1. Preface

1.1 Introduction

In the manufacturing and marketing of drugs, it is important to deliver drugs of a constant quality into the market in order to assure the safety and efficacy that has been proven and abides by the standards for manufacturing control and quality control. In line with this, "Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-Drugs" (hereinafter referred to as "GMP Ministerial Ordinance on Drugs and Quasi-drugs") was established according to the Pharmaceutical Affairs Law, marketing approval holders are required to comply with these standards for the manufacturing control and quality control at their manufacturing sites as one of the approval conditions. Furthermore, manufacturers are obliged to observe the Standards.

The implementation of analysis and testing has an important significance for the objective verification of the manufacturing control and quality control of products related to drugs; however partially because many of the stipulations for the analysis and testing in GMP Ministerial Ordinance on Drugs and Quasi-drugs are in rather comprehensive expression and partially because after the enforcement of the Revised Pharmaceutical Affairs Law, it becomes possible to totally entrust the analysis and testing to external testing institutions by manufacturers' own responsibility and judgment or other reasons, and highly necessary to have a guideline which shows concrete methods for the control of analysis and testing.

In the meantime, now is the time when, in association of the increase in international business transaction or others, quality-related-standards agreed upon in ICH, management methods of international standard basis including ISO and others prevail in Japan, so the guideline must also be one that boosts the credibility of analysis and testing at Japanese manufacturing sites in the global society.

Taking all these things into consideration, the "Guideline on Control of the GMP Quality Control Laboratory for Drugs and Quasi-drugs" has been prepared.

1. 2 Objectives of the Guideline

This Guideline intends to concretely show as many recommendation items as possible that are necessary for manufacturers when they conduct analysis and testing duties as the quality control specified in GMP Ministerial Ordinance on Drugs and Quasi-drugs, and for external testing institutions when they conduct analysis and testing duties appropriately. These recommendations include items indirectly related to quality control such as quality assurance or manufacturing control, etc., depending on items.

1. 3 Scope of Application

1) This Guideline is subjected to all of the analysis and testing (including those entrusted to others) to be done as the quality control in accordance with the stipulations in GMP Ministerial Ordinance on Drugs and Quasi-drugs. The analysis and testing includes those related to physiochemical, microbiological, veterinary and other fields, however, detailed items in a specific field are not handled in this Guideline.

2) This Guideline is targeted to all of the organizations that perform analysis and testing as the quality control specified in GMP Ministerial Ordinance on Drugs and Quasi-drugs, regardless of the size or form, etc. of business, or regardless of whether the organization is a testing institution performing analysis and testing exclusively or unit performing analysis and testing as a unit responsible for the analysis and testing in a manufacturer's organization.

3) Although the recommendation items in this Guideline complement the stipulations of GMP Ministerial Ordinance on Drugs and Quasi-drugs, these matters, excluding those required in the Ordinance or in other Laws, are expected to be applied and utilized selectively in accordance with the size, form or others of actual business. It is not necessary to carry out all of the recommendation items in this Guideline; only applicable parts need to be carried

out.

4) In this Guideline, "analysis and testing unit" means an organization that relates to the analysis and testing duties performed by the quality unit as a part of the manufacturing control and quality control.

2. Recommendation items for the control

2. 1 Organization

1) A manager should be appointed to manage and control analysis and testing duties in accordance on the basis of Article 6, Paragraph 1 and Paragraph 2 of GMP Ministerial Ordinance on Drugs and Quasi-drugs. The content and scope of the responsibility and authority of the manager should be defined in the document specified in Article 6, Paragraph 4 of GMP Ministerial Ordinance on Drugs and Quasi-drugs.

2) The analysis and testing unit should perform analysis and testing for the quality control and is responsible for the results of the analysis and testing.

3) The analysis and testing duties should be carried out by a sufficient number of employees who received appropriate education and training (refer to section 3.1) including those employees (including temporary employees) who perform the analysis and testing. The responsibility and scope of duties of the employees should be defined in advance in the document specified in Article 6, Paragraph 4 of GMP Ministerial Ordinance on Drugs and Quasi-drugs.

4) In preparation for cases of absence of the manager, a representative of the manager should be designated in advance from among employees who are well informed of the contents of duties.

2. 2 System for Management and Control of Quality related to Analysis and Testing

1) In order to maintain the System for Management and Control of Quality that has already been established in a manufacturer for the obedience of the stipulations specified in GMP Ministerial Ordinance on Drugs and Quasi-drugs, the manager of the analysis and testing unit should include "a system, for the employees engaged in analysis and testing duties, and for the duties of the analysis and testing unit" as a part of the System for Management and Control of Quality.

2) Documents related to the System for Management and Control of Quality related to Analysis and Testing Duties contain the following contents. Meanwhile, these documents may sometimes be prepared as a part of various operating procedures which are prepared pursuant of the stipulations of GMP Ministerial Ordinance on Drugs and Quasi-drugs.

a) Organization, personnel and training and education
b) Control of documents and records
c) Control of deviation and changes
d) Control of self-inspection and internal audit
e) Control items related to external entrusting
f) Control of environment
g) Grasping of specifications and standards, and suitability evaluation of analysis and testing methods
h) Control of buildings and facilities
i) Control of reagents, test solutions and reference standards
j) Control of sample collection, and collected samples

k) Assurance of results of analysis and tests
l) Procedures for planning, implementation, acceptance or rejection judgment, and reporting of analysis and testing
m) Control of reference samples
n) Stability monitoring

3) The documents related to the System for Management and Control of Quality related to Analysis and Testing Duties should be reviewed periodically in accordance with the changes in the organization or in contents of duties and be revised appropriately.

4) Procedures related to the System for Management and Control of Quality related to Analysis and Testing Duties should be checked and approved by related sections in the quality unit.

