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## Normative Documents

# Good Manufacturing Practice for Drugs (2010 Revision)

( MOH Decree No. 79 )

The Good Manufacturing Practice for Drugs (2010 Revision), adopted at the executive meeting of the Ministry of Health on October 19, 2010, is hereby promulgated and shall go into effect as of March 1, 2011.

Chen Zhu  
Minister of MOH  
January 17, 2011

## Good Manufacturing Practice (GMP) for Drugs

### Chapter 1 General Provisions

Article 1: These provisions of Good Manufacturing Practice (GMP) for Drugs, in accordance with the Drug Administration Law of the People's Republic of China and the Regulations for Implementation of the Drug Administration Law of the People's Republic of China, are enacted to regulate the manufacturing and quality management of Drugs.

Article 2: The manufacturer should establish a quality management system. The system should cover all factors that influence the quality of drugs, including all organized and planned activities with the objective of ensuring that the drugs are of the quality required for their intended use.

Article 3: GMP, as part of the quality management system, is the basic requirement of production and quality control of drugs, to ensure the products are consistently manufactured in accordance with the registration requirements, and are suitable for their intended use, by minimizing the risks of contamination, cross-contamination and mixups or errors in manufacturing process.

Article 4: The manufacturer should strictly implement GMP with integrity. Any falsification and fraud is forbidden.

### Chapter 2 Quality Management

#### Section 1 Principle

Article 5: The manufacturer should establish a quality objective to meet quality management requirements

so that all registration requirements related to drug safety, efficacy and quality are systematically implemented throughout the entire process of production, control, product release, storage and distribution, to ensure that the products are manufactured in accordance with the registration requirements, and are suitable for their intended use.

Article 6: The attainment of the quality objective is the responsibility of senior management and requires the participation and commitment by staff at all levels within the manufacturer, by the manufacturer's suppliers and by the distributors.

Article 7: The manufacturer should be adequately resourced with competent personnel, suitable and sufficient premises, equipment and facilities for achieving its quality objective.

## Section 2 Quality Assurance

Article 8: Quality Assurance is a part of the quality management system. The manufacturer should establish the Quality Assurance system with the support of a complete documentation system to ensure its effective operation.

Article 9: The system of Quality Assurance should ensure that:

1. Drugs are designed and developed in a way that takes account of the requirements of GMP.
2. Production and quality control operations are in compliance with GMP.
3. Managerial responsibilities are clearly specified.
4. Arrangements are made for the purchase and use of the correct starting and packaging materials.
5. All necessary controls on intermediate products are effectively carried out.
6. Qualifications and validations are carried out.
7. Drugs are correctly processed, checked, tested, and verified, according to the defined procedures.
8. Each batch of products is not released before the approval of the Qualified Person.
9. Satisfactory arrangements exist to ensure that the drugs are stored, distributed and subsequently handled.
10. Self-inspection is regularly carried out to appraise the effectiveness and applicability of the Quality Assurance system, according to the procedures.

Article 10: The basic requirements of production and quality control are that:

1. All manufacturing processes are clearly defined, systematically reviewed and shown to be capable of consistently manufacturing drugs of the required quality and complying with their specifications.
2. Steps of manufacturing processes and significant changes to the process are validated.
3. All necessary resources are provided including:
  - 1) Appropriately qualified and trained personnel;

- 2) Adequate premises and space;
  - 3) Suitable equipment and services;
  - 4) Correct starting materials, packaging materials and labels;
  - 5) Approved master manufacturing documents and operation procedures;
  - 6) Suitable storage and transport.
4. Instructions and procedures are written in clear and unambiguous language.
  5. Operators are trained to carry out procedures correctly.
  6. Records should be made during the entire manufacture and any deviations are investigated and recorded accordingly.
  7. Records of manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form.
  8. The distribution of the products minimizes any risk to their quality.
  9. A system is available to recall any batch of product, from sale or supply.
  10. Complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent reoccurrence.

### Section 3 Quality Control

Article 11: Quality Control is concerned with organization and documentation, and with sampling, testing and etc., which ensure that the necessary tests are actually carried out and that materials or products are not released, until their quality has been judged to be satisfactory.

Article 12: The basic requirements of Quality Control are that:

1. Adequate facilities, equipment, instruments and trained personnel are resourced, to ensure the related quality control activities are done effectively and reliably.
2. Approved procedures are available for sampling, inspection and testing starting materials, packaging materials, intermediate, bulk, and finished products, and stability study, and where appropriate for monitoring environmental conditions, to ensure the compliance with GMP.
3. Samples of starting materials, packaging materials, intermediate, bulk and finished products are taken by authorized personnel with approved methods.
4. Testing methods are validated or verified.
5. Records are made for sampling, inspecting and testing. Any deviations are investigated and recorded.
6. Records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification.
7. Sufficient reference samples of starting materials and finished products are retained to permit future

inspection and testing of the product when necessary, and that the finished product is retained in its final package unless exceptionally large packages are produced.

#### Section 4 Quality Risk Management

Article 13: Quality risk management is a systematic process for the assessment, control, communication and review of the risk to quality throughout the entire product life cycle. It can be applied both proactively and retrospectively.

Article 14: The evaluation of the risk to quality is based on scientific knowledge and experience, to ensure the quality of products.

Article 15: The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

### Chapter 3 Organization and Personnel

#### Section 1 Principle

Article 16: The manufacturer should establish a management structure and have an organization chart. The quality management department should be independent from other departments to carry out responsibilities of Quality Assurance and Quality Control. The quality management department can be structured into the quality assurance department and the quality control department separately.

Article 17: The quality management department should participate in all quality related activities, and review all GMP related documents. The responsibilities of quality management personnel are not permitted to be delegated to personnel of other departments.

Article 18: The manufacturer should have an adequate number of managerial and operating personnel with appropriate qualifications (with respect to, including education, training, and practical experience). The responsibilities of each department and each position should be clearly specified. There should be no gaps or unexplained overlaps in the responsibilities. The responsibilities placed on any one individual should not be extensive.

All personnel should be fully aware of and understand their responsibilities, be familiar with related requirements, and receive necessary training, including initial training and continuing training.

Article 19: Duties normally should not be delegated to other personnel. If deemed necessary, the duties can only be delegated to designated deputies of a satisfactory qualification level.

#### Section 2 Key Personnel

Article 20: Key posts should be occupied by full-time personnel, which should at least include the heads of the manufacturer, production management, quality management, and the Qualified Person.

The heads of production and quality management must be independent from each other. The head of the quality management and the Qualified Person can be the same person. Procedures should be established to ensure the independence of the Qualified Person for fulfilling responsibilities, without interference from the head of the manufacturer or other personnel.

Article 21: The head of the manufacturer

The head of the manufacturer is principally liable for product quality and routine operation. In order to

achieve the manufacturer's quality objective and compliance with GMP, the head of the manufacturer should provide necessary resources, make appropriate plan, organization and coordination, and ensure that the quality management department can fulfill its responsibilities independently.

#### Article 22: The head of production management

1. Qualification: The head of production management should, at a minimum, possess a college degree in pharmaceutical or relevant specialties (or with an intermediate professional technique certificate or a pharmacist's license), with at least three years of practical experience in pharmaceutical production and quality management, among which at least one year in production management, with necessary training relating to the products being manufactured.

#### 2. Main responsibilities:

- 1) To ensure that products are produced and stored according to approved master manufacturing documents in order to obtain the required quality;
- 2) To ensure strict implementation of the procedures relating to production operations;
- 3) To ensure that the batch records of processing and packaging are evaluated and signed by a designated person before they are sent to the quality management department;
- 4) To ensure that the premises and equipment are maintained and serviced to function in a sound operating state;
- 5) To ensure that the necessary validations are done;
- 6) To ensure that required initial and continuing training of personnel in production is carried out and adapted according to need.

#### Article 23: The head of quality management

1. Qualification: The head of the quality management should, at a minimum, possess a college degree in pharmaceutical or relevant specialties (or with an intermediate professional technique certificate or a pharmacist's license), with at least five years of practical experience in pharmaceutical production and quality management, among which at least one year in quality management, with necessary training relating to the products being manufactured.

#### 2. Main responsibilities:

- 1) To ensure that all starting materials, packaging materials, intermediate, bulk and finished products meet the registration requirements and specifications;
- 2) To ensure that the batch records are reviewed before product release;
- 3) To ensure that all necessary testing is carried out;
- 4) To approve specifications, sampling instructions, testing methods and other quality management procedures;
- 5) To review and approve all quality related changes;
- 6) To ensure all significant deviations and out-of-specification results are timely investigated and handled;

- 7) To approve and monitor any contract analysis;
- 8) To check the maintenance of premises and equipment for the purpose of maintaining a sound operating state;
- 9) To ensure the necessary qualifications or validations are done appropriately, and to review and approve validation protocols and reports;
- 10) To ensure self-inspection is done;
- 11) To assess and approve material suppliers;
- 12) To ensure all quality related complaints are timely and properly investigated and handled;
- 13) To ensure the implementation of on-going stability study and make the stability data available;
- 14) To ensure that the product quality reviews are done;
- 15) To ensure that the necessary initial and continuing training of personnel in Quality Control and Quality Assurance is carried out and adapted according to need.

Article 24: The heads of production and quality management generally have some shared, or jointly exercised, responsibilities relating to quality, including:

1. The review and approval of master manufacturing documents, procedures, etc;
2. The monitoring of manufacturing environment and plant hygiene;
3. Ensuring the critical equipment has been qualified;
4. Ensuring the completion of manufacturing process validation;
5. Ensuring the required initial and continuing training of all related personnel of the manufacturer is carried out and adapted according to need;
6. The approval and monitoring of contract manufacturers;
7. The designation and monitoring of storage conditions for materials and products;
8. The retention of records;
9. The monitoring of compliance with GMP;
10. The monitoring of the factors that may affect product quality.

Article 25: Qualified Person

1. Qualification: The Qualified Person should, at a minimum, possess a college degree in pharmaceutical or relevant specialties (or with an intermediate professional technique certificate or a pharmacist's license), with at least five years of practical experience in pharmaceutical production and quality management, with work experience in in-process control and quality testing.

The Qualified Person should possess necessary theoretical knowledge in relevant specialties be trained in product release so as to fulfill its responsibilities independently.

## 2. Main responsibilities:

- 1) To participate in quality management activities such as establishment of the quality system, self-inspection, external quality audit, validation, adverse drug reaction reporting and product recalls;
- 2) To be responsible for product release and to ensure that the production and testing of each batch of released products are in accordance with the related regulations, the registration requirements and specifications;
- 3) Prior to the release of each batch, the Qualified Person must issue a review record for product release according to the requirements in the above paragraph 2, and archive it to the batch record.

