I. GMP Guideline for Drug Products: Text

1 Introduction

1.1 Objective

In regard to general matters on manufacturing control and quality control of drug products (except for specified drug products such as sterile drugs and biological-origin drugs, etc.), this guideline intends to provide as specifically as possible the control methods that are related to the requirements of the GMP Ministerial Ordinance for Drugs and Quasi-drugs (and the GQP Ministerial Ordinance) but are not legally required or not clearly specified as requirements, and that need to be voluntarily addressed according to current knowledge, etc.

Consequently, this guideline covers the manufacturing control and quality control of drug products to which the GMP Ministerial Ordinance for Drugs and Quasi-drugs is applicable.

In this guideline "manufacturing" includes receipt of APIs, raw materials and labeling/packaging materials, production, packaging, labeling, examination/testing, storage, release from manufacturing sites, and other all operations related to manufacturing control and quality control at manufacturing sites for drug products. In this guideline the term "should" indicates recommendations for applying the relevant item unless there are alternative control methods that can provide equivalent levels of manufacturing control and quality control.

This guideline does not intend to cover safety and health for the personnel nor environmental protection.

2 Quality Management System

2.1 Principles

2.10 Each manufacturer should establish, document, and implement an effective system for supervising quality control. To establish and maintain the quality management system, the active participation of control supervisors and appropriate manufacturing staff should be involved.

2.11 The components of the quality management system should encompass the activities necessary for manufacturing control and quality control of drug products, as well as organizations and other required sources to implement the activities. In establishing the quality management system, all quality-related activities should be defined and documented.

2.12 The quality unit, independent of production units under the provision of Article 4, Paragraph 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, can be in the form of a separate unit or a single individual or group, depending upon the size and structure of the organization.

2.13 All quality-related activities should be recorded at the time they are performed.

2.14 Any deviation from established procedures should be documented and explained. As to critical deviations for which the effect on product quality cannot be denied, the quality unit should confirm the results of evaluation and necessary actions by the decision of release from the manufacturing site at the latest, under the provision of Article 15, Paragraph 1, Item 3 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs.

2.15 Neither the decision of release from manufacturing sites under the provision of Article 12, Paragraph 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, nor the use of raw materials, packaging/labeling materials or intermediate products in the next processes should be implemented before completion of evaluation by the quality unit, unless there are appropriate systems in place to allow for such use (e.g., release from manufacturing sites under quarantine or the use of raw materials or intermediate products pending completion of evaluation).

2.2 Responsibilities of Quality Unit

2.20 The quality unit should be involved in all quality-related matters.

2.21 The quality unit should review, confirm and approve all appropriate quality-related documents.

2.22 The main responsibilities of the independent quality unit should not be delegated. These responsibilities should be described in writing and should include but not necessarily be limited to:

1) Making decision of release from manufacturing site or rejection (hereinafter referred to as "decision of release"), and evaluating and deciding the use of intermediate products in the next processes in case they are used outside the control of the manufacturing company;
2) Establishing a system to release or reject raw materials, intermediate products, packaging and labeling materials;
3) Reviewing all manufacturing instructions, completed batch records and laboratory control records of critical processes of concerned lots when deciding the release of products from manufacturing sites;
4) Prior to deciding the release of products from manufacturing sites, making sure that critical deviations are investigated and resolved;
5) Approving the product master formula, manufacturing control standard code, hygienic control standard code, and all specifications and master manufacturing instructions;
6) Approving all procedures influencing product quality;
7) Confirming the results of self inspections and internal audits;
8) Approving contract matters on the quality aspects of suppliers of APIs and intermediate products;
9) Approving changes that potentially affect product quality
10) Confirming the plans and results of validation reported under the provision of Article 13, Paragraph 1, Item 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs;
11) Making sure that effective systems are used for maintaining and calibrating critical equipment;
12) Testing raw materials and packaging/labeling materials appropriately;
13) Making sure that there is stability data to support retest or expiry dates and storage conditions of APIs and/or intermediate products where necessary;
14) Performing product quality reviews (as defined in Chapter 2.5);
15) Making sure that training is performed; and
16) Constructing, maintaining, and managing a liaison system between the manufacturing distributor and manufacturing sites for the technical transfer and change control.