2. 3 Control of document

1) As an operating procedure for the management of all documents used for the analysis and testing duties among the written operating procedures prepared pursuant of the stipulations in Article 8, Paragraph 4, Item 9 of GMP Ministerial Ordinance on Drugs and Quasi-drugs, operating procedures that are clearly specified in Article 20, Item 1 of the Ordinance should be prepared and implemented, in addition to operating procedures that are for the review at the time of preparation or revision and for the recall at the time of document destruction.

2) Documents should be prepared in a way that mutual relationships among documents are easily understood.

3) In all cases when analysis and testing duties take place, the latest version of documents approved by the quality unit should always be used.

4) The following is an example of the layout of the documents, including operating procedures for analysis and testing, based on the stipulations in Article 8, Paragraph 5 of GMP Ministerial Ordinance on Drugs and Quasi-drugs. In the meantime, when electronic media are used as documents, the documents should remain easy to access .
   a) Operating procedures and validations reports for analysis and testing methods: Inside of an analysis and testing room
   b) Operating procedures for the operation of analysis and testing instruments: Places which are near the instruments and easy-to-reach
   c) Operating procedures for the control of reagents and test solutions: Places which are near the storage place of reagents and test solutions and easy-to-reach

5) All of the documents should be stored appropriately and safely, without being tampered with, for a specified period in a place which is devised for protection from loss or serious damage.

2. 4 Control of records

1) Each of all of the duties related to the analysis and testing duties should be recorded in control records of an analysis and testing room at the time when it is implemented, if it is defined to do so, or, if it is considered necessary to do so even though there is no definition.

2) At the time of preparation of records, filling-up should be done in a predetermined space in an easy-to-read way, and with not an easy-to-erase manner; and the date of the entry and the name of the filling-up person should be clearly described.

3) When a correction of the recorded items is made, the reason for the correction and the date of the correction should be described together with the signature and seal of the person making the correction. In addition, the pre-revision record should be maintained to be legible.

4) Analysis and testing records should contain complete data and descriptions related to all of the analysis and testing that are performed to confirm that the products, and labeling and packaging materials meet the specifications. Demanded contents include the following:

a) In addition to descriptive matters indicated in Chapter 3, 3-11 of Enforcement Notification, records on samples collected or obtained for analysis and testing should contain: names of manufactures or suppliers (if it is a juridical person, the name of the juridical person) (places where the samples were collected, if necessary); date of the collection of samples; and the date of acceptance of samples for analysis and testing (this is limited when this date is different from the date of collection of samples).

b) Description and reference matters (when corresponding matters are mentioned in published literatures, cite the source) related to the analysis and testing methods implemented should be given. Usually it is acceptable to describe information such as the number of operating procedures, etc., from which it is possible to specify the analysis and testing method

c) In addition to the descriptive matters indicated in Chapter 3, 3-11 of Enforcement Notification, records of the content of analysis and testing should contain: amounts of samples; reference standard materials (reference standard products); reagents; standard solutions; major analysis and testing equipment and instruments used; and judgment criteria of the results of analysis and testing.

d) All of raw data related to each analysis and test (including the process leading to the final result from which measurement units, conversion factors and equivalency factors become clear) should be identified appropriately in a way that makes the relation between the samples used and the lots or control units clear.

e) Signature, date of signing/applying seal and date of the review (records of double checking by a third party) of the person who reviewed the validity, completeness and compliance with established specifications of the master production records.

5) In addition to the analysis and testing records of products, and labeling and packaging materials, complete records on the following items should be prepared, checked and preserved.

a) At the time of change of analysis and testing method, the records on the evaluation of the change defined in Article 14, Item 1 of GMP Ministerial Ordinance on Drugs and Quasi-drugs should contain: the reason of the change; the results of verification proving that the changed analysis and testing method gives similar, correct and reliable results as the pre-changed method; and the data used for the verification (refer to Sections 2.6 and 3.4).

b) Checks, maintenance and periodic calibration of equipment, instruments, apparatuses and tools in the analysis and testing room.

c) All stability tests performed for products.

6) For all of the records and their copies, mutual interrelation and retrieval should be easy to control. Recorded matters should be easily picked up at the testing institutions where the matters were implemented. In the meantime, when the system is made that such records are available at the said testing institution by transfer from a storage place other than the said analysis and testing institutions using an electronic method or other methods whenever necessary, this system is allowed to be used. The following are examples of the control methods of records.

(a) To file related raw data and records for each fiscal year, after classifying them for each product, or labeling and packaging material, for lot number or control unit number, etc.

(b) Utilization of electronic media with retrieval system

7) All records or their copies should be stored appropriately and safely, without being tampered with, for a specified period in a place which is devised for protection from loss or serious damage.

2. 5 Control of deviation

1) Contents of deviations from procedures of analysis and testing duties should be made clear, and should be reported to the manager of the analysis and testing unit regardless whether they are serious or not. These procedures should be documented.

2) The manager of analysis and testing unit should conduct cause investigations, evaluate the influence on quality and judge about the measures of his/her analysis and testing unit, taking into consideration of the degree or conditions, etc. of the deviation.

3) When it becomes clear that a deviation is one of those previously specified for which the manager can take disposal action by his/her own authority as a result of the cause investigation and evaluation, the manager should instruct actions corresponding to the content directly to persons in charge in the analysis and testing unit. On the other hand, if it is judged, as a result of the cause investigation, that the deviation may relate to the quality of product, for example, cause serious influence on the judgment for product release from the manufacturing site, the manager should report the content and evaluation results, etc. of the deviation, a conclusion of his/her analysis and testing unit, and opinions on desirable actions and others to the person in charge of deviation control in the quality unit.

a) Examples of deviations for which the manager of analysis and testing unit can take actions by his/her authority:

In cases when a deviation is clear in its cause and relatively moderate in its degree, it is possible in some cases that the manager of analysis and testing unit can take easy and appropriately actions under the responsibility of the unit, for example, when the unit holds a sufficient amount of equivalents preserved samples. For example,