## Section 3 Training

Article 26: The manufacturer should designate a specific department or person(s) to take charge of training activities. A training program and plan reviewed or approved by the head of production management or quality management should be available. Training records should be retained.

Article 27: Training should be provided for all personnel in production and quality activities. The content of the training should be appropriate to the responsibilities assigned to them. Besides the training on the theory and practice of the Provisions, there should be training on relevant laws and regulations, and job related responsibilities and skills. The practical effectiveness of the training should be periodically assessed.

Article 28: Personnel working in high-risk areas (e.g. production areas for highly active, toxic, infectious or sensitizing materials) should be given specific training.

## Section 4 Personnel Hygiene

Article 29: All personnel should receive training of hygiene requirements. The manufacturer should establish personnel hygiene operation procedures to minimize the risks of contamination in drug production caused by personnel.

Article 30: The personnel hygiene operation procedures should include contents relating to the health, hygiene practices and clothing of personnel. Every person whose duties take him into the production and quality control areas should correctly understand and follow these procedures. The manufacturer should take measures to ensure the implementation of these procedures.

Article 31: The manufacturer should have management on the employee's health and establish health archives. Personnel engaged in manufacturing who is in direct contact with drugs should receive medical examination before being assigned to work, and the examination should be carried out at least annually afterward.

Article 32: The manufacturer should take measures to ensure that no person having open lesions on the exposed surface of the body, affected by an infectious disease or other diseases that may contaminate the products, is engaged in the manufacture of drugs.

Article 33: Visitors or untrained personnel should, preferably, not be taken into the production and quality control areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing.

Article 34: Every person entering manufacturing areas should wear protective garments as required. The material and style of garments, and way of gowning should be appropriate to the specific work conducted, and the required air cleanliness level.

Article 35: Persons entering clean areas should not wear make-up, jewelry or similar accessories.

Article 36: In production and storage areas, smoking or eating and drinking, or the storage of food, drink, cigarettes or personal medication, as well as other goods not for manufacturing should be prohibited.

Article 37: Direct contact should be avoided between the operator's hands and the exposed product, immediate packaging materials, as well as with any part of the equipment that comes into contact with the products.

## **Chapter4 Premises and Facilities**

### Section 1 Principle

Article 38: The location, design, lay-out, construction, adaption and maintenance of premises should suit the drug production requirements, and should minimize the risk of contamination, cross-contamination, mixups and errors, as well as permit effective cleaning, operation and maintenance.

Article 39: Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimal risk of causing contamination of materials or products.

Article 40: The manufacturer should have a neat manufacturing environment. The ground, roads, and transportation in plant area should not introduce contamination to the manufacturing. The general layout of production, administration, living and ancillary areas should be well designed to avoid interference from each other. Premises and buildings should be well designed to ensure the logical flow of materials and personnel.

Article 41: Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

Article 42: Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the product quality during their manufacture and storage, or the accurate functioning of equipment.

Article 43: Premises and facilities should be designed and equipped so as to afford maximum protection against the entry of insects or other animals. Necessary measures should be taken to avoid the contamination to equipment, materials and products caused by raticide, insecticide, fumigation reagent, etc.

Article 44: Measures should be taken in order to prevent the entry of unauthorized people. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.

Article 45: Drawings of premises, facilities and the fixed pipes should be archived as built or after modification.

### Section 2 Production Area

Article 46: In order to minimize the risks of contamination and cross-contamination, premises, facilities and equipment should be designed, laid out and used appropriately in accordance with the properties of the



manufactured product and its process, as well as the corresponding cleanliness level, and the following requirements should be met:

1. A comprehensive consideration of the aspects such as properties of products, processes and intended uses etc. should be given, so as to determine the feasibility of sharing premises, facilities and equipment for different products, along with an assessment reports.
2. Dedicated and self-contained premises, facilities and equipment must be used for the production of products with particular properties such as highly sensitizing products (e.g. penicillins) or biological preparations (e.g. Bacillus Calmette Guerin vaccine or any other products derived from live microorganisms). Dust generating operation areas in penicillin production should maintain relatively negative pressure, the exhaust air should be decontaminated as required, and the air outlet should be far away from the air inlet of other air-handling systems.
3. Dedicated facilities (e.g. a dedicated air handling system) and equipment must be used in production of  $\beta$ -lactam products and sex hormonal contraceptives, and their production areas must be strictly segregated from those of other products.
4. Dedicated facilities (e.g. a dedicated air handling system) and equipment should be used for some hormonal, cytotoxic and highly potent chemical products. In exceptional cases, the principle of campaign working in the same facilities and equipment can be accepted provided that specific precautions are taken and the necessary validations are made.
5. The exhaust air from the air handling system in above paragraphs 2, 3 and 4 should be decontaminated;
6. The production of non-drugs with adverse effects on drug should not be allowed in premises used for drugs.

Article 47: The adequacy of the production area and storage area should ensure the orderly positioning of equipment, materials, intermediate, bulk and finished products, so as to avoid mixups, cross-contamination between different products and materials, and to avoid the omissions or errors of any of the manufacturing or quality control steps.

Article 48: Production areas should be effectively ventilated, with air control facilities (including temperature, humidity and filtration) appropriate to the products handled, the operations undertaken within them and the external environment, to ensure that the production environment is in accordance with the requirements.

The air pressure differential between clean and non-clean areas, or between differently classified clean areas should not be less than 10Pa. When necessary, an appropriately-graded pressure differential should be maintained between rooms of different functions (operation rooms) with the same cleanliness level.

The exposed processing areas for oral liquid and solid preparations, drugs applied through tract (including recta), epidermal products, and other non-sterile products, as well as the exposed processing areas for handling immediate packaging materials should be designed as Grade D according to requirements in Annex 1 of GMP for sterile products. The manufacturer may take appropriate measures to monitor the microorganism, in accordance with product specifications and property.

Article 49: Interior surfaces (walls, floors and ceilings) of a clean area should be smooth, free from cracks, open joints and dust retention, and should not shed particulate matter, and should permit easy and effective cleaning and, if necessary, disinfection.

Article 50: Pipes, light fittings, ventilation points and other services should be designed and sited to avoid

the creation of recesses that are difficult to clean. As far as possible, they should be accessible from outside the manufacturing areas for maintenance.

Article 51: Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible, but when unavoidable, shallow channels are recommended to facilitate cleaning and disinfection.

Article 52: Weighing of starting materials for preparations usually should be carried out in a separate weighing room designed for that use.

Article 53: Operation areas where dust is generated (e.g. during sampling, weighing, mixing and packaging of dry materials and products) should be kept under relatively negative pressure, and specific measures should be taken to avoid dust diffusion and cross-contamination, and to facilitate cleaning.

Article 54: Premises or areas for the packaging of drugs should be reasonably designed and laid out, so as to avoid mixups or cross-contamination. Where several packaging lines are in the same area, there should be segregation in place.

Article 55: Production areas should be well lit, particularly where visual on-line controls are carried out.

Article 56: In-process controls areas may be set up within the production area without bringing any risk to product quality.

### Section 3 Storage Areas

Article 57: Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.

Article 58: Storage areas should be designed or constructed to ensure good storage conditions, with ventilation and lighting facilities. Where special storage conditions (e.g. temperature, humidity, light shade) and security are required, these should be provided, checked and monitored.

Article 59: Highly active materials or products and printed packaging materials should be stored in safe and secure areas.

Article 60: Receiving, dispatch and distribution bays should protect materials and products from the weather (e.g. raining, snowing). Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.

Article 61: Where a separate area is needed for the storage of materials in quarantine, the area must be clearly marked and its access restricted to authorized personnel.

Segregation should be provided for the storage of rejected, recalled or returned materials or products.

Any system replacing the physical quarantine should give equivalent security.

Article 62: There should normally be a separate sampling area for materials, which air-cleanliness levels should be the same as the corresponding production area. If sampling is performed in other areas or with other methods, it should be conducted in such a way as to prevent contamination or cross-contamination.

### Section 4 Quality Control Areas

Article 63: Quality Control laboratories usually should be separated from production areas. Laboratories for the control of biological, microbiological and radioisotopes should also be separated from each other.

Article 64: Laboratories should be designed to suit its intended use and avoid mixups and cross-contamination. There should be adequate space for samples handling, storage of retention and stability samples, and storage of records.

Article 65: Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, or interference of other external factors.

Article 66: Regulatory requirements should be met in laboratories handling particular substances, such as biological or radioactive samples.

Article 67: Experimental animal houses should be well isolated from other areas, and their design and construction should comply with relevant regulatory requirements. There should be dedicated air handling facilities and separate entrance for animal access.

#### Section 5 Ancillary Areas

Article 68: Rest and refreshment rooms should not bring any hazard to production, storage and quality control areas.

Article 69: Facilities for changing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not communicate directly with production or storage areas.

Article 70: Maintenance workshops should as far as possible be separated from production areas. Whenever parts and tools are stored in the clean area, they should be kept in rooms or lockers reserved for that use.

### **Chapter 5 Equipment**

#### Section 1 Principle

Article 71: The design, selection, installation, adaption and maintenance of equipment should be suitable for its intended use, minimize the risk of contamination, cross-contamination, mixups or errors, and facilitate operation, cleaning, maintenance, as well as disinfection or sterilization if necessary.

Article 72: Procedures for the use, cleaning, maintenance and repair of the equipment should be established, and their operation records should be retained.

Article 73: The documents and records for equipment procurement, installation, and qualification should be archived.

#### Section 2 Design and Installation

Article 74: Production equipment should not present any hazard to drug quality. The surface of the production equipment that come into direct contact with the drug should be smooth, spotless, and easy to clean, disinfect, sterilize and anti-corrosive. It must not be reactive, additive or absorptive to affect product quality.

Article 75: Weighing, measuring equipment, instruments and gauges of an appropriate range and precision should be available.

Article 76: Appropriate washing and cleaning equipment should be chosen and used in order not to be a source of contamination.

Article 77: Lubricant and refrigerant etc. used in the equipment should not contaminate products or containers. Food grade or equivalent lubricant should be used whenever possible.

Article 78: Procedures for purchase, check and acceptance, storage, maintenance, dispensing and discarding of the production molds should be established. The molds should be kept by designated personnel in dedicated cabinets and recorded accordingly.

### Section 3 Maintenance and Repair

Article 79: Repair and maintenance operations should not present any hazard to product quality.

Article 80: Preventive maintenance plans and procedures should be established, and the maintenance and repair activities should be recorded.

Article 81: Equipment that has undergone change or major repair should not be put into use until it is re-qualified.

### Section 4 Usage and Cleaning

Article 82: Clear operating procedures should be available for major items of production and test equipment.

Article 83: Production equipment should be operated within qualified parameter range.

Article 84: Production equipment should be cleaned according to detailed operation procedures.

