmacopoeia, etc. need not to be described; however, the applicability of such pharmacopoeia method and rationale for adopting the test methods should be described.

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 tables including references to raw data.

Reference Standards

Reference standards to be used in tests of subject substances and impurities 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.

4.2.2 Technology Transfer Plan

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.
To compare 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 stability 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
  - Physical and chemical properties (including physicochemical properties)
  - 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
  - Formula and contents
  - Elucidation of dissolution profile
  - 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 and hygroscopicity)
  - 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 toxicity and stability 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 (test method number
- 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)

4.3 Technology Transfer of Drug Substances

During R&D processes prior to technology transfer of drug substances, information indicated in 4.3.1 to 4.3.3 should be collected, and based on these information, technology transfer documentation including those indicated from 4.3.4 onward should be prepared.

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

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, crystal slurry, 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)
- 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 control
- Information on reprocess and rework (places 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 (physical and chemical, microbiological, endotoxin and physicochemical properties, etc.)
- Validations for test methods of drug substances and intermediates

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

Manufacturing processes of drug substances often involve handling of unstable chemical substances, and they are unsteady processes 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 pattern 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 pattern of exothermic reaction and its effects)
- Effects of facilities (validity of required capacity of utility, and effects from temperature distribution, dead volume, and overheating of laminar film)
- Confirmation of fluctuations due to scale-up (phenomenon which did not appear at flask levels)

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 pattern (reproducibility of established temperature pattern and effects on quality)
- Effects on facilities (temperature pattern, changes in flow pattern, effects of local concentration distribution and temperature distribution, supercooling of laminar film, and scaling)
- Prediction of time for solid-liquid separation and its effects (stability of slurry waiting for filtration)

- Confirmation of ease of operation (problems at actual equipment levels such as slurry emission, transfer, and churn load)

4.3.3 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 impurities that cannot be eliminated in purification.

Establishment of Critical Parameters Affecting Quality

To search parameters among those controlling the above processes which may affect quality of final drug substances, such as generation and elimination of impurities, and physicochemical properties of final drug substances, and establish range of control.

Establishment of Other Parameters

Parameters not affecting quality of final drug substances are not subject to validations; however, they are subject to change control and change histories should be recorded.

4.3.4 Development Report on Synthetic Drug Substances

Items concerning drug substances and intermediates to be described are as follows:

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

4.3.5 Technology Transfer of Synthetic Drug Substances from R&D Department to Manufacturing Department

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 development report
  - Master batch records of manufacturing of investigational drugs or samples (format of manufacturing records)
  - Manufacturing records of investigational drugs or samples (batches for establishment of specifications for application, validation batches, etc.)
  - Plan and report of process validations
  - Items of in-process control: IPC (test methods and specifications)
  - Investigation report on causes of abnormalities (if occurred)

- **Information on Cleaning Procedures**
  - Master batch record of cleaning
  - Record of cleaning
  - Plan and report of cleaning validation

- Test methods and specifications
- Validation report on analytical methods used for cleaning validation

- **Information on Analytical Methods**
  - Development report on analytical methods or those corresponding to the development 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 OOS (out of specification)
- **Information on Methods of Storage/Transportation**
  - Container/closure system
  - Date of retest/expiry date
  - 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
  - Critical 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 Potent Substances, etc.)**
  - Cleaning area (temperature, humidity, microorganism monitoring, airborne particles, and control of differential pressure)
  - Information on safety
    - ✧ Safety information of hazardous 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

4.4 Technology Transfer of Drug Products

During R&D processes prior to technology transfer of drug products, information indicated in 4.4.1 to 4.4.3 should be collected, and based on these information, technology transfer documentation including those indicated from 4.4.4 onward should be prepared.

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

(Solid form)

Items Concerning Compositions

- Physicochemical properties of drug substances (crystal form, melting point, solubility, distribution coefficient, hygroscopicity, degradation products, impurities, particle size, particle size distribution, wetness, moisture, and handling, etc.)
- Biopharmaceutical properties of drug substances (hygroscopicity and dose dependency,

etc.)

- Stability of drug substances (temperature, humidity, and light)
- Incompatibility of drub substances with raw materials of drug products
- Initial formula design of drug products (absorbability and dose dependency, etc.)
- Formula design of prototype drug products
- Formula design of final drug products (reasons for combining individual inactive ingredients and validities)
- Change histories of formula during development and rationales for assurance of equivalence
- Packaging design
- Stability of drug products (temperature, humidity, and light)
- Information on drug substances, raw materials of drug products, and packaging materials (such as specifications, packaging manufacturers, Drug Master File (DMF) and MSDS)
- Information on origins of drug substances and raw materials of drug products (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, and coated tablets)
- Manufacturing methods of initial drug products (manufacturing flows, manufacturing conditions, and in-process control)
- Manufacturing methods of prototype drug products (manufacturing flows, manufacturing conditions, and in-process control)
- Manufacturing methods of final prescribed drug products (manufacturing flows, manufacturing conditions, in-process control, scale-up, and validation)
- Information on other important processes and manufacturing procedures (information on determination of granulation end-point, determination of mixing time with lubricants, cleaning methods, and cleaning validation, etc.)