- When there is a deviation from the regulations in the operating procedures for analysis and testing methods such as weighing error, miss operation at sample preparation, etc. → When analysis and testing is under way, it should be stopped and repeated from the appropriate step according to the instruction from the manager. It should be judged whether or not additional analysis and testing or reanalysis and retesting is necessary, according to necessity.
- When it becomes clear that the expiration date of a reagent had passed after the completion of analysis and testing → It should be judged whether or not additional analysis and testing or reanalysis and retesting is necessary. The influence on results of analysis and testing in the past up to the expiration date should be evaluated.
- When analysis and testing is carried out without performing a defined calibration of analysis and testing equipment and tools → The influence on results of analysis and testing should be evaluated and it should be judged whether or not additional analysis and testing or reanalysis and retesting is necessary. Calibration of analysis and testing equipment and tools should be immediately instructed.
- When necessary items are not described on the label of a sample → Necessary information should be confirmed immediately and should be described correctly.

b) Examples of deviations that may relate to quality:

These are such critical deviations which may markedly damage the credibility of results of analysis and testing, or deviations which are found in such a condition that equivalent samples are no longer available, or that was found only after the judgment of the analysis and testing was made, being not able to take actions by the analysis and testing unit only. The following are examples:

- When it is a kind of deviation mentioned in the above a), but it was found only after the end of the judgment of analysis and testing and additionally judged necessary to carry out additional analysis and testing or reanalysis and retesting → It should be instructed to again carry out analysis and testing of the said items, and if necessary, it should be instructed to again carry out the collection of samples or other necessary works.
- When it becomes clear that the defined analysis and testing has not been completed in some

items → It should be instructed to carry out analysis and testing of the said items, and if necessary, it should be instructed to again carry out the collection of samples or other necessary works.

- When it becomes clear that analysis and testing was done using a wrong analysis and testing method → The analysis and testing should be carried out again using the correct analysis and testing method. It should be instructed to re-collect samples, if necessary.

Both cases a) and b) are given only as an example to the last, and therefore each case should be appropriately judged and dealt with following the respective content of the deviation. In addition, such actions for the prevention of recurrence as the review of education and training program or others, according to necessity, should be taken.

4) Records should be preserved in a form from which the relationship between the content of the deviation and the investigation, judgment and actions for the deviation is confirmed in the future. These procedures should be documented.

2. 6 Change control

1) When procedures for analysis and testing duties are to be changed for some reason, a defined procedure, which contains the following contents, should be documented in advance and the change should be carried out following this procedure. In the meantime, the procedure after b) should be carried out not only by the analysis and testing unit but by depending on results of consultations with the quality unit and other related units.

a) Proposal for the change of procedures of analysis and testing duties. The proposal should be made according to the pre-determined method.

b) Acceptance of the change proposal in the quality unit, and primary evaluation of the influence of the said change.

c) Decision making for the action measures based on the content of change and the results of influence evaluation. In the meantime, it may go directly to procedure f) in some cases depending on the result of the said evaluation. The following are examples of evaluations and actions:

- In cases when words in sentences are to be corrected, no specific validity investigation is needed if the content of procedures before the change is judged to be practically maintained.
- In cases when analysis and testing methods are to be changed, whether or not actions such as re-validation or additional analysis and testing are necessary for the change should be investigated; and if it is judged necessary, a plan for the analysis and testing related to the said actions should be established.
- In cases when it is judged that approval application or notification for the change is required according to the Pharmaceutical Affairs Law, the fact should be notified to related units.

d) The protocol related to the investigation of the validity of the change should be prepared according to necessity. The protocol should contain standards for the evaluation of the validity.

e) The investigation of the validity of the change should be conducted according to necessity. A report about the results of the investigation should be prepared in a way that makes the degree of influence of the change on the quality of products clear.

f) A draft for the content of the change should be prepared (if necessary, attach the reports, etc. of the investigation of the validity of the change).

g) The content of the draft should be confirmed as the quality unit, and if the validity of the change was investigated, the reports thereof should be evaluated as the final evaluation.

h) Approval or disapproval of the change by the quality unit.

i) The changes of all of the specifications and standards related to the change and the revision and destruction of related procedures, etc. should be carried out.

j) Employees should be well informed with the content of the change, and education and

training for the implementation should be carried out.

2) All documents related to the change from proposal to approval, including the protocol and report of the investigation of the validity related to the changes in analysis and testing method, should be reviewed by related units and the approval from the quality unit should be obtained.

3) When analysis and testing duties are to be implemented based on the approved change, revision or destruction of related documents and education and training of employees, etc. should be completed beforehand.

4) Works related to the change control of analysis and testing should be recorded; and the records should be preserved. In addition, history records showing the changed date and reasons of the change should be prepared and retained for all of the documents which were changed so that time course of the change becomes clear.

2. 7 Self-inspection and internal audit

1) The analysis and testing unit should take the initiative in complying with GMP Ministerial Ordinance on Drugs and Quasi-drugs and other laws, and should conduct, in addition to the self-inspection specified in GMP Ministerial Ordinance on Drugs and Quasi-drugs, periodic internal audit according to the predetermined procedures, in order to ensure that the part of analysis and testing in the System for Control and Management of Quality are operated appropriately. Analysis and testing duties subjected to the self-inspection and internal audit include the following duties. Meanwhile, concerning external testing institutions, refer to section 2.8.
   a) Judgment of results of analysis and testing.
   b) Actions for the out-of-specification results of analysis and testing
   c) Control of all serious deviations in analysis and testing.
   d) Control of all changes in analysis and testing methods.
   e) Implemented corrective actions (including actions for the results of previous self-inspection and internal audit).

2) Those who perform internal audit should not be those who are engaged by themselves in duties subjected to the internal audit, as a rule, similarly as in the case of the self-inspection mentioned in the Enforcement Notification. Meanwhile, those who perform the self-inspection or internal audit should be qualified in advance for the duties; and it is desirable to establish a certification system for the qualification.