Operation procedures for the cleaning of production equipment should specify a detailed and complete cleaning method, equipment and tools for cleaning, names and preparation methods of detergents, methods of removing identification marks of the previous batch, methods of protecting cleaned equipment from contamination prior to use, the maximum storage time after cleaning, and methods of checking the cleanliness status of equipment before use, so as to enable operators to clean the equipment in a reproducible and effective manner.

Where equipment needs to be disassembled, sequence and methods for disassembling and reassembling of equipment need to be set up. Where equipment needs to be disinfected or sterilized, methods for disinfecting or sterilizing, name of the detergent and its preparation need to be included in the procedures. The maximum intervals between the completion of production and cleaning of equipment should also be specified when necessary.

Article 85: Production equipment after cleaning should be stored in a clean and dry condition.

Article 86: Log books should be established for equipment and instruments used for drug production and testing, to record the use, cleaning, maintenance and repair activities, along with the date, time, and the name, strength, batch number, etc., of the drug produced and tested.

Article 87: Production equipment should be clearly labeled to indicate the equipment reference number and the contents (e.g. product name, strength, batch number, etc.). The equipment without contents should be labeled to indicate its cleaning status.

Article 88: Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labeled as defective.

Article 89: Main fixed pipes should be clearly labeled to indicate the contents and the direction of flow.

#### Section 5 Calibration

Article 90: Weighing and measuring equipment, gauges, recording and control equipment and all instruments used in production and testing should be calibrated and checked at defined intervals according to the operation procedures and calibration plans, and related records should be retained. Calibration should cover the range used in production and testing.

Article 91: Key weighing, measuring equipment, gauges, recording and control equipment used in production and testing should be calibrated to ensure that data readout is accurate and reliable.

Article 92: Calibration should be done with standard measuring instruments meeting regulatory requirements. Calibration records should include the name, code, calibration validity date and number of accreditation certificate to ensure their traceability.

Article 93: Weighing and measuring equipment, gauges, recording and control equipment should be clearly labeled to indicate the calibration validity date.

Article 94: Weighing and measuring equipment, gauges, recording and control equipment which are not calibrated or beyond the shelf life or inaccurate should not be used.

Article 95: Automated or electronic equipment used in production, packaging and storage should be regularly calibrated and checked according to procedures, in order to ensure their proper functioning. Calibration and checks should be recorded accordingly.

#### Section 6 Water for Pharmaceutical Use

Article 96: Water for pharmaceutical use should be suitable for its intended use, and meet the specifications of the Chinese Pharmacopeia and the related requirements. It should at least be sourced from drinking water.

Article 97: Water treatment plants and distribution systems should be designed, constructed, operated and maintained so as to ensure that water for pharmaceutical use meets the defined specifications. They should not be operated beyond their designed capacity.

Article 98: The materials of storage tanks and pipes for transport of purified water and water for injection should be non-toxic and corrosion resistant. The vent of storage tanks should be installed with non-fiber releasing hydrophobic microorganism retention filter. Dead legs should be avoided in the design and installation of pipelines.

Article 99: Purified water and water for injection should be produced, stored and distributed in a manner that prevents microbial growth. Purified water can be circulated, and water for injection can be circulated at a temperature above 70°C.

Article 100: The quality of water for pharmaceutical use and its water sources should be monitored at defined intervals, and recorded accordingly.

Article 101: The pipes for purified water and water for injection should be cleaned and sanitized according to operation procedures and recorded accordingly. If bioburden of water for pharmaceutical use exceeds alert or action limits, actions should be taken according to operation procedures.

## Chapter 6 Materials and Products

### Section 1 Principle

Article 102: Starting materials and immediate packaging materials used for drug production should meet the required specifications. Ink printed directly on drug should meet the food grade requirements.

Imported starting materials should comply with importation regulations.

Article 103: Operation procedures for handling and managing materials and products should be established to ensure the proper receiving, storage, dispensing, use and distribution of materials and products, to prevent any risk of contamination, cross-contamination, mixups and errors.

All handling of materials and products should be carried out according to operation procedures and master manufacturing documents, and recorded accordingly.

Article 104: Quality assessment should be performed for the determination and change of material suppliers, and procurement can only be carried out after the suppliers have been approved by quality management department.

Article 105: Materials and products should be transported in a manner to protect their quality. Where special requirements are needed, the transportation conditions should be verified.

Article 106: The operation procedures should be established for the receipt of each delivery of starting materials and immediate and printed packaging materials. All incoming materials should be checked to ensure that the delivery corresponds to the purchase order, and is from a supplier that has been approved by the quality management department.

Outer packages of materials should be labeled with the required information, and cleaned where necessary. Damage to outer packages or any other problem that might adversely affect the quality of materials should be reported to the quality management department, investigated, and recorded.

Each receipt should be recorded, including:

1. The name of the material on the delivery note and the containers;
2. The "in-house" name and/or code of material;
3. The date of receipt;
4. The name of the supplier, and of the producer if different;
5. The batch number of the supplier, and of the producer if different;
6. The total quantity, and number of containers received;
7. The batch number or serial number assigned after receipt;
8. Any relevant comment (e.g. state of the containers).

Article 107: Incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution.

Article 108: All materials and products should be stored in an orderly fashion according to their nature, to permit batch segregation and stock rotation. Their dispensing and distribution should comply with the principle of first-in-first-out and first-expiry-first-out.

Article 109: Where computerized storage systems are used, operation procedures should be in place to prevent mixups and errors of materials and products in cases of system malfunction or outage, etc.

Where fully computerized storage systems are used for identification, the information of materials and products may not be necessarily labeled in a written form.

## Section 2 Starting Materials

Article 110: Appropriate operation procedures should be established, defining proper measures such as checking or testing, to verify the correctness of the identity of starting materials in each package.

Article 111: If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.

Article 112: Starting materials in the storage area should be appropriately labeled. Labels should bear at least the following information:

1. The designated name and the internal code reference of the material;
2. A batch number given at receipt;
3. The quality status of the contents (e.g. in quarantine, released, rejected, sampled);
4. The shelf life or re-test date.

Article 113: Only starting materials which have been approved to release by the quality management department and which are within their shelf life or re-test date should be used.

Article 114: The storage of starting materials should be in accordance with the expiry or re-test date. Re-test should be carried out for materials within the shelf life in case of encountering any abnormal situations that may adversely affect the quality of materials.

Article 115: Dispensing should only be carried out by designated personnel according to operation procedures. After being checked, materials should be accurately weighed or measured, and well labeled.

Article 116: Each dispensed material and its weight or volume should be independently checked by another person, and the check recorded.

Article 117: Materials dispensed for each batch should be kept together and conspicuously labeled as such.

## Section 3 Intermediate and Bulk Products

Article 118: Intermediate and bulk products should be kept under appropriate conditions.

Article 119: Intermediate and bulk products should be clearly labeled, including at least the following information:

1. The name of the product and the internal code reference;

2. The batch number;
3. Quantity or weight (e.g. gross weight, net weight);
4. Process steps (if necessary);
5. The quality status of the product (e.g. in quarantine, released, rejected and sampled, if necessary).

#### Section 4 Packaging Materials

Article 120: The requirements for management and control of immediate and printed packaging materials should be the same as for starting materials.

Article 121: Packaging materials should be issued for use only by designated personnel according to operation procedures. Measures should be taken to prevent mixups and errors to ensure the correct use of packaging materials for drug production.

Article 122: Procedures for the design, review and approval of printed packaging materials should be established to ensure the contents printed are in line with what is approved by drug regulatory department. . Specific documents should be established, to store the original specimen of printed packaging materials approved with signature.

Article 123: When the version of a printed packaging material is changed, actions should be taken to ensure that the correct version is used for production. It is recommended that the obsolete stencil plates be withdrawn and destroyed.

Article 124: Printed packaging materials should be properly stored in specific area so as to exclude unauthorized access. Cut labels and other loose printed packaging materials should be stored and transported in separate closed containers so as to avoid mixups.

Article 125: Printed packaging materials should be kept by designated person and dispensed according to operation procedures and requests.

Article 126: Each delivery or batch of immediate or printed packaging materials should be given a specific reference number or identification mark, indicating product name and batch number.

Article 127: Outdated or obsolete printed packaging materials should be destroyed and its disposal recorded.

#### Section 5 Finished Products

Article 128: Finished products should be held in quarantine until release.

Article 129: Finished products should be stored under conditions in accordance with the approved specifications of drug registration.

#### Section 6 Controlled Materials and Products

Article 130: Check and acceptance, storage and managing of narcotics, psychotropic, and medicinal toxic drugs (including traditional Chinese medicinal materials) for medical use, radioactive drugs, pharmaceutical precursor chemicals, flammable and explosive materials and other dangerous goods should strictly follow government regulations.



## Section 7 Others

Article 131: Each packaging container of rejected materials, intermediate, bulk and finished products should be clearly marked, and properly stored in restricted areas.

Article 132: The handling of rejected materials, intermediate, bulk and finished products should be approved by head of quality management, and recorded accordingly.

Article 133: The recovery should be authorized beforehand. This recovery should be carried out after a thorough evaluation of the quality risks involved, and recorded accordingly. The shelf life of the recovered product should start from the date when its earliest batch is produced.

Article 134: The reworking of finished preparations is prohibited. The rejected intermediate, bulk and finished preparations usually should not be reprocessed. Reprocessing is only permitted if the quality of the final product is not affected, the specifications are met, and that it is done according to a predefined and approved operation procedure after a thorough evaluation of the risks involved. The reprocessing should be recorded accordingly.

Article 135: The need for additional testing and stability test of any finished product that has been reprocessed, reworked or into which a recovered product has been incorporated, should be considered by the quality management department.

Article 136: The manufacturer should establish operation procedures for handling returned products with related records including at least: the product name, batch number, strength, quantity, return entity and address, reasons and date for return and final decision.

The returned products of the same batch but from different distributors should be recorded, stored and disposed separately.

Article 137: Returned products may be considered for re-packaging or re-distribution for sale only after checking, testing and investigation so as to prove with evidence that their quality is not adversely affected, and after assessment by the quality management department according to operation procedures. At minimum, the following factors such as nature of the drug product, required storage conditions, its current condition and history, and the time elapsed since it was distributed, should be taken into account in this assessment. The returned product not complying with the storage and transport requirement should be destroyed under supervision of the quality management department. Where any doubt arises over the quality of the returned product, it should not be re-distributed.

Where the returned product is to be recovered, the recovered product should meet both the defined specifications and requirements in Article 133.

Any action taken and the outcome should be appropriately recorded.

## Chapter 7 Qualification and Validation

Article 138: The manufacturer should identify what qualification or validation work is needed, to prove that the critical attributes of the operations can be controlled effectively. The scope and extent of qualification or validation should be determined through risk assessment.