2.3 Responsibility of Production Unit

The responsibility of production units should be described in writing, and should include but not necessarily be limited to:

1) Preparing the master manufacturing instructions according to the product master formula, manufacturing control standard code and hygienic control standard code under the provision of Article 10, Paragraph 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, as well as reviewing, approving and distributing the completed manufacturing instructions;
2) For all production lots, reviewing manufacturing instructions and batch records and ensuring that the instructions are completed, the records are appropriately prepared, and both are signed or sealed.
3) Making sure that all production deviations are reported to and evaluated by persons predesignated under the provision of Article 15, Paragraph 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, and that critical

deviations are investigated and the conclusions are recorded;

4) Confirming cleanliness of buildings and facilities under the provision of Article 10, Paragraph 6 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, while making sure that the relevant buildings and facilities are sanitized and sterilized when necessary;
5) Making sure that validation plans and reports prepared by persons predesignated under the provision of Article 13, Paragraph 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs are reported to and reviewed and approved by the quality unit;
6) Evaluating proposed changes in product, process or equipment; and
7) Making sure that new and, when appropriate, modified facilities and equipment are qualified.

2.4 Self Inspection and Internal Audits

2.40 In order to verify compliance with the principles of GMP for drugs, regular self inspection and internal audits should be performed in accordance with an approved schedule. While the self inspection is performed by each manufacturing site, the internal audits are conducted across the whole manufacturer by an auditing team consisting of internal and external staffs of the manufacturing site. Confirmation under the GQP Ministerial Ordinance that can provide equivalent levels of confirmation can substitute the internal audits.

2.41 Self inspection or internal audit findings and the resulting corrective actions should be documented and brought to the attention of control supervisors. Agreed corrective actions should be completed in a timely and effective manner.

2.5 Product Quality Review

2.50 Regular quality reviews of products should be conducted by the quality unit with the objective of verifying the consistency of the process. Such reviews should be conducted and documented at least annually, and should include at least:

1) A review of results of critical ones among acceptance testing of raw materials and packaging/labeling materials, in-process control, and inspection and testing of products;
2) A review of all batches or control units that failed to meet established specification(s);
3) A review of all critical deviations or non-conformances and related investigations;
4) A review of any changes carried out to the processes or analytical methods;
5) A review of results of the stability monitoring program;
6) A review of all quality-related returns, complaints and recalls; and
7) A review of adequacy of corrective actions.

2.51 The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. When corrective actions are required, the reason should be documented. Agreed corrective actions should be completed in a timely and effective manner.

2.6 Technical Transfer

2.60 There are two types of technical transfer, that is, the technical transfer from the R&D to production, and the technical transfer after commercialization. In each case, technical information and quality information subject to the transfer should be documented, and the necessary information should be shared between the parties involved in the transfer.

2.61 The information to be shared (documents) includes the following as examples:
R&D report - The report that summarizes the information on the manufacturing technique and quality obtained by research and development. That is, the information that clearly shows the quality design of drug product, as well as the raw materials and packaging/labeling materials, manufacturing method, specifications and test methods, and that also shows the justification for establishing these matters.
Technical transfer documents - Product specifications that prescribe the specifications and product quality including the manufacturing method and assessment method of the drug products subject to technical transfer, and technical transfer plan/report prepared on the basis of product specifications.

2.62 The system for the responsibility in the organization related to transfer should be clarified for both parties (the transferring party and receiving party).

2.63 All the matters related to technical transfer should be approved or confirmed by the quality unit.

2.64 The consistency of manufacturing quality before and after technical transfer should be confirmed by the process validation, etc. at the final step of technical transfer.