3) Results of the internal audit and subsequent corrective actions should be documented, similarly as in the case of the self-inspection mentioned in the GMP Ministerial Ordinance on Drugs and Quasi-drugs. In addition, they should be reported to responsible persons concerned, in order to alert them to appropriate operation of the relevant parts of analysis and testing in the System for Control of Quality Control.

4) Corrective actions related to the analysis and testing that are decided to perform according to the results of self-inspection and internal audit should be implemented at an appropriate time, and with an effective method, and if necessary, the subsequent effect should be confirmed.

2. 8 Confirmation items in the contract analysis

1) In cases when an analysis and testing specified in GMP Ministerial Ordinance on Drugs and Quasi-drugs is entrusted to an external testing institution, the institution is subject to the stipulations of the Ordinance; the institution should pay special attention to the following points, in deep consideration of business form.
   a) Prevention of contamination and cross-contamination of samples

b) Maintenance of analysis and testing data traceability
c) Confirmation of actions for samples, and analysis and testing methods, in advance of the implementation of the analysis and testing
d) Securing safe, and reliable methods for the transportation of samples

2) The contract-giver and contract-acceptor should prepare documents for the agreement concerning the contract analysis. In the agreement, responsibility assignment of each party for performing the analysis and testing specified in GMP Ministerial Ordinance on Drugs and Quasi-drugs should be concretely described as well as those specified in Enforcement Notification.

3) In the agreement document, the contract-giver should be given the privilege of inspecting the contract-acceptor's facilities in order to facilitate confirmation of the compliance with GMP Ministerial Ordinance on Drugs and Quasi-drugs. The contract-giver should conduct the periodic inspection on the external testing institutions and make evaluation; the targets of the inspection and evaluation should include not only technological level of the analysis and testing, but also whether or not predetermined procedures, etc. are appropriately performed and also whether or not the contract-giver functions as the person concerned with the analysis and testing parts in the System for Control of Quality Control.

4) Both parties of the contract-giver and contract-acceptor should conclude an agreement in writing between them for storage condition of data of records related to the analysis and testing performed at the external testing institution (the condition should be based on the regulations in GMP Ministerial Ordinance on Drugs and Quasi-drugs or other related laws). When it is decided that the external testing institution preserves raw data of the records related to the analysis and testing, it should be made that the data are available for use immediately upon request of the contract-giver.

5) Any of the changes related to analysis and testing methods or judgment criteria in external testing institutions should not be implemented by its own judgment of the external testing institution unless otherwise approved by the contract-giver.

6) In cases of the occurrence of a critical deviation related to analysis and testing or a result of out of specification in the analysis and testing, both parties of the contract-giver and contract-acceptor should conclude an agreement in writing in advance for the reporting system of such occurrence.

3. Recommendation items for Technological Aspects

3. 1 Personnel and Training

1) Employees who engaged in analysis and testing duties should be those who are well informed of GMP and the quality system related to analysis and testing duties, and received sufficient training corresponding to the content of duties.

2) The manager of an analysis and testing unit should objectively evaluate results of the training performed for the employees in the analysis and testing unit, and perform periodic review of the education and training program in order to appropriately reflect the review results on the program. Items of the objective evaluation include, for example, confirmation of task performance capacity or technological accomplishment level of the analysis and testing, or confirmation of the consistency of training records of persons in charge of training and those receiving training.

3) Corresponding to the degree of past history of receiving training and the degree of job experience, a more professional education and training program should be imposed and the

result thereof should be confirmed, if necessary, in consideration of the specificity of the content of sampling or analysis and testing duties. Establishment of a certification system for the qualification is one example for this confirmation.

4) Persons in charge of training who teach how to practice sampling, analysis and testing operations, etc. by means of practical demonstration at sites should be those who have sufficient experience and knowledge about the said duties. Since persons in charge of training are expected to be able to convey knowledge and experience appropriately through the training to trainees, it is desirable to qualify them by some type of qualification. And this qualification is desirable to be renewed periodically, after the competency or fitness has been evaluated based on the effect of the training or on others. Items for the evaluation of competency, for example, include the degree of consistency of training records, results of questionnaires of trainees, and the evaluation of training results of trainees by a third party, etc. Objective evaluation is important in all evaluations.

5) All education and training programs, and training records and evaluation records of the training performed based on the programs should be arranged each employee, and preserved.

3. 2 Facilities and Environment

1) A quality unit should have an analysis and testing room(s) of an appropriate environment that can be used freely according to necessity, and sufficiently assures data reliability.

2) The analysis and testing room should be separate from manufacturing working places. If analysis and testing for the process control is conducted in manufacturing working places, it should be confirmed that manufacturing does not exert a undesirable influence on the analysis and testing and in addition, the analysis and testing duties related to the quality control do not exert an undesirable influence on the manufacturing and quality of products.

3) Requirements for the control of the analysis and testing room and the maintenance of environment should be decided upon and documented in advance.

4) The analysis and testing room should be designed corresponding to the duties carried out inside the room, by securing sufficient and appropriate space for preventing mix-up, contamination, and cross-contamination from occurring and for storing collected samples and analysis and testing records, etc.

3. 3 Grasping of Specifications and Standards

1) In the analysis and testing unit, the latest specifications and testing methods for the products, and labeling and packaging materials subject to the analysis and testing should be prepared as documents, and the documents should be kept in a way that the employees who perform analysis and testing duties can utilize them at any time.

2) Contents of the specifications and testing methods which are prepared as documents in the analysis and testing unit should be consistent with the contents described in the Marketing Approval Letter (Notification Letter) or official compendia (including self-imposed specifications, if any). (It should be arranged so that referring to the master of the Marketing Approval Letter (Notification Letter) is possible.)

3) In the analysis and testing unit, documents of the analysis and testing methods and judgment criteria related to the in-process control, which is carried out as part of the manufacturing control, should be prepared according to necessity. These analysis and testing methods and judgment criteria, which are not defined in the Marketing Approval Letter (Notification Letter) or official compendia, should be established based on the information obtained during

the development stages.