Article 139: The premises, facilities, equipment and testing instruments should be qualified. The validated manufacturing process, operation procedures and testing methods should be used for production, operation and testing, and this validated state should be maintained.

Article 140: Documents and records should be established for qualification and validation as an evidence for

the following intended purposes:

1. Design qualification is to verify that the design of the premises, facilities and equipment is suitable for the intended use and in compliance with the Provisions;
2. Installation qualification is to verify that the premises, facilities and equipment have been built and installed in accordance with their design specifications;
3. Operational qualification is to verify that the premises, facilities and equipment operate in accordance with their design specifications;
4. Performance qualification is to verify that the premises, facilities and equipment, under normal operating procedures and process conditions, can consistently meet performance specifications;
5. Process validation is to verify that a manufacturing process, operated within established parameters, can consistently produce products that are suitable for their intended use and in accordance with the registration requirements.

Article 141: Before any new manufacturing formula or process is adopted, its suitability for routine production should be validated. The manufacturing process by using the defined starting materials and equipment, should consistently produce products suitable for their intended use and in accordance with the registration requirements.

Article 142: Qualification or validation should be performed when there is a change in major factors influencing the product quality, including any change in starting materials, immediate packaging materials, production equipment and environment (or premises), manufacturing process or testing method, etc. Where necessary, the changes should be approved by drug regulatory departments.

Article 143: Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure, to effectively prevent contamination and cross-contamination. In cleaning validation, a comprehensive consideration should include factors such as the use of the equipment, the detergents and disinfectants used, the sampling methods and locations, the relevant recovery rate of sampling, the nature and limit of residues, and the sensitivity of the testing method for residues.

Article 144: Qualification and validation should not be considered as a one time activity. After initial qualification and validation, requalification or revalidation should be carried out according to the product quality review. Critical manufacturing processes and operation procedures should be revalidated at defined intervals to ensure the intended outcome.

Article 145: The manufacturer should make a validation master plan to document the key information of qualification and validation.

Article 146: Requirements should be defined in the validation master plan or other relevant documents to maintain the consistent status of premises, facilities, equipment, testing instruments, process, operation procedures and testing methods.

Article 147: The qualification or validation protocol should be prepared based on its object. The protocol should be reviewed and approved. Responsibilities should be specified in the protocol.

Article 148: Qualification or validation should be implemented in accordance with a predefined and approved protocol, and be recorded. Upon completion of qualification or validation, a report should be prepared, reviewed and approved. The qualification or validation result and conclusion (including comments and suggestions) should be recorded and archived.

Article 149: Master manufacturing documents and operation procedures should be established according to the validation results.

## **Chapter 8 Documentation Management**

### Section 1 Principle

Article 150: Documentation constitutes an essential part of the quality assurance system. The manufacturer should have error-free written documents of specifications, manufacturing formula, processing instruction, operation procedures, records and etc.

Article 151: Manufacturer should establish operation procedures for documentation management to systematically design, prepare, review, approve and distribute the documents. Documents related to the Provisions should be reviewed by the quality management department.

Article 152: The content of documents should comply with the requirement of the drug manufacturing license, the registration requirements and etc, to facilitate the tracing of batch history.

Article 153: Operation procedures should be followed for drafting, revision, review, approval, replacement or withdrawal, reproduction, storage and destruction of documents; and relevant records for distribution, withdrawal, reproduction and destruction of documents should be in place.

Article 154: The drafting, revision, review and approval of documents should be signed and dated by appropriate personnel.

Article 155: Document should have title, nature, purpose, document number and version number. The text should be definitive, clear, understandable and unambiguous.

Article 156: Documents should be laid out in an orderly fashion and be easy to check.

Article 157: The reproduction of master documents must not introduce any error. Reproduced documents should be clear and legible.

Article 158: Documents should be regularly reviewed and revised. When a document has been revised, systems should exist to prevent inadvertent use of superseded documents. Distributed documents in use should be the approved current version. Those superseded and outdated documents should not be accessible in operating area except for archiving.

Article 159: Records should be made at the time each activity related to the Provisions is taken and in such a way that activities concerning the manufacture, quality control and quality assurance of products are traceable. Sufficient space should be provided for data entering in the record. The record should be entered timely and truthfully, and the handwriting should be clear, legible and indelible.

Article 160: When collecting records, graphs, plots, etc., those printed out from the production equipments and testing instruments should be adopted where possible, and the product or sample name, batch number, equipment information should be recorded along with the operator's dated signature.

Article 161: Records should be kept in a neat fashion without tearing up or uncontrolled alteration. Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded. When transcription is needed, the original record should not be destroyed, and be kept as attachment of the transcribed record instead.

Article 162: Each batch of drug should have a batch record, which includes related records of processing, packaging, testing, release, and etc. This batch record should be retained for at least one year after the product shelf life by the quality management department. Important documents such as specifications, master manufacturing documents, operation procedures, and the reports of stability study, qualification, validation and changes should be retained for long term.

Article 163: Where data are to be recorded by electronic data processing systems, photographic technique or other reliable means, operation procedures related to the system should be available; and the accuracy of the records should be checked.

If documentation is handled by electronic data processing methods, only authorized persons should be able to enter or modify data in the system and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently checked.

Batch records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, paper or other means. It is particularly important that the data are safe, and readily available throughout the period of retention.

## Section 2 Specifications

Article 164: There should be appropriately authorized and dated specifications for materials and finished products; where appropriate, they should be also available for intermediate or bulk products.

Article 165: Specifications for materials should include, if applicable:

1. Basic information of materials, including:
  - 1) Name designated by the manufacturer and internal code reference;
  - 2) The reference of specifications;
  - 3) The approved suppliers;
  - 4) A specimen or sample of printed packaging materials.
2. Sampling and testing procedures or references to relevant operation procedures;
3. Qualitative and quantitative requirements with acceptance limits;
4. Storage conditions and precautions;
5. The shelf life or re-test date.

Article 166: Specifications for intermediate and bulk products should be available, if these are purchased or dispatched. If the test results of the intermediate products are used for the evaluation of the finished product, the specifications should be similar to those for finished products, as appropriate.

Article 167: Specifications for finished products should include:

1. The designated name of the product and the code reference;
2. The reference to the formula (where applicable);

3. The strength, dosage form and package type;
4. Sampling and testing procedures or references to relevant operation procedures;
5. The qualitative and quantitative requirements, with acceptance limits;
6. The storage conditions and precautions;
7. The shelf-life.

### Section 3 Master Manufacturing Documents

Article 168: A master manufacturing document approved by the manufacturer should exist for each batch size of every drug. A packaging instruction should exist for every package type of different drug strengths and dosage forms. The establishment of master manufacturing documents should be based on the process approved at the time of registration.

Article 169: Master manufacturing documents should not be changed without authorization. When revision is needed, they should be revised, reviewed and approved according to relevant operation procedures.

Article 170: The master manufacturing documents should at least include:

#### 1. The Master Manufacturing Formula:

- 1) The name of the product, and its reference code;
- 2) A description of the dosage form, strength of the product, and batch size;
- 3) A list of all starting materials to be used, with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing); When conversion between measuring methods or units is needed, the calculation method should be specified.

#### 2. The Processing Instructions should include:

- 1) A statement of the processing location and the equipment to be used (e.g. operation room's location and reference number, cleanliness level, necessary temperature and humidity requirements, equipment type and reference number);
- 2) The methods, or the reference of relevant procedures, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilizing);
- 3) Detailed stepwise processing and process parameter instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
- 4) The instructions for any in-process controls with their limits;
- 5) A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable, and the methods for reconciliation and acceptance limits;
- 6) The requirements for bulk storage of the products, including the container, labeling and special storage conditions;

7) Any special precautions to be observed.

3. The packaging instructions should include:

- 1) The pack size expressed in terms of the number, weight or volume of the product in the final container;
- 2) A complete list of all the packaging materials required for a standard batch size, including name, quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;
- 3) An example or reproduction of the printed packaging materials and specimens, indicating where to apply batch number references, and shelf-life of the product;
- 4) Special precautions to be observed, including an examination of the area and equipment in order to ascertain the line clearance before packaging operations begin;
- 5) A description of the packaging operation, including any significant subsidiary operations, any precaution for equipment to be used and checks on packaging materials prior to use;
- 6) Details of in-process controls with instructions for sampling and acceptance limits;
- 7) Methods for reconciliation and acceptance limits about bulk products and printed packaging materials.

#### Section 4 Batch Processing Records

Article 171: A batch processing record should be kept for each batch of product so that the production history and quality related status of that batch can be traced.

Article 172: A batch processing record should be based on the relevant parts of the currently approved master manufacturing documents. Such records should be designed to avoid transcription errors. The record should carry the product name, dosage form, strength and batch number on every page.

Article 173: The master batch processing records should be reviewed and approved by the heads of production and quality management. The reproduction and issuance should be managed and recorded according to operation procedures, and only one copy of reproduced master records can be issued for the manufacture of each batch.

Article 174: During processing, each operation should be recorded timely, and after the operation, the records should be confirmed, signed and dated by the operation personnel.

Article 175: A batch processing record should include:

1. The product name, strength, batch number;
2. Dates and time of commencement, and of completion of intermediate stages and production;
3. The signatures of the person responsible for each stage of production;
4. Signatures of the operator of different steps of production and, where appropriate, of the person who checked each of these operations (e.g. weighing);
5. The batch number and the quantities of each starting material actually weighed (including the batch

number and amount of any recovered or reprocessed products added);

6. Any relevant processing operation or event, process parameters and control limits, and the reference number of major equipment used;

7. A record of the results obtained from in-process controls and the signatures of the person(s) carrying them out;

8. The amount of product obtained at different stages of manufacture, and reconciliation when necessary;

9. Records on special problems or abnormal events, including detailed description or investigation report for any deviation with signed authorization.

#### Section 5 Batch Packaging Record

Article 176: A batch packaging record should be kept for each batch or part batch processed so that batch packaging operations and quality can be traced.

Article 177: A batch packaging record should be based on the relevant parts of the Packaging Instructions, and avoid transcription errors. The record should carry the product name, strength, package size and batch number on every page.

Article 178: The batch packaging record should carry the batch number and the quantity of bulk product, as well as the batch number and the planned quantity of finished product. The requirements of review, approval, reproducing and issuance of original blank batch packaging record is the same as that of original blank batch processing record.

Article 179: During packaging, each operation should be recorded timely, and after the operation, the records should be confirmed, signed and dated by the operation personnel.