Items Concerning Facilities and Equipments

- Information on equipment cleaning (cleaning methods, cleaning solvents and sampling methods)
- Information on equipments (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 (physical and chemical, and microorganism)
- Specifications and test methods of raw materials of drug products (grade, physical and chemical, and microorganism)
- Specifications and test methods of packaging materials (specifications, physical and chemical, and microorganism)
- Acceptance criteria for product assessment (internal control criteria based on stability, etc.) and specifications for application (specifications for approval 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, and overages, etc.)
- Information on stability of drug substances (heat, light and gas)
- 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.)
- 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 gas)

Items Concerning Manufacturing Methods

- Information on selection of dosage forms (solution, freeze dry or powder preparations; relations between those dosage forms and stability)
- Information on determination of container/closure system and its validity (eluting materials from containers or closures, interactions between drug products and containers (absorbability), 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 (physical and chemical, microbiological, and endotoxin, etc.)
- Specifications and test methods of raw materials of drug products (physical and chemical, microbiological, and endotoxin, etc.)
- Specifications and test methods of containers and closures (physical and chemical, microbiological, and endotoxin, etc.)
- Specifications and test methods of packaging materials (specifications, etc.)
- Specifications and test methods of products (physical and chemical, microbiological, and endotoxin, 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.)

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

(Solid Form)

- Mixing conditions in mixing process of raw materials (uniformity of contents)

- Granulation conditions in granulation process (determination of granulation end-point, tablet hardness, and elution)
- 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 elution)
- 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 or minor constitutes such as protein which are highly sensitive to oxygen, water and light, 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)
- Validity of cleaning of containers and closures (cleaning validation, drying and residual moisture, etc.)
- Validity of sterilization of containers and closures (validations of sterilization and removal of ethyl, and drying and 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 drying process (cycle 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
- Development of sterilization methods of facilities and validation of sterilization
- Validity of in-process control of sterile operation (culture media filling test, etc.)
- Methods of environmental management and monitoring data (methods of sterilization)
- Control parameters of important processes and process test data
- Data of all batches of preclinical lots and investigational drug lots, etc.

4.4.3 Development Report

The development report should contain the following elements.

- Rationale for selection of dosage forms
- Explanation of formula design
- Development history including different manufacturing methods used for manufacturing investigational drugs
- Consideration of scale-up
- Finally determined manufacturing methods
- Change history of processes
- Quality profile of manufactured batches
- Specifications and test methods of final drug products
- Rationale for establishment of important processes
- Control range of process parameters
- References to existing reports and literatures, etc.

4.4.4 Information of Technology Transfer of Drug Products

Information of technology transfer are shown as follows.

Information on Manufacturing Methods

- Development report on drug products or those corresponding to the development report
- Master batch records of manufacture (format of manufacturing records)
- Manufacturing records (batches for establishment of specifications for approval and validation batches, etc.)
- Plan and report of process validations
- Items of in-process control: IPC (test methods and specifications)
- Investigation report on causes of abnormalities (if occurred)

Information on Test and Packaging

- Inspection procedures (precision of inspection and limit of defects)
- Container closure system
- Specifications of primary packaging (moisture proof and light blocking, etc.) and conformity to primary packaging materials

Information on Cleaning Procedures

- Master batch records of cleaning
- Records of cleaning
- Plan and report of cleaning validations
- 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 development report
- Test methods and specifications (raw materials, drug substances, final drug products, container/closure, and packaging materials)
- Validation report on release test methods
- Stability tests (validation report on analytical methods, plan and report of stability tests, packaging conditions, reference standards, and relevant reports)
- Investigation report on causes of OOS (out of specification)

Information on Storage and Transportation Methods

- Specifications of secondary packaging
- Expiry date
- Transportation conditions and tests

- Information on sensitivity to temperature, humidity, and light
- Instructions of temperature monitoring for drug products which need cold storage

Information on Facilities

- Structural materials
- Category and type of main facility

Information on Environmental Management

- Cleaning area (temperature and humidity, microorganism monitoring, airborne particles, and control of differential pressure)
- Information on safety
  - Safety information of hazardous raw materials, drug substances, and final drug products

Information on Industrial Hygiene/Occupational Health

- Protection for operators
- Protection for products

5. Points of Concern For Preparing Technology Transfer Documentation

For smooth technology transfer, transferring and transferred parties should establish organizations in conformity to GMP, and appropriately document and record necessary information relevant to the technology transfer. In this regard, summaries are already described in the above; however, it is recommended to prepare the following documents.