3 Personnel

3.1 Personnel Qualifications

3.10 All the employees involved in the manufacture and quality of drug products should understand GMP.

3.11 For the purpose of appropriate conduct of jobs and supervision, the manufacturer should position an appropriate number of those who have received appropriate education and training or those who have had experiences.

3.12 The responsibilities of persons working in the production unit and quality unit and the management system should be prescribed in documents.

3.2 Education and Training

3.20 The persons predesignated under the provision of Article 19 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs (hereinafter referred to as "training and education manager") should conduct initial and continuous training (including the training related to hygiene) that is required for all the employees involved in the manufacture and quality of drug products (that is, staffs who enter the manufacturing area or laboratory area, including those engaged in the maintenance and cleaning, as well as staffs of the quality unit, etc.). The training and education records should be periodically evaluated.

3.21 The employees who are to be engaged in a new job should receive the education and training appropriate for the job including the basics of GMP. Continuous education and training thereafter should also be conducted.

3.22 An education and training program should be prepared for each job of those who are to receive education and training. The education and training program should be prepared by the production unit, quality unit and other departments involved. The program should be approved by the training and education manager. The education and training program should be regularly reviewed.

3.23 The quality unit should confirm the education and training program with its implementation records.

3.24 Special education and training should be given to the employees who work in the areas where contamination causes problems, for example, the clean area and the area where physiologically active, toxic and highly infectious or sensitizing substances are handled.

3.25 Visitors or employees who have not received education and training should not be allowed to enter the manufacturing area and laboratory area. In unavoidable cases, these persons should be appropriately instructed, such as notifying them of precautions in advance.

3.3 Personnel Hygiene Control

3.30 Appropriate health care of personnel should be practiced.

3.31 Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn when necessary, to protect raw materials and products from contamination.

3.32 Personnel should avoid as much as possible the direct contact with the object that may affect product quality.

3.33 Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

3.34 Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising product quality. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect product quality until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the products.

4 Buildings and Facilities

4.1 Design and Construction of Buildings and Facilities

4.10 Buildings and facilities should be located, designed, and constructed to facilitate cleaning, maintenance, and operations there as appropriate to the type and stage of manufacture of the products. The facility should also be designed to minimize potential contamination and cross-contamination. Where microbiological limits have been established for the product, facilities should also be designed to eliminate the exposure to objectionable microbiological contaminants as appropriate.

4.11 Buildings and facilities should have adequate space for the orderly placement of equipment and raw materials to prevent mix-ups and contamination or cross-contamination.

4.12 Appropriate buildings and facilities, where raw materials and packaging/labeling materials are stored in a manner to avoid contamination by microorganism and foreign matters, should be provided.

4.13 Buildings and facilities should be designed so that the flow of raw materials, packaging/labeling materials and personnel through the manufacturing site can prevent mix-ups and contamination or cross-contamination.

4.14 There should be defined areas or other control systems in manufacturing sites for the following activities:

- Receipt, identification, sampling, quarantine and pending release or rejection of raw materials and packaging/labeling materials;
- Storage of rejected raw materials and rejected packaging/labeling materials that were separated from accepted ones, for example in locked containers;
- Storage of accepted raw materials, containers and plugs
- Manufacturing and processing
- Storage of returned products
- Storage of intermediate products (when appropriate)
- Sterilization operation (only in the case of sterile drug product)
- Packaging and labeling
- Storage of products pending release or rejection
- Storage of products decided to be released
- Storage of products decided to be rejected
- Inspection and testing
- In-process control inspection and testing (when appropriate)

4.15 Washing facilities prescribed in the Article 6, Paragraph 3 of the Regulations for buildings and facilities should be equipped with hot and cold water as appropriate, soap or detergent, air driers or single service towels. The washing and toilet facilities should be separated from, but easily accessible from, manufacturing areas. When necessary, an appropriate facility for taking a shower and changing clothes should be installed.