Article 180: The batch packaging record should include:

1. The product name, strength, package size, batch number, manufacturing date and shelf life;

2. The date(s) and times of the packaging operations;

3. The signatures of the responsible person carrying out the packaging operation;

4. The signatures of the operators of the different steps;

5. The name, batch number and actually used quantities of each kind of packaging materials;

6. Records of checks according to master manufacturing documents, including the results of in-process controls;

7. Details of the packaging operations carried out, including reference numbers to equipment and the packaging lines used;

8. Samples of printed packaging materials used, with printed batch number, shelf life and other contents ; for printed packaging materials that are inconvenient to archive together with the batch packaging record, a reproduction bearing the abovementioned contents may be retained;

9. Records on special problems or abnormal events, including detailed description or investigation report for

any deviation from master manufacturing documents, with signed authorization;

10. The name and reference number of all printed packaging materials and bulk product, quantities of the issued, used, destroyed or returned products, the actual quantities and reconciliation.

### Section 6 Operation Procedures and Records

Article 181: Operation procedures should include the title, code, version number, issuing department, effective date, distribution list, along with the dated signatures of author, reviewer and approver, the title, content, and change history.

Article 182: Premises, equipment, materials, documents and records should have codes (or reference numbers). Operation procedures should be established for the numbering/coding system to ensure the uniqueness of the codes (or reference numbers).

Article 183: There should be operation procedures and the associated records of actions taken and conclusions reached for:

1. Qualification and validation;
2. Equipment assembly and calibration;
3. Maintenance, cleaning and sanitation of premises and equipment;
4. Personnel matters including training, clothing, hygiene;
5. Environmental monitoring;
6. Pest control;
7. Change control;
8. Deviation handling;
9. Complaints;
10. Recalls;
11. Returns.

## Chapter 9 Production Management

### Section 1 Principle

Article 184: The production and packaging of all drugs should follow approved manufacturing formula and processing instructions and operation procedures with records retained, in order to ensure the drugs meet defined quality specifications and conform to drug manufacturing licensing and registration approval requirements.

Article 185: Operation procedures should be established to differentiate production batches, and the differentiations of production batches should achieve homogenous quality and property of the product within the same batch.



Article 186: Operation procedures should be established to determine the manufacturing date and batch number. Each batch of product should have a unique batch number. Unless stipulated in other regulations, the manufacturing date should be no later than the commencing date of the last blending operation for formulation or filling (sealing) of the product. The packaging date of the product should not be used as its manufacturing date.

Article 187: For each product batch, checks on yields and reconciliation of quantities should be carried out to ensure that there are no discrepancies outside of the acceptable limits. If a discrepancy is found, investigations should be performed to find out the reason, and the batch can only be released after it has been made clear that no potential quality risks exist.

Article 188: Operations on different products should not be carried out simultaneously in the same room unless there is no risk of mixups or cross-contamination.

Article 189: At every stage of processing, products and materials should be protected from microbial and other contamination.

Article 190: When working with dry materials or products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active, toxic or sensitizing materials or products.

Article 191: At all times during processing, containers of all materials, intermediate or bulk products, major items of equipment, and where appropriate rooms used should be labeled or otherwise identified with an indication of the product or material being processed, its strength and batch number. Where applicable, this indication should also mention the stage of the manufacturing process.

Article 192: Labels applied to containers, equipment or facilities should be clear, unambiguous and in the format approved by relevant departments of the manufacturer. In addition to the wording on the labels, different colors may be used to distinguish the status of these items (e.g. quarantined, accepted, rejected, or cleaned.).

Article 193: Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

Article 194: The line clearance should be carried out upon completion of each batch production to ensure that no materials, products or documents relevant to the batch are left over in the equipment and operation area. The previous clearance should be checked prior to the commencement of the subsequent batch.

Article 195: Any deviation from master manufacturing documents or operation procedures should be avoided as far as possible. Once a deviation occurs, operation procedures for deviation handling should be followed.

Article 196: Access to production premises should be restricted to authorized personnel.

## Section 2 Prevention of Contamination and Cross-contamination in Production

Article 197: Measures should be taken to avoid, as far as possible, contamination and cross-contamination during production, for example:

1. Production in segregated areas for different products;
2. Using campaign production;

3. Providing appropriate air-locks and air extraction; keep pressure differentials between areas with different cleanliness levels;
4. Minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
5. Keeping dedicated protective clothing inside areas where products with special risk of cross-contamination are processed;
6. Using cleaning and decontamination procedures that are validated or of known effectiveness; where appropriate, testing the residue on the surface direct contact with materials;
7. Using "closed systems" of production;
8. Drying equipment should have air filters in inlet, and devices to prevent air back flow in outlet,
9. Utensils that are fragile, liable to shed particulate matter or go moldy should be avoided in the production and cleaning operations. When sieves are used, there should be measures against contamination caused by breaking of sieves,
10. Processing steps such as preparation, filtration, filling/sealing and sterilization of liquid products should be completed within the defined time limits;
11. The shelf life and storage conditions should be established for intermediate products of semi-solid preparations, such as ointments, creams and gels, and of suppositories.

Article 198: Measures to prevent contamination and cross-contamination should be checked regularly and evaluated for their suitability and effectiveness.

### Section 3 Processing Operations

Article 199: Before any new production is started, the equipment and work area should be checked to ensure that no product residues, documents or materials not required for the current operation are left, and the equipment is clean and ready to operate, and the check result should be recorded accordingly.

Before the processing operation starts , the names, codes, batch numbers and labeling of all materials and intermediate products should also be checked , to guarantee that they are correct and in accordance with the requirements.

Article 200: Any in-process controls and necessary environmental monitoring should be carried out and recorded.

Article 201: The line clearance must be carried out and recorded by the operators upon completion of each stage of a production batch. The record should include the number of the operating room, the name and batch number of the product, the process step, the date of clearance, the checklist and the results, the signatures of the person responsible for the clearance and the verifier. The records should be incorporated into the batch processing record.

### Section 4 Packaging Operations

Article 202: Packaging operation procedures should specify the measures to minimize the risk of contamination, cross-contamination, mixups or errors.

Article 203: Before packaging, checks should be performed to ensure that the work area, packaging lines,

printing machines and other equipment are clean or ready for use, and that they are free from any products and documents left from the last batch, or materials not relating to the packaging of this batch. The results should be recorded accordingly.

Article 204: Before the packaging operation, all packaging materials drawn for use should also be checked for correctness, and the name, strength, quantity, and quality status of bulk products and all packaging materials should be checked to ensure the conformity with master manufacturing documents.

Article 205: The name, strength, batch number and batch size of the product being handled should be displayed at each packaging area or line.

Article 206: Appropriate segregation or other precautions to effectively prevent contamination, cross-contamination or mixups should be adopted if several packaging lines are working simultaneously.

Article 207: Containers for filling should be clean before filling. Attention should be given to avoiding any contaminants such as glass fragments and metal particles.

Article 208: Filling and sealing should be followed as quickly as possible by labeling. If it is not the case, appropriate operation procedures should be applied to ensure that no mixups or mislabeling can occur.

Article 209: The printed information (e.g. batch number or shelf life) of the separate printing or on-site printing during the packaging operation should be checked to ensure its correctness, and the check recorded. If printing by hand, the check frequency should be increased.

Article 210: Special care should be taken when using cut-labels and when over-printing is carried out off-line, to avoid mixups.

Article 211: Checks should be carried out to ensure that any electronic code readers, label counters or similar devices are functioning correctly. Such checks should be recorded.

Article 212: Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

Article 213: In-process control of the product during packaging should include at least the following information:

1. The appearance of the packages;
2. Whether the packages are complete;
3. Whether the products and packaging materials are correct;
4. Whether the printed information is correct;
5. The correct functioning of on-line monitors.

Samples taken away from the packaging line should not be returned to prevent the products from mixups or contamination.

Article 214: Where repackage is needed for products due to unusual event during packaging, special examination, investigation should be conducted, and repackaging should be approved by authorized personnel. Detailed record should be kept for the repackage operation.

Article 215: Any significant discrepancy, observed during reconciliation of the amount of bulk products, printed packaging materials or finished products, should be investigated. Finished products should not be released without the investigation conclusion.

Article 216: Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed, and the destruction recorded. An operation procedure should be followed if un-printed packaging materials are returned to stock.

## **Chapter 10 Quality Control and Quality Assurance**

### **Section 1 Management of Quality Control Laboratories**

Article 217: The personnel, facilities, and equipment in the quality control laboratories should be appropriate to the tasks imposed by the product nature and the scale of the manufacturing operations.

The use of contract laboratories, not applicable under normal circumstances, in conformity with the principles of contract analysis detailed in Chapter 11, can be accepted for particular reasons, but this should be stated in the certificate of analysis.

Article 218: The head of quality control should have appropriate qualifications and experience in managing laboratories and can manage one or more control laboratories within the same manufacturer.

Article 219: Testing technician in quality control laboratories should at least have a relevant technical school or high school education, have received job related practical training, and passed the examination.

Article 220: Necessary reference books such as pharmacopeias and standards spectrum, and primary reference substances such as reference standards and reference substances, should be available in quality control laboratories.

Article 221: Documentation in the quality control laboratories should be in accordance with the principles in Chapter 8 and meet the following requirements:

1. The quality control laboratories should at least have the following detailed documents:

- 1) Specifications;
- 2) Sampling operation procedures and records;
- 3) Testing operation procedures and records (including testing records or laboratory notebooks);
- 4) Testing reports or certificates;
- 5) Operation procedures, records and reports of environmental monitoring, where required;
- 6) Validation reports and records of testing methods, where applicable;
- 7) Operation procedures and records of the calibration of instruments, and use, cleaning and maintenance of equipment.

2. Testing records of each batch of drug should cover testing records of all the intermediate, bulk and finished products to ensure the testing history of the batch is traceable.

3. For some kinds of data (e.g. testing results, environment monitoring data, microorganism monitoring

data of water for pharmaceutical use), it is recommended that records be kept in a manner permitting trend evaluation.

4. In addition to the information of the batch record, other original data or records should be retained and readily available.

Article 222: Sampling should at least meet the following requirements:

1. Personnel of quality management department should have the authority to access to production and storage areas for sampling and investigation.

2. The sampling process should be done in accordance with approved operation procedures. Operation procedures should well describe:

1) Person(s) authorized to take samples;

2) The method of sampling;

3) The equipment to be used;

4) The amount of sample to be taken;

5) Instructions for sub-division of the sample;

6) The type and condition of the sample container to be used;

7) Handling and labeling of the remains after sampling and the samples;

8) Precautions of sampling, including preventive measures taken to minimize risks in sampling process, especially for sterile materials or hazardous materials, and precautions to prevent contamination and cross-contamination in the sampling process;

9) The storage conditions;

10) The cleaning methods and storage requirements of sampling equipment.

3. The sampling method should be scientific and rational to ensure good representativeness.

4. Reference samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. the beginning or the end of a process).

5. Sample containers should bear a label indicating the information such as sample name, batch number, date of sampling, containers from which samples have been drawn, and person taking the sample.