4) The analysis and testing methods and judgment criteria related to the in-process control, which is carried out as part of the manufacturing control, should also be reviewed and approved by the quality unit similarly as in the case of the analysis and testing methods related to the quality control specified in the Product Master Formula.

3. 4 Qualification Evaluation of Analysis and Testing Methods

1) All analysis and testing methods should be scientific and appropriate so that they can assure the compliance of products, and labeling and packaging materials with pre-determined specifications/standards.

2) All of the specifications and testing methods, including their changes, should be drafted by an adequate unit, reviewed and subsequently approved by the quality unit.

3) The analysis and testing unit should confirm the validity of an analysis and testing method, and the unit should also obtain such bases of the validity as validation data, etc. which were acquired during the research and development stages in order to maintain the consistency of the analysis and testing method. As for the analytical method used for the analysis and testing, it should be confirmed that validation for the analytical method was performed appropriately in consideration of attributes, etc. included in the ICH guidelines on validation of analytical methods.

4) When an analytical method used in the analysis and testing is not described in the official compendia including the Japanese Pharmacopoeia or in other published literatures, validation for the analytical method should be done in an appropriate unit. The scope and degree of the validation should be decided according to the object of the analytical method or the stage of manufacturing process or others.

5) Qualification of all of the analysis and testing methods used for the analysis and testing, including cases when an analytical method used in the analysis and testing is described in the official compendia including the Japanese Pharmacopoeia or in other well recognized literatures, should be verified under the actual condition (including equipment, instruments, reagents and test solutions which are used) in the analysis and testing room, and accordingly, records of the results should be prepared. Analysis and testing methods are occasionally technology transferred: between a research & development unit and analysis and testing unit at a manufacturing site; between plural numbers of analysis and testing units of manufacturers; or between an analysis and testing unit in a research & development unit or at manufacturing sites and external testing institutions. In any one of these cases, it is important to confirm in advance about whether expected reasonable results are surely obtained or whether precision of the analysis and testing has no problem, by implementing the analysis and testing for obtaining data, using the equipment and instruments, reagents and test solutions, and standard reference substances, all of which are expected to be used, under a test environment in the analysis and testing room, to where the method is to be transferred, prior to the actual business operation of the analysis and testing at the transferred place.

6) When the analytical method is to be changed, analytical method validation should be implemented according to the degree of the said change. All of the changes implemented for the said analytical method based on the results of the analytical method validation should be documented, which should be preserved together with the protocol and reports of the analytical method validation. The said reports should contain the reason of the change and appropriate and concrete data in order to make possible verifying that it is possible to obtain data by the changed method similarly and as accurate and reliable as the pre-changed analysis and testing method.

7) Documents of the latest analytical method validation on analysis and testing methods, including data thereof, should be displayed in a way that employees who perform analysis and testing duties can access them at any time when it becomes necessary.

3. 5 Equipment/Instruments and Calibration

1) In the analysis and testing room, equipment and instruments that are required for assuring data reliability sufficiently should be installed.

2) In order to clearly indicate that it is in compliance with applicable control items, labeling on equipment and instruments, etc. or other measures should be implemented in accordance with necessity.

3) Duties related to calibration are allowed to be entrusted to external organizations under the responsibility of the quality unit if they are defined so beforehand in quality control standard code, etc.

4) At the time of calibration of equipment or instruments, etc., when there is a standard procedure that makes inspection of the standards of weighing possible, such procedure should be used.

5) The condition of the status of the calibration of important equipment and instruments can be proven should be maintained. One example of the measures is placing a label indicating the result of calibration and the next planned calibration date, etc. on equipment and instruments.

6) Equipment or instruments, etc. not complying with the calibration standard should not be used. As measures to prevent the miss-use of such equipment or instruments, etc., one example is placing a label indicating "not for use" on the equipment or instruments, etc. that are not in compliance with the standards for calibration, or overrun the calibration period.

7) Operational performance confirmation of the equipment or instruments, etc. to be used should be done using appropriate procedures including system suitability tests.

8) In cases where it becomes known that one piece of equipment or one instrument, etc. related to critical analysis and testing items is deviated from the calibration standards, it is required to make necessary investigations for judging whether or not the deviation has exerted influence on results of the analysis and testing carried out using the equipment or instruments, etc. since the previous calibration. One example method of the investigation is to implement analysis and testing on products manufactured during the same said period by using normal equipment or instruments, etc. in order to confirm the existence or non-existence of problems in specifications of quality that were to be assured by the analysis and testing performed with the use of the said equipment or instruments, etc. If abnormality should be found as a result of the investigation, actions should be taken quickly by having discussion with a related section, etc., according to necessity.

3. 6 Reagents / Test Solutions

1) Concerning reagents and test solutions, procedures concerning purchasing or procurement, safety handling, preparation methods, storage, and use should be defined and documented in advance.

2) Reagents should be controlled according to the procedures, and should be indicated by name, safety information, storage condition, date of purchase, expiration date, and, if necessary, the date of opening.

3) Already prepared materials including test solutions should be controlled according to the procedures, and records on the preparation should be prepared. The expiration date of the already prepared test solutions, etc. should be established appropriately in consideration of the characteristics and stability of the materials. Already prepared materials should be indicated by name, preparation number or date of preparation, name(s) of person(s) who prepared the materials, expiration date, and, if necessary, storage condition and conversion coefficient, etc. It is also necessary to indicate name, etc. for containers of water for analysis and testing, as well as dispensed solvents for analysis and testing.

4) Water for the analysis and testing of enough quality that does not exert influence on results of analysis and testing should be secured. In cases when water for the analysis and testing is purchased and used, the quality should be confirmed according to necessity, and records should be prepared on it. In cases when water for the analysis and testing is manufactured using in house equipment, the equipment should be maintained and controlled, and the quality of water should be checked periodically; and records should be prepared for it.