4.16 Laboratory areas/operations should normally be separated from manufacturing areas. Some laboratory areas, in particular for in-process controls, can be located in manufacturing areas, provided that the operations of the manufacturing process do not adversely affect accuracy of the inspection/testing, and the laboratory and its operations do not adversely affect manufacturing processes or products.

4.17 The laboratory should be appropriately designed for the operations conducted there. Appropriate arrangement should be made such as providing sufficient space to prevent any mix-ups, contamination and cross-contamination. Sufficient and appropriate space for storage of collected samples and records should be provided.

4.2 Buildings and Facilities for Utilities

4.20 As to all utilities that could affect product quality (e.g., steam, gases, compressed air, etc.), appropriate monitoring should be performed to check whether they conform to the specifications predefined to control them. Necessary actions should be taken when limits are exceeded.

4.21 Buildings and facilities necessary for adequate ventilation, air filtration and exhaust should be provided. These buildings and facilities should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of room pressure, microorganisms, dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where products are exposed to the air inside the manufacturing site.

4.22 If air is recirculated to manufacturing areas, appropriate measures should be taken on the buildings and facilities to minimize risks of contamination and cross-contamination.

4.23 Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of products.

4.24 Drains should be of adequate size and should be provided with an air break or a suitable device to prevent backward flow, when appropriate.

4.3 Buildings and Facilities for Purifying Water

4.30 Purifying water should be demonstrated to be suitable for its intended use. When any water outside the standards listed in the compendium is used, the internal standard with valid ground should be established and documented.

4.31 Unless otherwise justified, purifying water should, at a minimum, meet the water quality standards based on Japanese Pharmacopoeia or Tap Water Law, or World Health Organization (WHO) guidelines for drinking water quality.

4.32 If purifying water is insufficient to assure product quality, and enhanced microbiological/physicochemical control limits are called for, appropriate specifications for necessary items among physicochemical attributes, total microbial counts, numbers of specific microorganisms and/or endotoxins should be established.

4.33 Where water used in the process is purifyed by the manufacturer to achieve a defined quality, the purification process should be validated and monitored by establishing appropriate control limits, and for this purpose, necessary buildings and facilities should be provided.

4.4 Buildings and Facilities for Containment

4.40 Dedicated manufacturing areas, which can include facilities, air treatment equipment and/or process equipment, should be employed in the production of highly sensitizing drug products, such as penicillins or cephalosporins. Sufficient attention should be given to prevention of cross-contamination and containment in inspection/testing of the sensitizing products in the laboratory.

4.41 Dedicated manufacturing areas should also be considered when drug products with high pharmacological activity or toxicity are involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.

4.42 Appropriate measures should be established and implemented to prevent cross-contamination from personnel, raw materials and packaging/labeling materials moving from the above dedicated manufacturing areas to another dedicated area.

4.43 Any manufacturing activities (including weighing, milling, or packaging) of highly toxic agrichemical products such as herbicides and pesticides should not be conducted using the buildings and facilities and/or equipment being used for the manufacturing of other drug products. Handling and storage of these highly toxic agrichemicals should be separated from other drug products.

4.5 Sewage and Refuse

4.50 Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) from manufacturing sites and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly distinguished from those for products, raw materials and packaging/labeling materials by labeling of identification.

4.6 Sanitation and Maintenance

4.60 Buildings and facilities used in the manufacture of products should be properly maintained, repaired and retained in a clean condition.

4.61 Written procedures should be established assigning responsibility for sanitation of the building and facilities and describing the cleaning schedules, methods, equipment, and materials to be used.

4.62 When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labeling materials, and products.

5 Process Equipment

5.1 Design and Construction

5.10 Equipment used in the manufacturing control and quality control of products (hereinafter referred to as "process equipment") should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.

5.11 Process equipment should be constructed so that surfaces that contact products do not alter the quality of the product beyond the official or other established specifications.

5.12 Process equipment should only be used within its qualified operating range.

5.13 Major process equipment (e.g., blender, tabletting machine) used during the manufacturing of products should be appropriately identified.