6. Samples should be stored under prescribed storage conditions.

Article 223: The test of materials and products of various production stages should at least meet the following requirements:

1. The manufacturer should ensure that full test is done according to the registered testing methods.

2. Testing methods should be validated under any of the following situations:

- 1) Adoption of a new testing method;
  - 2) Change of testing methods;
  - 3) Testing method adopted is not included in the Chinese Pharmacopoeia or other official standards;
  - 4) Other testing methods requested by regulations for validation.
3. The manufacturer should verify those testing methods that do not need validation so as to ensure the accuracy and reliability of testing data.
4. Written operation procedures for testing should be in place to specify testing methods, apparatus and instruments to be used, and the content of the procedures should be consistent with the verified or validated testing methods.
5. The test results obtained should be recorded in a traceable manner and checked to make sure that they are consistent with each other. Any calculations should be critically examined.
6. The test record should include at least the following content:
- 1) Name of the material or product, dosage form, strength, batch number or shipping batch number, where appropriate, the name of the manufacturer and/or supplier;
  - 2) References to the relevant specifications and testing procedures;
  - 3) Type and serial numbers of apparatus or instruments;
  - 4) Preparation batch numbers of solutions and culture media, the source and lot number of reference standards;
  - 5) Related information of animals used for testing;
  - 6) Testing process, including preparation of reference solution, operation of individual tests, necessary data of environment temperature and humidity;
  - 7) Test results, including observations, calculations, spectrum or plots, and reference to the No. of any certificate of analysis;
  - 8) Dates of testing;
  - 9) Dates and signatures of the persons who performed the testing;
  - 10) Dates and signatures of the persons who verified the testing and the calculations.
7. All the in-process controls, including those made by manufacturing personnel, should be performed according to methods approved by the quality management department, and the results recorded;
8. Laboratory volumetric glassware, reagents, solutions, reference standards and culture media should be tested;
9. Animals used for testing should, where appropriate, be inspected and quarantined before use. They should be maintained and controlled in a manner that meets the regulations of lab animal management.

They should be identified, and records should be maintained, showing the history of their use.

Article 224: Operation procedures for investigation of testing results out of specification should be established in quality control laboratories. Any out of specification results must be fully investigated following the operation procedures and recorded accordingly.

Article 225: The reference samples are materials or products that are being kept by the manufacturer according to the operation procedures for quality traceability or investigation. Samples for product stability study are not reference samples.

The following requirements should be met for reference samples:

1. The reference samples should be managed according to operation procedures.
2. The reference samples should be representative of the batch of material or product from which they are taken.
3. Reference samples of finished products:
  - 1) There should be reference samples for each batch. Where a batch is packaged into several distinct packaging operations, at least one reference sample should be taken from each individual packaging operation.
  - 2) The package of reference samples should be identical to the products in the market. If the package of reference samples of active pharmaceutical ingredients (API) cannot be the same as the form in the market, a simulated package may be adopted.
  - 3) The retained sample should consist of at least twice the quantity necessary for full tests (excluding sterility and pyrogen test, etc.) in specifications approved in drug registration.
  - 4) The reference samples should be visually examined at least once a year during storage period unless the visual examination will affect the sample integrity. Any abnormality should be fully investigated and corresponding actions should be taken.
  - 5) Visual inspection of reference samples should be recorded.
  - 6) Reference samples should be stored in conditions accordance with the approved registration requirements for at least one year after the shelf life.
  - 7) When drug manufacturing is ceased or a manufacturer closes down, the reference samples should be transferred to an authorized storage site and the local drug regulatory department should be informed so that they can obtain the sample when necessary.
4. Reference samples of materials:
  - 1) The samples should be retained for every batch of starting materials and immediate packaging materials used for preparation. It is not necessary to retain some immediate packaging materials (such as infusion bottles) if the finished product has already been retained.
  - 2) The samples of materials should be of a size at least sufficient to perform the identification test.
  - 3) Except for those less stable starting materials, reference samples of starting materials (other than solvents, gases or water for pharmaceutical use used in the manufacturing process) and immediate

packaging materials should be retained for at least two years after the release of product. That period may be shortened if the shelf life of the materials is shorter.

4) The reference samples of materials should be stored in defined conditions, and air tightly sealed when necessary.

Article 226: The management of laboratory reagents, solutions, culture media and test microorganisms should meet at least the following requirements:

1. Laboratory reagents and culture media should be purchased from reliable suppliers, and when necessary, the supplier should be assessed.

2. There should be records for the receipt of laboratory reagents, solutions and culture media, the date of receipt should be indicated on the container where necessary.

3. The preparation, storage and use of the laboratory reagents, solutions and culture media should follow the relevant requirements or instructions. In special cases, the laboratory reagents should be identified or tested upon reception or before use.

4. The batch number, preparation date, and name of the operator should be indicated on the labels of solutions and prepared culture media, and a preparation record (including sterilization) should be available. The shelf life and special storage conditions of unstable laboratory reagents, solutions and culture media should be indicated on the label. For reference solutions and titration solutions, the latest standardization date and calibration factor should be labeled, and the standardization records should be available.

5. Test on suitability of prepared culture media should be performed and documented. The records for use of culture media should be available.

6. Microorganisms required for relevant tests should be available. And operation procedures for storage, subculture, use, and disposal of test microorganisms should be established and recorded accordingly.

7. The test microorganism should be properly labeled with at least the following information: name of microorganism, code, generation, generation date/subculture date and operator.

8. The test microorganism should be stored according to the specified storage conditions. The manner and period of storage should not have adverse effects to the growth characteristics of the test microorganism.

Article 227: The management of the standard substances or reference substances should meet at least the following requirements:

1. The standard substances or reference substances should be used and stored under specified storage conditions.

2. The standard substances or reference substances should be properly labeled with at least the following information: name, batch number, data of preparation (if available), shelf life (if available), open date, purity or titration, and storage condition.

3. Where in-house working standard substances or reference substances are to be self-prepared, the manufacturer should establish specifications of the working standards and operation procedures for the preparation, identification, testing, approval and storage. Each lot of in-house working standard substance or reference substance should be standardized against an official standard substance or reference substance, and shelf life established. In addition, the working standard substances or reference substances should be standardized regularly to demonstrate that their potency or assay is stable within shelf life. The



process and result of the standardization should be recorded.

## Section 2 Release of the Materials and Products

Article 228: Operation procedures for release of the materials and products should be respectively established with well defined criteria and responsibilities. Relevant records should be available.

Article 229: The following requirements should at least be met in materials release:

1. The quality assessment of the materials should at least include checks of producers' certificates of analysis, integrity and sealing of packaging, and test result.
2. A clear conclusion should be given to the quality assessment of materials, such as release, reject or other decisions.
3. The release of materials should be approved with signature by a designated person.

Article 230: The following requirements should at least be met in products release:

1. Each batch of drugs, prior to release, should undergo quality assessment, so as to ensure that the products and manufacturing comply with the registration requirements and the Provisions, and the following activities should be confirmed:

- 1) The main manufacturing processes and testing methods are validated.
  - 2) All necessary inspections and tests are completed; the actual production condition and record are considered comprehensively.
  - 3) All the necessary production and quality control are completed and signed by relevant responsible persons.
  - 4) Changes are closed according to related procedures. Those needing approval of the regulatory department are approved.
  - 5) Required sampling, inspection, testing and review caused by changes or deviations are completed.
  - 6) Deviations related to this batch are clearly explained or illustrated, or thoroughly investigated and appropriately handled; if other batches are involved in the deviation, all batches should be dealt together.
2. Product quality assessment should have a clear conclusion, such as release, reject or other decisions.
  3. The release of each batch of products should be approved with signature by the Qualified Person.
  4. Lot release certificate should be obtained for vaccines, blood products, in-vitro diagnostic reagents used in blood screening, and other biological products stipulated by the State Food and Drug Administration prior to final release.

## Section 3 On-going Stability Program

Article 231: The purpose of the on-going stability program is to monitor the product over its shelf life to permit the detection of any manufacture related stability issue (e.g. changes in levels of impurities or dissolution profile) , and to determine that the product quality remains, and can be expected to remain, within specifications under the labeled storage conditions.

Article 232: The on-going stability program mainly applies to the drug in the package in which it is sold, but consideration should also be given to the inclusion in the program of bulk product. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied under ambient conditions. In addition, consideration should be given to intermediate products that are stored and used over prolonged periods.

Article 233: The on-going stability program should be described in a protocol and results formalized as a report. The equipment used for the on-going stability program (in particular, the equipment and facilities for stability study) should be qualified and maintained following the general rules of Chapters 7 and 5.

Article 234: The protocol for an on-going stability program should extend to the end of the shelf life period and should at least include the following contents:

1. Number of batch(es) per strength and different batch sizes;
2. Relevant physical, chemical, microbiological and biological testing methods, with consideration of the specified stability study testing methods;
3. Reference to testing methods;
4. Acceptance criteria;
5. Description of the container closure system(s);
6. Testing intervals (time points);
7. Conditions of storage (standardized conditions of Chinese Pharmacopoeia for long term testing, consistent with the product labeling, should be used);
8. Test items, if less than the quality specifications of a finished product, it should be justified.

Article 235: The number of batches and frequency of testing should provide a sufficient amount of data to allow trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, should be included in the stability program, unless none are produced during that year.

Article 236: In certain situations, additional batches should be included in the on-going stability program. For example, an on-going stability study should be conducted after any significant change or significant deviation to the process or package. Besides, any reworking, reprocessing or recovery batches should be also considered included in the program, unless the validation and stability studies have been passed.

Article 237: Results of on-going stability studies should be made available to key personnel and, in particular, to the Authorized Person(s). Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement between the parties concerned. Results of on-going stability studies should be available at both sites for review by regulatory authority.

Article 238: Out-of-specification results or significant atypical trends should be investigated. Any confirmed out-of-specification result, or significant negative trend, the manufacturer should consider the possible impact on the marketed products. If necessary, a recall should be carried out, and investigation result and actions taken should be reported to the local drug regulatory department.

Article 239: A summary of all the data generated, including any interim conclusions on the program, should be written and maintained. This summary should be subjected to periodic review.

#### Section 4 Change Control

Article 240: The manufacturer should establish a change control system to evaluate and manage all changes which could have an impact on product quality. Any change requiring approval from the drug regulatory department should only be applied after obtaining the approval.

Article 241: Operation procedures should be established to define the request, assessment, review, approval and implementation of changes in starting materials, packaging materials, specifications, testing methods, operation procedures, premises, facilities, equipment, instruments, manufacturing process and computer software. The quality management department should assign a designated person to take charge of the change control.

Article 242: For all changes, the potential impact on product quality should be evaluated. The manufacturer should classify the changes (e.g. major or minor) depending on their nature and extent, and the effects these changes may impact on product quality. Scientific evidences should be provided to determine what validation activities, additional tests and stability studies are needed.