5) Reagents and test solutions should be those that can be applicable to the analysis and testing, and the samples. If necessary, the suitability of them should be evaluated beforehand.

6) For safely and stable handling of reagents, relevant laws and regulations should be abided by, and at the same time, information related to the said reagents should be collected.

3. 7 Reference Standards Materials

1) In order to prevent contamination and degradation, etc. of the reference standard materials from occurrence, procedures for the purchase or other procurement methods, safety handling, transportation, storage and use should be defined and documented.

2) Primary reference standard materials should be procured appropriately, and stored according to the condition designated by the suppliers. When primary reference material is accepted, a record on necessary items such as name, purity, safety information, storage condition, where it is procured from, date of procurement, expiration date and others should be prepared, and should be controlled after indicating necessary items on the containers in a way that they can be easily identified. Reference standard materials (reference standards) should be stored according to the pre-defined storage condition.

3) In cases when a primary reference standard cannot be procured from an officially authorized supplier, an "in-house primary standard" should be established. The in-house reference standard material should be prepared by implementing purification procedures, according to necessity, on material procured appropriately. It should be confirmed that the material is the said compound ("identification") by determining the structural formula using nuclear magnetic resonance spectroscopy and infrared absorption spectroscopy, etc. In addition, the entity of impurities should be identified as much as possible, and after that, appropriate analysis and testing should be implemented to absolutely prove the purity. Records on raw materials, purification, identification and purity should be prepared and reserved.

4) When a primary reference standard is used, the object of the use and the amount of used should be recorded, and the records should be preserved.

5) When a secondary reference standard is prepared, its lot suitability should be evaluated by implementing the comparison with the primary reference standard prior to the first use of it. In addition, the primary reference standard used in the comparison should be identified. The secondary reference standard should be re-evaluated periodically according to the procedures specified beforehand.

6) During the period that the product is being shipped from the manufacturing site and used, the reference standard material of necessary and sufficient amount for the analysis and testing should be controlled in a way that the material is available anytime when it becomes necessary.

3. 8 Planning of Analysis and Testing

1) In the quality unit, following procedures that are necessary for analysis and testing duties should be defined, and specified in written operating procedures, etc. in advance.
   a) Procedures for concrete analysis and testing operations;
   b) Procedures for sampling and for judgment of analysis and testing;
   c) Procedures for the preparation and approval of the analysis and testing protocols or analysis and testing instructions (hereinafter referred to as "the analysis and testing protocols, etc.").
   d) Procedures for the implementation of analysis and testing based on the analysis and testing protocols, etc.
   e) Other procedures necessary for the appropriate implementation of analysis and testing

2) Written procedures for analysis and testing operations should be prepared independently for each product. Operating procedures of the analysis and testing room should be more concrete and more specific in operational procedures than those generalized expressions of analysis and testing seen in the Marketing Approval Letter (Notification Letter) or in official compendia, so that it facilitates the easy implementation of accurate analysis and testing.

3) It is desirable to prepare written procedures by several employees. At the preparation, the manager of analysis and testing unit, a person(s) who is qualified as a trainer (for example, a person indicated in section 3.1-4) or a person(s) who is recognized as having equivalent experience and technology level, and a person(s) who is well informed with the content of analysis and testing should participate according to necessity. It is desirable that the procedure prepared is reviewed by several persons (excluding the person(s) who prepared the procedure) who have equivalent experience and a technology level as high as the person(s) who prepared the procedure.

4) When preparing the analysis and testing protocols, etc., the following matters should be confirmed.
   a) Written procedures for the analysis and testing corresponding to samples are adjusted and made available at any time for employees related to analysis and testing duties.
   b) The validation data or suitability confirmation data related to analysis and testing methods exist, and they are arranged in a way that employees in the analysis and testing unit can utilize at any time necessary.
   c) Equipment and instruments are those that correspond to the analysis and testing methods and samples.
   d) Reagents and test solutions are those that correspond to the analysis and testing methods and samples.

5) In cases of contact analysis, a contract-giver's approval for written procedures prepared for independently for each product and the analysis and testing protocols, etc. should be obtained. As for a plan for accepting samples, the contract-giver and the contract-acceptor should sufficiently discuss and make an agreement for the procedures for acceptance and also for action procedures at the time of the change of the procedures in advance.

3. 9 Sampling

1) Sampling methods should be scientific and appropriate for assuring that the products, and labeling and packaging materials meet pre-determined quality standards.

2) In advance of implementing the sampling, a sampling plan should be prepared for each

implementation. The sampling plan should usually be prepared by an appropriate unit in consideration of the production schedule, etc. Preparation is allowed as a part of analysis and testing protocol. In cases of contract analysis, it is desirable to make an agreement beforehand in details about: section for the preparation of the protocol for sampling; section or person or title who performs the sampling; methods for the transfer-in and transfer-out of samples; and schedule, etc.

3) The samples should be representative ones of the lot or control unit, and be appropriate for the object of analysis and testing; and the ground thereof should be documented.

4) Sampling should be done by a person in the analysis and testing unit as a rule, however, sampling by a designated person of the manufacturing unit, who has undergone necessary training, is also allowed under the responsibility of the quality unit when there is an appropriate reason, for example, in cases when the sampling must be done under aseptic conditions or in cases when the sampling must be done depending on the condition of process, etc. When the sampling is to be done by a person of the manufacturing unit, which should be clearly mentioned in the quality control standard code, etc., additionally, in order to secure the appropriate implmentation of the sampling, attention is required, for example, by the manager of analysis and testing unit and the manager of the manfuacturing unit keeping close communication regarding the matter.

5) At describing the sampling procedures in the quality control standard code, the procedures should be established in consideration of the significance of products, and labeling and packaging materials, dispersion of quality, past quality history of the suppliers, and necessary amount for analysis and testing, etc. It is desirable to specify the procedures using drawings, etc. showing sampling places according to necessity so that it facilitates the certain implementation of the sampling.