5.14 Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact products so as not to alter their quality beyond the official or other established specifications. Wherever possible, food grade lubricants and oils should be used.

5.15 Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.

5.16 A set of current drawings should be maintained for process equipment and critical installations (e.g., instrumentation and utility systems).

5.2 Maintenance and Cleaning of Process Equipment

5.20 Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of process equipment.

5.21 Written procedures should be established for cleaning of process equipment and its subsequent release for use in the manufacture control and quality control of products. Cleaning procedures should contain sufficient details to enable operators to clean each type of process equipment in a reproducible and effective manner. These procedures should include:

- Assignment of responsibility for cleaning of process equipment;
- Cleaning schedules, including, where appropriate, sanitizing schedule;
- A complete description of the methods and materials, including dilution of cleaning agents used to clean process equipment;
- When appropriate, instructions for disassembling and reassembling each article of process equipment to ensure proper cleaning;
- Instructions for the removal or obliteration of previous batch identification;
- Instructions for the protection of clean equipment from contamination prior to

use;
- Inspection/testing of equipment for cleanliness immediately before use, if practical; and
- Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate. Establishing the cleaning expiry date for equipment cleaning implementation, when appropriate.

5.22 Process equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter product quality beyond the official or other established specifications.

5.23 Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or product, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g., degradants or objectionable levels of micro-organisms).

5.24 Non-dedicated equipment should be cleaned between productions of different products to prevent cross-contamination.

5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.

5.26 Process equipment should be identified as to its contents and its cleanliness status by appropriate means.

5.27 Confirm that filters to use at the last stage of product manufacturing process do not discharge fiber.

5.3 Calibration

5.30 Control, weighing, monitoring and test equipment that is critical for assuring product quality should be calibrated according to written procedures and an established schedule. A list of measuring instruments for each unit of equipment should be prepared, the risk related to product quality should be assessed, and the presence or absence of calibration as well as the calibration frequency should be clarified.

5.31 Calibration of process equipment should be performed using standards traceable to certified standards, if existing.

5.32 The current calibration status of critical equipment and measuring instruments should be known and verifiable. A calibration seal should be affixed to each equipment and measuring instrument. The contents of such seal include the result of calibration, scheduled date of next calibration.

5.33 Measuring instruments that do not meet calibration criteria should not be used. Any measuring instruments that do not meet the calibration criteria or any

measuring instruments whose calibration expiry date has expired should be labeled as "not permitted for use."

5.34 Deviations from approved standards of calibration on critical measuring instruments should be investigated to determine if they could have had an effect on quality of products manufactured with this equipment after the last successful calibration.
As to investigation methods, for example, there is a method to check the presence or absence of any problems by conducting tests with proper measuring instruments on the quality standard determined by those instruments using the stored product (reserve sample) manufactured after the last successful calibration. If any abnormality is detected as a result of investigation, implementation of necessary actions should be discussed.

5.4 Computerized Systems

5.40 Computerized systems related to manufacturing control and quality control of products should be validated. The degree and scope of the validation should be decided considering diversity, complexity and criticality of the computerized application.

5.41 Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.

5.42 Commercially available software that has been qualified does not require the same level of testing as that for the computerized systems designed specifically for the process. If an existing system was not validated at time of installation but appropriate documentation is available, a retrospective validation can be conducted.

5.43 Data of computerized systems should be sufficiently controlled to prevent unauthorized access to or change in the data. Data should be controlled to prevent their omissions. In case that any data are changed, all changed data, previous entry, name of person who made the change, and date/time when the change was made should be recorded.

5.44 Written procedures should be available for the operation and maintenance of computerized systems.

5.45 In case that critical data are entered manually, whether the accurate entry was made should be reviewed. This review can be conducted by the second operator or by the system itself.

5.46 Any failure in computerized systems that can affect product quality, or the reliability of records or test results should be recorded and investigated.

5.47 Changes to the computerized system should be made according to a change

procedure, and the content of the change should be approved ultimately by the quality unit, documented and investigated. Records should be retained of all changes, including modifications and enhancements made to the hardware, software and any other critical components of the system. These records should demonstrate that the system is ultimately maintained in a validated state.