Article 243: Change that may affect the product quality is proposed by an application department, steps should be taken to do assessment, and then establish an implementation plan with defined responsibilities, followed by its final review and approval by the quality management department. The implementation of change should be fully recorded.

Article 244: When changes involve key quality factors such as starting materials, immediate packaging materials, manufacturing process, major equipment, etc., the quality of at least the first three batches produced after the change should be evaluated. If the change has potential impact on the shelf life, stability studies should also be conducted.

Article 245: When implementing changes, measures should be taken to ensure that all documents affected by the changes are revised.

Article 246: All documents and records related to changes should be kept by quality management department.

#### Section 5 Deviation Handling

Article 247: The head of each department should ensure that all personnel of his department follow manufacturing process, specifications, testing methods and operation procedures to prevent deviations.

Article 248: The manufacturer should establish operation procedures for deviation handling, define the reporting, recording, investigation, treatment and corrective actions adopted and all should be recorded accordingly.

Article 249: The potential impact of any deviation on product quality should be assessed. The manufacturer may classify the deviations (e.g. as minor or major) depending on the nature and scope of the deviations and extent of the potential impact on product quality. Additional tests and impact on the shelf life should be considered for the assessment of major deviations, and if necessary, stability studies should also be carried out for products involved in major deviations.

Article 250: Any deviation from manufacturing process, material reconciliation, specifications, testing

methods and operation procedures etc. should be recorded, and promptly reported to the person in charge and the quality management department with a clear description. Full investigation for major deviations should be carried out by the quality management department in conjunction with other departments, and a report should be filed. All deviation reports should be reviewed and signed by the designated personnel of the quality management department.

The manufacturer should take preventive actions to effectively avoid the re-occurrence of similar deviations.

Article 251: The quality management department should be responsible for classifying deviations, and for the retention of all documents and records related to investigation and handling of deviations.

#### Section 6 Corrective Actions and Preventive Actions

Article 252: The manufacturer should establish a corrective actions and preventive actions (CAPA) system, for the investigation of complaints, recalls, deviations, findings of self-inspections or external inspections, process performances and quality monitoring trends, etc, and take corrective actions and preventive actions. The extent and formality of investigations should be commensurate with the level of risk. The CAPA system should result in enhanced product and process understanding, and product and process improvements.

Article 253: The manufacturer should establish operation procedures for the implementation of CAPA, including at least the following:

1. To identify existing or potential quality issues by analyzing complaints, recalls, deviations, findings of self-inspections or external inspections, monitoring trends of process performance and quality and quality data from other sources; when necessary, statistical approaches should be employed;
2. To investigate causes related to the product, process and quality assurance system;
3. To determine necessary CAPA measures for preventing issues from re-occurring;
4. To evaluate the applicability, effectiveness and sufficiency of CAPA taken;
5. To record all changes during CAPA implementation;
6. To ensure that the related information is delivered to the Qualified Person and the person directly in charge of preventing issues from re-occurring;
7. To ensure that the related information and its CAPA pass the review by the senior management.

Article 254: CAPA implementation should be recorded and retained by the quality management department.

#### Section 7 Supplier Assessment and Approval

Article 255: The quality management department should perform quality assessment of all production materials suppliers, on-site audit to key materials suppliers (especially the producers) in conjunction with other departments, and exercise its veto against the suppliers who fails to conform to the requirements of quality assessment.

The determination of key materials should comprehensively take into account of the quality risk of the drugs produced by the manufacturer, the materials consumption and the impact on product quality.

The legal person of the manufacturer, the head of the manufacturer and other personnel should not interfere with or impede the independent quality assessment performed by the quality management department for

materials suppliers

Article 256: Operation procedures for assessment and approval of materials suppliers should be established to define the suppliers' qualifications, selection criteria, quality assessment methods, assessment criteria, and approval procedures of material suppliers.

Where the quality assessment needs to be done by way of on-site quality audit, the content and frequency of the audit, the composition and qualifications of auditors should also be defined. Where small scale pilot production is needed, the batch size, manufacturing processing procedures, specifications, and stability study protocol should also be defined.

Article 257: Designated person should be appointed by the quality management department for supplier quality assessment and on-site quality audit, as well as issuing the lists of approved suppliers. The designated person should have relevant regulatory and technical knowledge, and sufficient practical experiences in quality assessment and on-site quality audit.

Article 258: The on-site quality audit should verify the authenticity of the supplier's qualification certificates and certificates of analysis, and verify the testing conditions. In order to fully assess the quality assurance system of the suppliers, its personnel and organization, premises, facilities, equipment, materials management, manufacturing process procedures, production management, as well as the equipment, instruments and documentation management, etc., of the quality control laboratories should be checked. . An on-site audit report should be prepared.

Article 259: When necessary, small scale pilot production should be carried out with the samples provided by key material suppliers, and the stability study for the products from pilot production should be performed.

Article 260: Assessment of material suppliers by the quality management department should at least include: the supplier's qualification certificates, specifications and certificates of analysis, the manufacturer's testing data and reports of material samples. Where on-site audit and small scale pilot production are performed, the assessment should also include on-site audit report, certificates of analysis and stability study report of small scale pilot products.

Article 261: Where changing a materials supplier, quality assessment should be performed for the new supplier. Where changing a key material supplier, validation and stability study for the product should be conducted.

Article 262: Quality management department should distribute the list of approved suppliers to material management department. The list should at least include the names of materials, sizes/strengths, specifications, names and addresses of the material producers, names of the distributors (if any), etc., and be updated timely.

Article 263: Quality management department should sign a quality agreement with a key material supplier to define the quality responsibilities of each party.

Article 264: Quality management department should perform periodic assessment or on-site quality audit for material supplier, retrospective review of materials test results, records of quality complaints and non-conformance handling. In case of occurrence of materials quality problems, or significant changes of critical factors that may impact quality, such as production conditions, manufacturing process, specifications and testing methods, an on-site quality audit should be performed as soon as possible.

Article 265: The manufacturer should establish a quality archive for each material supplier, which includes the supplier's qualification certificates, quality agreements, specifications, sample testing data and reports, supplier's certificates of analysis, on-site quality audit reports, product stability study report, periodic quality

review reports, etc.

### Section 8 Product Quality Review

Article 266: Quality review for each drug produced should be conducted annually according to operation procedures, with the objective of verifying the consistency of the existing processes, the appropriateness of current specifications for both starting materials and finished product, to highlight any adverse trends timely, and to identify product and process improvements. Historical data from the previous such reviews should be considered; internal audit should be carried out to confirm the effectiveness of such reviews.

Quality reviews may be grouped by dosage forms, such as solid preparations, liquid preparations, sterile products, and etc., where scientifically justified.

Reports should be prepared after review.

Quality reviews performed by the manufacturer should include at least the followings:

1. All changes of starting materials used for the product, especially those materials from new suppliers;
2. Critical in-process controls and testing results of finished product;
3. All batches that failed to meet the established specifications and their investigations;
4. All significant deviations and related investigations, and the effectiveness of corrective and preventative actions taken;
5. All changes of the process or testing methods;
6. Changes approved by or submitted to drug registration for the record;
7. The results of the stability program and any adverse trend;
8. All quality-related returns, complaints, recalls and the investigations;
9. The performance and adequacy of any corrective action taken for product process or equipment;
10. The work accomplished according to post-marketing requirements of registration for the drug newly approved and with changes;
11. The qualification status of relevant equipment and utilities, such as HVAC, water, compressed gases, etc;
12. The fulfillment of technical agreements for contract manufacture or analysis.

Article 267: The result of quality review should be evaluated. An assessment advice about whether corrective and preventative actions need to be taken, or requalification or revalidation to be conducted, should be raised and explanation provided. All these actions should be completed in time and effectively.

Article 268: For contract manufacturing, a written technical agreement should be in place between contract giver and contract acceptor, which defines their respective responsibilities of the product quality review to ensure that the quality review is performed on schedule according to the requirements.

### Section 9 Complaints and Adverse Drug Reaction Reports

Article 269: Adverse drug reactions (ADRs) reporting and monitoring system should be established, and managed by a specific organization staffed with specialized personnel.

Article 270: The ADRs should be actively collected, recorded in detail, evaluated, investigated, and handled. Actions should be taken timely to control any potential risk. ADRs should be reported to the regulatory department as required.

Article 271: Operation procedures should be established to define the process of recording, evaluating, investigating, and handling of complaints. The measures for a complaint due to a possible product defect should also be defined. Consideration of the necessity of a recall from the market should be included.

Article 272: There should be designated person(s) supported by sufficient staff for investigating and handling of the quality complaints, and the Qualified Person should be made aware of any complaints and investigations.

Article 273: All the complaints should be recorded and reviewed. Any complaint concerning a product quality defect should be recorded with all the original details and thoroughly investigated.

Article 274: If a product defect is discovered or suspected in one batch, consideration should be given to checking other batches in order to determine whether they are also affected.

Article 275: Investigation and handling of a complaint should be recorded, and product information of related batches should also be included.

Article 276: Complaint records should be reviewed regularly, in order to find problems which require attention, occur repeatedly, and possibly need a recall of drugs from the market. Actions should be taken accordingly.

Article 277: The manufacturer should take actions timely for manufacturing failure, drug deterioration, or any other serious quality problems. If necessary, actions taken should be reported to the local drug regulatory department.

## **Chapter 11 Contract Manufacture and Analysis**

### Section 1 Principle

Article 278: To ensure the product quality of contract manufacture, and the accuracy and reliability of contract analysis, there must be a written contract between the contract giver and the contract acceptor, which clearly establishes the duties of each party, and covers the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it.

Article 279: All arrangements for contract manufacture and analysis including any proposed changes in technical or other arrangements should be in accordance with the drug manufacturing licensing and registration requirements for the product concerned.

### Section 2 The Contract Giver

Article 280: The contract giver is responsible for assessing the contract acceptor, via on-site audit of the conditions, technical levels and quality management status, to confirm its competence to carry out the contracted operations, and to ensure the compliance with the Provisions.

Article 281: The contract giver should provide the contract acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the drug registration and any other

legitimate requirements.

The contract giver should ensure that the contract acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to the environment, premises, equipment, personnel, and other materials or products of the contract acceptor.

Article 282: The contract giver should supervise the entire process of contract manufacturing or analysis.

Article 283: The contract giver should ensure that all of the materials and products comply with corresponding specifications.

### Section 3 The Contract Acceptor

Article 284: The contract acceptor must have adequate premises and equipment, knowledge and experience, and competent personnel to carry out satisfactorily the manufacture or analysis work ordered by the contract giver.

Article 285: The contract acceptor should ensure that all materials, intermediate and bulk products delivered by the contract giver are suitable for their intended use.