1) Documents to clarify applicable technologies, burden shares, responsibilities, and approval systems, etc. concerning the technology transfer (written agreements and memorandums, etc.)
2) Organizations of technology transfer (at both of transferring and transferred parties)
3) Development report
4) Product specifications
5) Technology transfer Plan
6) Technology transfer Report

Concerning 1), 3) and 4) which need comments on descriptions, this chapter will show details of items to describe, and points of concern for description.

5.1 Documents To Clarify Applicable Technologies, Burden Shares and Responsibility System, etc. Concerning Technology Transfer

The following chart shows details of items to be described in documents clarifying applicable technologies, burden shares, responsibilities, and approval system, etc. concerning technology transfer, and points of concern for description. Any types and forms of the documents are acceptable if they include the items in the following chart, and no duplications of the items stipulated or described in detail in other technology transfer documents are required.

Items	Details	Remarks
1 GMP compliance		
1.1 Organizations	Organizational framework, organization chart, department (person) in charge, and separation between manufacturing and quality departments	
1.2 Supervisor	Clarify supervisor of technology transfer (manufacturing supervisor is acceptable) and his/her responsibilities.	
1.3 Responsibility system	Clarify organization and its responsibilities, document control system, persons in charge of manufacturing department and quality control department.	
1.4 Structure and equipments	Maintenance, inspection and calibration of manufacturing facilities and equipments, and antipollution measurements, etc.	
1.5 Documentation and records	Clarify all technology transfer documentations. Describe control methods of documentation and records, and storage period.	SOP list may substitute the documentation and records, if under the control of GMP; however, “cleaning categories” and “cleaning methods of facilities and equipments” should be described in detail.

1.6	Manufacturing control	Standard manufacturing procedure, and manufacturing instructions and records Industrial hygiene control methods of buildings and facilities Industrial hygiene control methods of operators Report on manufacturing control and quality control Control methods of raw materials, intermediates, and products	For existing products, existing GMP documents can be used.
1.7	Quality control	Determination of test results and report methods Control method of reference samples Maintenance and inspection of pilot facilities and equipments Control methods of test results Control methods of reference standards, reagents, and test solutions, etc. Handling of retest	
1.8	Product release	Control methods of release (procedures and judge)	
1.9	Validation	Organization for validation Describe communication and confirmation methods, discussion, and approval, etc. concerning validations. Facility qualification	
1.10	Change control	Specify handling of change controls in advance.	
1.11	Deviations	Clarify handling of abnormalities, deviations, and OOS.	
4	Other necessary items		
4.1	Persons in charge	Describe persons in charge at both parties.	
4.2	Periodic report	Describe formats of periodic reports, such as annual report.	
4.3	Changes in technology transfer documentation such as required specifications and product specifications	Describe communication and confirmation methods and necessary formats for changes.	
4.4	Retention of technology transfer documentation such as required specifications and product specifications	Specify retention period and disposal time.	
4.5	Revision history	Documents should be replaced according to revisions.	
4.6	Others	Handling of not specified items	

5.2 Technical information to be Described in the Development Report, and Product Specification, etc.

The following chart shows technical information and points of concern to be described in documents such as the development report, and product specification, etc. of drug substances.

Items	Details	Remarks
Report on design of drug substances		
1 Change history of process design and manufacturing methods during development	• History of manufacturing methods of drug substance used in Phase I, II and III studies, etc., bioequivalence of drug substance quality, and justification for starting materials and manufacturing methods, etc.	
2 Information on final product		
2.1 Product name	• Scheduled brand name in the certificate of approval	• Not necessary, if not yet determined.
2.2 Specifications and test methods	• Describe all of specifications and test methods described in the certificate of approval.	• Describe agreed specifications as well, if any.
2.2.1 Raw materials	• Specifications and test methods of raw materials to be used	• Clarify suppliers. • Test results
2.2.2 Container and closure	• Specifications and test methods of container and closure to be used	• Clarify suppliers. • Test results
2.2.3 Packaging and labeling materials	• Specifications and test methods of packaging and labeling materials to be used	• Clarify suppliers. • Test results
2.2.4 Intermediates	• Sampling procedures, specifications and test methods of intermediates	• For intermediates not to be isolated, description can be omitted, provided that the rationale should be described in the development report. • Describe added specifications for trading (such as acceptance criteria for product assessment), if any.
2.2.5 Drug substance	• Sampling procedures, specifications and test methods of drug substance	• Describe added specifications for trading (such as acceptance criteria for product assessment), if any.
2.2.6 Form of test results	• Attach sample form of manufacturer.	
2.3 Manufacturing methods and procedures, etc.	• Describe manufacturing flows, manufacturing procedures, in-process control, and required facility capacity, etc. as detail as possible.	• Describe scientific evidence based data (including stability data to determine unit operating conditions) in the development report. • Confirm important parameters at the time of predictive validation and change validation.
2.4 Packaging methods and procedures, etc.	• Describe packaging methods and procedures.	
2.5 Storage conditions	• Describe storage conditions of raw materials, intermediates, and drug substances.	• Temperature and humidity ranges, light, and container in use • Describe evidence data in the development report.