5.48 If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems related to GMP.

5.49 Data can be recorded by another means in addition to the computerized system.

6 Documentation and Records

6.1 Documentation

6.10 All documents related to the quality management system should be prepared, reviewed, approved and distributed according to written procedures. Such documents can be in paper or electronic form.

6.11 Written procedures should be prepared to control appropriately the issuance, revision, superseding and withdrawal of all documents. The latest version should be controlled by maintaining all document histories.

6.12 A procedure should be established for retaining all appropriate documents (e.g., development history records, scale-up reports, technical transfer reports, validation protocols/reports on manufacturing processes, equipment and analytical methods, product master formula, hygienic control standard code, manufacturing control standard code, quality control standard code, written procedures, master manufacturing instructions, manufacturing instructions and corresponding batch records, records on cleaning/use/calibration of equipment, raw material records, laboratory control records, inventory records, and training records). The retention periods for these documents should be specified.

6.13 The documents should be prepared in a language and context that are understandable to the personnel who are engaged in activities related to the manufacturing control and quality control of products at manufacturing sites.

6.14 The documents should be prepared so as to demonstrate the mutual relation among the documents clearly.

6.15 When preparing records, the name of the person who made entries should be written by indelible way in predefined spaces directly after performing the activities. Corrections to entries should be dated and signed or sealed, and the original entry should be kept readable. In case of correction of records that would affect the product quality (yield, analytical values of process control, etc.), reason for the corrections should be provided.

6.16 The original records or their copies should be readily available during their retention period at the site where the relevant activities have been performed. Records that can be promptly retrieved from another archiving site by electronic or other means are acceptable.

6.17 Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.

6.18 If electronic signatures are used on documents, they should be certified and assured

of specific use by each individual.

6.2 Specifications

6.20 Specifications should be established and documented for raw materials used for manufacturing of products. As to packaging/labeling materials used for manufacturing that may critically affect product quality, specifications should be established where applicable. For in-process control items, acceptance criteria should be predefined and documented.

6.3 Manufacturing Instructions and Batch Records

6.30 Manufacturing instructions should mention the standards for decision of release to the next processes. When master manufacturing instructions should be prepared, a person in the production unit who is responsible for preparation of the master manufacturing instructions should enter the date and sign or seal on the master manufacturing instructions. The quality unit should confirm the content of the master manufacturing instructions, and enter the date and sign or seal of a person in the unit, who is responsible, on the master manufacturing instructions.

6.31 Product manufacturing records prepared for each lot (hereinafter referred to as "batch record") should include the complete information related to the manufacturing control of each lot. The batch record should be confirmed by a person in the production unit who is responsible for preparation of the batch record to assure that the batch record is a correct version and has been prepared legibly and accurately according to the appropriate manufacturing instruction.

6.32 When manufacturing instructions and batch records are issued, they should be dated and signed or sealed, and numbered with specific lot numbers or identification numbers. In continuous production, the product code together with the date and time should be used as the specific identifier until the final number is allocated.

6.33 The items to be documented on the major processes in the manufacturing instructions and batch records should include:

1) Dates and, where applicable, times;
2) Major equipment used;
3) Specific identification of each lot, including weights, measures, and lot numbers or control numbers of raw materials and packaging/labeling materials used during manufacturing;
4) Results recorded for critical process parameters;
5) Any sampling performed;
6) Signatures or seals of the persons performing and directly supervising or checking activities in each critical process;
7) In-process and laboratory test results;
8) Actual yield at appropriate steps or times;
9) Description of packaging and label for products;
10) Any deviation noted, its evaluation, investigation conducted (where

applicable) or reference to that investigation results if stored separately; and
11) Results of decision for release to the next processes.

6.4 Equipment Cleaning and Use Record

6.40 Records of major equipment use, cleaning, sanitization and/or sterilization and maintenance should provide the date, time (where applicable), product name, and lot number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.