Article 286: The contract acceptor should refrain from any activity which may adversely affect the quality of the product manufactured and/or analyzed for the contract giver.

### Section 4 The Contract

Article 287: A contract should be drawn up between the contract giver and the contract acceptor which specifies their respective responsibilities relating to the manufacture and control of the product. Technical aspects of the contract should be drawn up by competent persons with suitable knowledge in the pharmaceutical technology, analysis and the provisions. All arrangements for manufacture and analysis must be in accordance with the drug registration requirements and agreed by both parties.

Article 288: The contract should specify the way in which the qualified person approving to release the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements of the Marketing Authorization.

Article 289: The contract should describe clearly who is responsible for purchasing materials, testing and releasing materials, undertaking production and quality controls (including in-process controls), and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the contract acceptor should take samples at the premises of the contract giver.

Article 290: The contract should define that processing, testing and distribution records and samples kept by the contract acceptor, should be available to the contract giver whenever needed. Any records relevant to assessing the quality of a product in the event of complaints, a suspected defect or recalls must be accessible to the contract giver.

Article 291: The contract should clearly define that the contract giver can conduct on-site inspection or audit to the contract acceptor.

Article 292: The contract should define that the contract acceptor has the obligation to accept the inspection conducted by drug regulatory department.

## Chapter 12 Product Distribution and Recalls



### Section 1 Principle

Article 293: The manufacturer should establish a recall system, if necessary, to recall promptly and effectively any batch of products with potential safety risks from the market.

Article 294: Products returned and recalled due to quality problems should be destroyed under supervision according to requirements, except for those proved by evidences that the quality has not been compromised.

### Section 2 Distribution

Article 295: Each batch of product should have a distribution record. Based on the record, the sale of each batch should be traceable, when necessary, all the products should be able to be taken back timely. The distribution record should include information such as the product name, strength, batch number, quantity, customer name, address, and contact details, date of shipment, mode of transport, etc.

Article 296: Only two batches of remnant products are allowed in one shared package. The two batch numbers shall be indicated on the outside of the package, and a record for the shared packaging should be made.

Article 297: The distribution records should be retained for at least one year after the shelf life of the finished product.

### Section 3 Recalls

Article 298: Operation procedures for recall should be established to ensure the effectiveness of recalls.

Article 299: A person should be designated as responsible for execution and coordination of recalls and should be supported by sufficient staff. This responsible person should be independent of the sales and marketing organization. If this person is not the Authorized Person, the latter should be made aware of any recall activity.

Article 300: Recall operations should be capable of being initiated at any time and carried out promptly.

Article 301: Where a decision is made to recall a product from the market due to its existing or potential safety risks, it should be reported immediately to the drug regulatory department.

Article 302: The distribution records should be readily available to the person(s) responsible for recalls.

Article 303: Recalled products should be identified and stored separately in a secure area awaiting a decision on their fate.

Article 304: The progress of the recall process should be recorded, and a final report should be issued, including the distributed and recalled quantities of the products, along with the reconciliation between them.

Article 305: The effectiveness of the product recall system should be evaluated regularly.

## **Chapter 13 Self Inspections**

### Section 1 Principle

Article 306: Self inspections should be organized periodically by the quality management department to monitor the implementation of the Provisions, evaluate whether the manufacturer is in compliance with

them, and to propose necessary corrective and preventive actions.

## Section 2 Self Inspections

Article 307: A plan should be available for self inspections, and periodical inspections should be conducted on organization and personnel, premises, facilities, equipment, materials and products, qualification and validation, documentation management, production management, quality control and quality assurance, contract manufacture and analysis, product distribution and recalls, and etc.

Article 308: Self inspections should be conducted in an independent, systematic, and all inclusive way by the designated person(s) of the manufacturer. Independent quality audits by external experts are also acceptable.

Article 309: All self inspections should be recorded. Reports should be prepared at the completion of self-inspections, and all the observations made during the inspections, conclusions of evaluation, and proposals for corrective and preventative actions should at least be included. Self inspection status should be reported to the senior management of the manufacturer.

## Chapter 14 Supplementary Provisions

Article 310: The Provisions are basic requirements for manufacturing and quality management of drugs. Special requirements for sterile products, biological products and blood products, etc., or the manufacturing and quality management activities, shall be separately enacted as annexes by the State Food and Drug Administration.

Article 311: Manufacturers may use validated alternative approaches to meet the requirements of the Provisions.

Article 312: Glossary:

1. Packaging: All operations, including filling and labeling, which a bulk product has to undergo in order to become a finished product. Aseptic filling, filling of products for terminal sterilization, and etc., are not regarded as packaging.
2. Packaging materials: Any materials employed in the packaging of a drug, including immediate packaging materials, container in direct contact with drugs, and printed packaging materials, but excluding any outer packaging materials used for transportation or shipment.
3. Operation Procedures: Approved documents to guide operations related to the manufacture of drugs, such as equipment operation, maintenance and cleaning, validation, environmental control, sampling, testing, and etc. Also refer to as standard operating procedure (SOP).
4. Product: Includes the intermediate, bulk and finished product of drug.
5. Product Lifecycle: All stages of the product from its development, launch to market, till discontinuation.
6. Finished Product: A product which has undergone all stages of production, including packaging in its final container.
7. Reworking: Subjecting all or part of a batch of intermediate or bulk product which fails to meet the specifications to an alternate manufacturing process in order to meet the predetermined specifications.
8. Bulk Product: Any product which has completed all processing stages up to, but not including, final

packaging.

9. Quarantine: The status of starting or packaging materials, intermediate, bulk or finished products isolated physically or by other effective means whilst storing and awaiting a decision on their release or refusal before dispensing or marketing.

10. Dispense: A series of operations to circulate materials, intermediate products, bulk products, documents, production molds, etc. within the manufacturer.

11. Retest date: The date when a starting or packaging material, after storage for a certain period, should be re-examined to ensure that it is still suitable for its intended use. The retest date is determined by the manufacturer.

12. Distribution: A series of operations to send the product from manufacturer to the distributor or customer, including loading, transportation, and etc.

13. Reprocessing: Subjecting all or part of a batch of intermediate, bulk or finished products that fails to meet the specifications to a previous step of the same manufacturing process in order to meet the predetermined specifications.

14. Release: The operation to make decisions, such as approval to use, distribution into the market, or others, by evaluating the quality of a batch of material or product.

15. Senior Management: Personnel on the top level of the manufacturer to command and control it, and have the power and responsibility to allocate resources.

16. Master manufacturing documents: A document or set of documents established with the purpose to produce a specified quantity of a finished product, which include the manufacturing formula, processing and packaging instructions, and specify the quantities of starting and packaging materials, process parameters and conditions, a processing description (including in-process controls), and precautions, etc.

17. Supplier: A party providing materials, equipment, instruments, reagents or services, such as manufacturer, distributor, etc.

18. Recovery: The introduction of all or part of previous batches of the required quality into another batch of the same product at a defined stage of manufacture.

19. Computerized system: A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.

20. Cross-contamination: Contamination of raw materials and excipients (starting materials) or of a product with another material or product.

21. Calibration: The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring, recording or controlling instrument or system (especially weighing), or values represented by a material measure, and the corresponding known values of a reference standard.

22. Campaign production: A manner adopted in a non-dedicated production area to exclusively produce a product in a given period of time, conduct a thorough cleaning of the production area, facilities, equipment, tools, utensils, and etc. and then switch to another product.

23. Clean area: A room (or an area) with defined environmental control of particulate and microbial contamination, constructed, outfitted and used in such a way as to reduce the introduction, generation and

retention of contaminants within the room or area.

24. Alert limit: Established criteria giving early warning of drift of the critical variables of a system from normal conditions, while not reaching the action limit, which are not necessarily grounds for definitive corrective action.

25. Action limit: Established criteria indicating that the critical variables of a system are out of acceptable range, and requiring investigation and corrective action.

26. Out of specification: All events that the testing results fail to meet the regulatory standards or acceptance criteria established by the manufacturer.

27. Batch (or lot): A defined quantity of starting material, packaging material or finished product processed in one process or series of processes so that it could be expected as homogeneous. To complete certain stages of manufacture, it may be necessary to divide a batch into a number of subbatches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

For example, the homogeneous product that solid or semi-solid preparations for oral or topical use are produced within the same blender by one blending prior to molding or filling should be regarded as one batch. The homogeneous product that liquid preparations for oral or topical use are produced by final mixing prior to filling (sealing) should be regarded as one batch.

28. Batch number (or lot number): A distinctive combination of numbers and/or letters which specifically identifies a batch.

29. Batch record: All relevant documents and records for the disposition of a batch and includes processing, quality analysis and release review information. Such documentation can be used to trace all history and information related to the quality of finished product.

30. Air lock: An enclosed space with two or more doors, and which is interposed between two or more rooms (e.g. of differing class of cleanliness), for the purpose of controlling the air-flow between those rooms when people or materials need to enter or exit. An air-lock is designed for and used by either people or materials.

31. Manufacturer: Referred to as manufacturer of drugs, unless specified otherwise in the Provisions.

32. Qualification: A series of actions proving that the premises, facilities and equipment work correctly and actually lead to the expected results.

33. Return: Actions of sending back drugs to the manufacturer.

34. Documentation: The documentation in the Provisions includes specifications, master manufacturing documents, operation procedures, records, reports, and etc.

35. Materials: Raw materials and excipients packaging materials, and etc.

For example, the raw materials for chemical drug preparations are referred to as active pharmaceutical ingredients (APIs); those for biological products are referred to as raw ingredients; those for traditional Chinese medicine preparations are referred to as Chinese crude drugs, prepared slices of Chinese crude drugs and outsourced traditional Chinese medicine extracts; and the raw materials for the APIs are referred to any substances used in the manufacture of APIs excluding packaging materials.

36. Reconciliation: A comparison, making due allowance for normal variation, between the amount of product or materials theoretically produced or used, and actually produced or used plus loss collected.

37. Contamination: Adverse impacts of impurities with chemical or microbiological properties or foreign matters, into starting materials, intermediate, bulk, or finished products during production, sampling, packaging or repackaging, storage or transport.

38. Validation: A series of actions of proving that any operation procedure (or method), manufacturing process or system actually leads to the expected results.

39. Printed packaging materials: Any packaging materials with specified patterns and printed content, such as printed aluminum foil, labels, insert sheets, and card boxes, and etc.

40. Starting materials: Any substance used in the production of a drug, but excluding packaging materials.

41. Intermediate product: Partly processed product which must undergo further manufacturing steps before it becomes a bulk product.

42. In-process control: Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specification. The control of the environment or equipment may also be regarded as a part of in-process control.

Article 313: The Provisions shall be effective from March 1st, 2011. According to Article 9 of the Drug Administration Law of the People's Republic of China, the specific implementation details and steps shall be formulated by State Food and Drug Administration.

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