2.6 Expiry date	• Expiry dates of raw materials, intermediates, and drug substances	• Describe evidence data in the development report. • Describe stability data as much as possible.
2.7 Transportation conditions	• Describe transportation conditions and cautions for transportation of raw materials, intermediates and drug substances.	
2.8 Information on safety	• Describe information on safety of raw materials, intermediates, and drug substances. • Describe information on safety of each unit operation (reaction and post-treatment, etc.).	• Attach MSDS as much as possible. • Attach safety data of processes as much as possible.
3 Stability		
3.1 Raw materials		• Describe physicochemical safety (temperature, humidity, and light). • Describe microbiological safety.
3.2 Intermediates		
3.3 Drug substances		
4 Environmental assessment	• Describe influence on environment.	• Describe waste disposal methods as well.

The following chart shows technical information and points of concern of drug products to be described in documents such as the development report, and product specification, etc.

Items	Details	Remarks
Report on drug product design		
1 Properties of drug substances	• Physicochemical and pharmaceutical properties necessary for drug product design (such as dissolution, particle size, hygroscopicity, incompatibility, absorbability and stability, etc.)	
2 Change history of formula design and manufacturing methods during development *	• History of formula and manufacturing methods of drug product used for exploratory pharmacokinetic study, Phase I study, proof of concept (POC) study, Phase II and Phase III studies, bioequivalence between different drug products, formula of final drug product, and rational for the manufacturing methods, etc.	
3 Information on final drug product		
3.1 Product name	• Scheduled brand name in the certificate of approval	• Not necessary, if not yet determined.
3.2 Indications and dosage and administration	• Indications in the certificate of approval	• Not necessary, if not yet determined.
3.3 Ingredients/contents	• Ingredients/contents in the certificate of approval	• In case of revision of contents, its rationale should be included.
3.4 Specifications and test methods	• Describe all specifications and test methods in the certificate of approval.	• Describe agreed specifications, if any.
3.4.1 Drug substances	• Specifications and test methods of drug substances to be used	• Clarify suppliers. • DMF No., if any, and letter of authorization (LOA)

3.4.2 Drug substance raw materials	• Specifications and test methods of drug substance raw materials to be used	• Clarify suppliers. • DMF No., if any, and letter of authorization (LOA)
3.4.3 Primary packaging materials	• Specifications and test methods of primary packaging materials	• Clarify suppliers. • DMF No., if any, and letter of authorization (LOA)
3.4.4 Secondary packaging materials	• Specifications and test methods of secondary packaging materials	
3.4.5 Intermediates	• Specifications and test methods of intermediates	
3.4.6 Final products	• Specifications and test methods of final products	• Describe applied specifications for application and/or specifications before shipment, if any.
3.4.7 Forms of test results	• Attach sample form of an manufacturer.	
3.5 Manufacturing methods and manufacturing procedures, etc.	• Describe manufacturing flows, manufacturing procedures, and in-process control as detail as possible.	
3.6 Packaging methods and packaging procedures, etc.	• Describe packaging flows, packaging procedures, and in-process control as detail as possible.	
3.7 Storage conditions	• Storage conditions of drug substances, drug product raw materials, primary packaging materials, secondary packaging materials, intermediates, and final products	Temperature and humidity ranges, light and container in use
3.8 Expiry date	• Expiry dates of drug substances, drug product raw materials, primary packaging materials, secondary packaging materials, intermediates, and final products	• Describe rationale for expiry dates. • Describe stability data as much as possible.
3.9 Transportation conditions	• Describe transportation conditions of drug substances, drug product raw materials, primary packaging materials, secondary packaging materials, intermediates, and final products, and cautions for their transportation.	
3.10 Information on safety	• Describe information on safety of drug substances, drug product raw materials, primary packaging materials, secondary packaging materials, intermediates and final products.	• Attach MSDS as much as possible.
4 Stability		
4.1 Drug substance		• Describe physicochemical stability (temperature, humidity, and light). • Describe microbiological stability as well.
4.2 Intermediates		
4.3 Final products		
5 Environmental assessment	• Describe influence on environment.	• Describe waste disposal methods as well.