6.41 If equipment is dedicated for manufacturing one product, the individual equipment records are not necessary if the lot number of the product follows in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.

6.5 Use Records of Labeling and Packaging Materials

6.50 Use records of labeling and packaging materials used for the product should be prepared per lot or control unit of the product and should include:
- For each lot and each receipt; name of supplier, identification number of supplier (if available), control number at the time of receipt, and date of receipt;
- Results of testing on conformity with predefined specifications and results of the decision;
- Records of inventory and use of materials; and
- The final actions to deal with rejected labeling and packaging materials.

6.51 Approved master labels for labeling and packaging materials should be retained and maintained for comparison to the used labels per lot or control unit of the product.

6.6 Laboratory Control Records

6.60 Laboratory control records should include complete data derived from all tests conducted to ensure compliance with the established specifications, as follows:
1) Descriptions of samples collected for testing, including the name of raw materials and packaging/labeling materials, supplier name, lot number or control unit number, date of sampling, and sampling quantity where applicable;
2) Comments or reference to each testing method used;
3) Descriptions of the quantity of samples used for each test, measured values, reference standards, reagents, preparation of standard solutions, and other cross-references;
4) Complete records of all raw data obtained in each test, in addition to graphs, charts, and spectra from laboratory instruments, which should be properly identified to show the specific materials and their lots tested;
5) Record of all calculations performed in connection with the test, including

units of measure, conversion coefficients, and equivalency coefficients;

6) Descriptions about the evaluation of test results and the comparison with acceptance criteria;
7) Signatures or seals of persons who performed each test and dates when the tests were performed; and
8) A signature or seal of a responsible person in the quality unit and the date to show that the original records have been reviewed for accuracy, completeness, and compliance with established specifications.

6.61 Complete records should be maintained for:

1) Any modifications to established analytical methods;
2) Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices;
3) All stability testing performed on products; and
4) Out-of-specification (OOS) investigations

7 Control of Raw Materials and Packaging/Labeling Materials

7.1 General Controls

7.10 The quality control standard codes defined in Article 8, Paragraph 3 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should include descriptions about receipt, identification, storage, handling, sampling, testing, procedure for approval or rejection, and reassessment of raw materials and packaging/labeling materials.

7.11 A system for assessment of suppliers of critical raw materials and packaging/labeling materials should be provided.

7.12 Raw materials and packaging/labeling materials should be purchased from suppliers approved by the quality unit, and only those that conform with the predefined specifications should be accepted.

7.13 If a supplier of critical raw materials or packaging/labeling materials is not itself the manufacturer of them, the name and address of the manufacturer of the relevant raw materials or packaging/labeling materials with their quality information should be provided.

7.14 Change of suppliers of critical raw materials and packaging/labeling materials should be treated as defined in Chapter 13 (Change Control).

7.2 Receipt and Quarantine of Raw Materials and Packaging/Labeling Materials

7.20 Upon receipt and before approval of use, visual inspection should be performed to check labeling of each container or group of containers of raw materials and packaging/labeling materials (including description of correlation between the labeling by suppliers and the in-house labeling, if they are different), container damage, broken seals and evidence of tampering or contamination. Raw materials and packaging/labeling materials should be held under quarantine during sample collection and required testing, and until approved for release for use.

7.21 In case that newly received raw materials and packaging/labeling materials are to be blended with existing stocks (e.g., solvents in a large volume storage tank), the incoming materials should be tested in advance and identified as appropriate, and then blended. Procedures should be available to prevent inadequate mix-up of incoming raw materials and packaging/labeling materials with existing stocks.

7.22 In case that raw materials and packaging/labeling materials are transported by non-dedicated tankers, confirm that no cross-contamination occurs in the tankers. Confirmation method can include the following:

- Certificate of cleaning
- Testing for minute impurities
- Onsite audit of the supplier

7.23 Large volume storage containers, their equipped piping, filling and discharge lines