6) At the time of implementing a change or giving a special instruction for the sampling amount decided beforehand, it should be arranged so that such change or instruction is implemented only after clearly describing the content and reason of the change in the sampling protocol, and the recording of the works is surely done; and at the same time, special attention should be paid in order to avoid mistakes in analysis and testing afterward.

7) The sampling should be done at a pre-determined place, using a procedure that prevents the contamination of samples and the contamination to other raw materials, labeling and packaging materials, and products.

8) Concerning the raw materials, labeling and packaging materials, and products from which samples were taken, they should be controlled so as not to be used in the subsequent manufacturing process or to be put in the market mistakenly, using some clearly acknowledgeable measures, for example, by placing a label indicating " under analysis and testing".

9) Sampling should be done while paying attention to the following points:
   a) If necessary, containers subjected to the sampling should be cleaned before the sampling.
   b) If necessary, sampling should be done by aseptic sampling method using aseptic sampling utensils.
   c) When special conditions are established for sampling, the sampling should be done according to the conditions. One example is a condition in which each sample collected from upper, middle or lower parts of a container is prohibited to mix.
   d) In order to prevent a mix-up of samples, a container for collected samples should be indicated by necessary items including: name of sample, lot number or control number, sampling date and name of sample collector, etc.

e) When sampling is complete for a container, the container should be indicated clearly that a sample has already been taken (for example, by fixing a label indicating "under analysis and testing").

f) At the time of sampling for the in-process control, the integrity of the collected samples should be assured.

3. 10 Control of Samples

1) The quality unit should take necessary action so that the appropriate sample distinction of collected samples is done in order to avoid the mix-up with other samples. Placing a label or bar-code indicating necessary items is an example measure for avoiding mix-up with other samples.

2) Information for the appropriate sample distinction includes: name, lot number or control number, number of the analysis and testing of sample, sampling date, name of sample collector, sampling place, sampling amount, and storage condition, etc. This information should be indicated on the sample container according to necessity. If necessary, it should also be indicated whether it is before or after the implementation of analysis and testing, and whether it was qualified or disqualified in the analysis and testing, etc.

3) The samples should be stored using a method for preventing contamination or cross-contamination, under a storage condition specified for the prevention of degradation or alteration. According to necessity, the control status of the temperature during storage should be recorded, and records should be preserved.

4) The receipt and distribution, name of distributor, destination of the distribution, and date of distribution should be recorded, and a record should be preserved.

5) In cases when analysis and testing are entrusted to external testing institutions, samples should be transported by a safe and certain method, and a record on the acceptance of the sample should be prepared and preserved. The control status of temperature during transportation should be recorded according to necessity, and the records should be preserved.

6) Prior to the implementation of analysis and testing, the person in charge from the analysis and testing unit should confirm that the distributed samples are those corresponding to the planned analysis and testing.

3. 11 Implementation of Analysis and Testing

1) The manager of the analysis and testing unit should establish in advance a procedure as to how the person in charge of analysis and testing report the result of analysis and testing, and obtain the approval of the quality unit.

2) The person in charge of analysis and testing duties should receive training about the operational procedures of analysis and testing and understand them sufficiently, prior to the implementation of the analysis and testing.

3) The person in charge of analysis and testing duties should implement the analysis and testing, in accordance with the instructions from the manager, according to the analysis and testing protocols, etc. as well as to the written procedures related to analysis and testing operations. At the time of implementing analysis and testing, work sheets and flow charts, etc. should be used according to necessity in order to make the implementation procedures certain.

4) All raw data obtained during the course of implementation of analysis and testing should be confirmed by persons other than the person(s) in charge, and records on the confirmation

should be prepared.

5) The person in charge in the analysis and testing unit should report the result of analysis and testing, including those confirmation records by person(s) other than the person in charge, to the manger in writing.

3. 12 Assurance of Results of Analysis and Testing

1) Person(s) other than the person in charge in the said analysis and testing unit should confirm that the result of analysis and testing was obtained by implementing the specified analysis and testing methods corresponding to the collected samples, according to the operational procedures. Confirmation methods include confirmation of written procedures used for the said analysis and testing, and review of records on the said analysis and testing, etc.

2) The quality unit should appropriately define in advance the specifications for the control in addition to the specifications in the Marketing Approval Letter (Notification Letter) or in the Japanese Pharmacopoeia or other official compendia, and use these specifications at the time of the judgment of results of analysis and testing. The specifications for the control as well as the specifications in the Marketing Approval Letter (Notification Letter) or in the Japanese Pharmacopoeia or other official compendia, should be those that sufficiently assure the quality of the products, and labeling and packaging materials subjected to the analysis and testing, from statistics and other scientific prospects.

3) Having discussions with other related units about the out-of-specification in the results of analysis and testing, the quality unit should define and document the procedures for the cause investigation and counter measures as well as the responsibility and authority in advance for the case. It is desirable to consider the following points, in consideration of the effects on quality of products.

a) When an out-of-specification in the result of analysis and testing is confirmed, it should be reported promptly to the manager of analysis and testing unit.

b) Upon receiving a report of the out-of-specification in the analysis and testing, including in the case of discovery by oneself, the manager of analysis and testing unit should take actions according to the pre-determined cause investigation and action procedures.

c) As initial actions, the analysis and testing unit should, for example:
   - Confirm the content of the result and make judgment promptly about appropriate action.
   - Make necessary communication with related units according to the procedures.
   - Investigate whether or not there are any deviations during the implementation of analysis and testing concerning each of the results of out-of-specification, and take records.
   - Perform the investigation to specify the scope of influence of the results of out-of-specification.
   - When it becomes necessary to carry out the re-sampling or reanalysis and retesting after the discovery of the results of out-of-specification, issue an instruction in writing.

d) The manager of analysis and testing unit should report the result of the cause investigation carried out by the analysis and testing unit to necessary related units after, if necessary, adding its opinions on whether or not a critical problem is present, etc. excluding cases where it is defined in advance that the problem is allowed to be dealt with under his/her own responsibility and authority. Examples of cases where the manager of analysis and testing unit is allowed to deal with his/her own responsibility and authority include cases when a problem is caused by simple cacography or minor mistakes in analysis and testing, or similar matters.

e) In cases where there is a deviation whose influence on quality of products cannot be denied or possibility of the influence is judged high by the analysis and testing unit, the content and results of the cause investigation carried out by the analysis and testing unit,

together with the opinions on the possible influence on the quality of products, should be documented and promptly reported to the related units. Meanwhile, concerning external testing institutions, refer to Section 2.8, Item 6.

f) The quality unit should review the content and results of all investigations and decide whether it is approvable or not, prior to making a decision (yes or no) for the product release from the manufacturing site. And, if it is necessary to impose improvement in some points, necessary actions should be taken timely. Auditing on related unit(s) should be done according to necessity.

g) Training should be carried out corresponding to the results of the out-of-specification in the analysis and testing.

4) In cases of the implementation of analysis and testing, re-sampling or reanalysis and retesting should not be carried out without reason. In cases when a re-sampling or reanalysis and retesting is to be carried out based on a formal instruction, the reason or the reason and actions in response to the results of the analysis and testing, respectively, should be recorded.

3. 13 Judgment and Reporting of Results of Analysis and Testing

1) The quality unit should define the following items in written procedures and observe them.

a) Establishment of the judgment criteria and method of the acceptance or rejection of the analysis and testing.
b) Reporting and approving of the result of judgment of the analysis and testing
c) Reporting and actions at the time of occurrence of the result of out-of-specification in the analysis and testing.
d) Judgment of the necessity of the reanalysis and retesting.
e) Disposal of rejected products
f) Issuance of certificate of analysis

2) The manager of analysis and testing unit should review the reports from the person in charge in the analysis and testing unit and make judgment about acceptance or rejection of the result of analysis and testing. In the meantime, this acceptance or rejection judgment constitutes the base for the approval or disapproval of the product release from the manufacturing site, so the judgment criteria should be those that assure the compliance with the specifications in Marketing Approval (Notification) Letter or in the Japanese Pharmacopoeia or other official compendia.

3) In order to prevent mix-up, a container of the products, and labeling and packaging materials subjected to the judgment should be indicated the result of the judgment whether it is accepted or rejected, by fixing a label showing "qualified" or "not-qualified", or by other methods, so that clear distinction becomes possible.

4) The manager of analysis and testing unit should report the result of analysis and testing of products and labeling and packaging materials, from which the judgment of acceptance or rejection was made, to the quality unit. The reporting should be done according to the predetermined procedures.

5) At the time of issuance of the certificate of analysis, the following items should be observed.

a) The quality unit should issue the certificate of analysis for each lot or control lots of the product, or labeling and packaging materials, upon request.
b) The certificate of analysis should be made so that it can be clearly identified that it is a certificate of analysis, and it should be indicated by: name of the object subjected to analysis and testing; lot number or control number; specifications; numerical results (only when the result of analysis and testing is numerical data); and judgment result, etc.
c) In the certificate of analysis, a person designated beforehand in the quality unit, should enter the date and subscribe or apply a stamp/seal. It should be indicated by the name of the

manufacturers (name of a juridical person, if it is a juridical person) (following to the Enforcement Notification, if it is an external testing institution), etc., according to necessity.

3. 14 Control of Reference Samples

1) It should be reminded that the reference sample is a reserve for the possible occasion of the evaluation of quality of an already released lot in the future, and not for monitoring the stability of the lot.

2) Products of drug substances:
The reference samples should be stored in a similar packaging form to the products of drug substances, or be stored in a form that is protected equivalent to or greater than the packaging form for normal release from the manufacturing site.

3) Products of drug products (for only those which are subjected to the qualification judgment for product release into the market):
As a rule, the reference sample should be stored in the same packaging form as the marketed products.

4) In order to avoid mistaken use, the reference samples should be labeled clearly so that there is no confusion regarding sample identification.

5) All of the reference samples preserved should be controlled in a way that the history of each of them becomes clear.

3. 15 Stability Monitoring

1) The plan for continuous monitoring of the stability should be established and implemented for: the evaluation and confirmation of time-course stability of a product's quality; confirmation of the appropriate storage condition of drug substance products and retest date or expiration date, etc. The implementation procedures for stability monitoring should be established independently for each product and documented.

2) Items for analysis and testing of the stability monitoring should be those that are sufficient for appropriate evaluation of the stability. Also, analysis and testing methods used for the monitoring should be those which are implemented with analytical validation.

3) The samples used for the stability monitoring should be collected from the products in the final packaging form (excluding intermediate products). Collecting samples from intermediate products packaged in a form that is guaranteed the stability is allowed, if there is no problem. Concerning drug substance products, the samples should be stored in a container of equivalent quality to the container for the marketing. For example, in cases when a drug product is released from the manufacturing site after packaging in a fiber drum having an inner bag as a primary container, the sample should be stored in a bag of the same material or in a small scale drum having the same or identical composition of materials to the marketing product (additionally, for details of the stability monitoring of the drug substances, refer to the "Good Manufacturing Practice Guideline for Active Pharmaceutical Ingredients").

4) The stability monitoring should be carried out independently for each product and for more than one lot per year as a rule (excluding cases when there is no production in that corresponding year). In the meantime, the frequency of the analysis and testing should be at level from which the stability is able to be evaluated sufficiently, and possible to increase or decrease according to the accumulation of information, etc. related to the stability. However, the base of the decision should be documented.

5) The storage condition should be based on the regulations specified in the ICH stability guideline, according to necessity.

6) In cases when it is judged that assurance of the shelf-life or expiration date may become impossible as a result of the stability monitoring, evaluations of reference samples of other lots should also be performed; and according to the results, appropriate actions should be implemented.