Guidance of Good Manufacturing Practice for Packaging Materials for Medicinal Products

Contents

Preface

This guidance is drafted in accordance with the rules of GB / T 1.1-2009.

This guidance is under the jurisdiction of China National Pharmaceutical Packaging Association.

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Introduction

The purpose of this guidance is to guide drug packaging material manufacturers to establish a quality management system to ensure that the products are suitable for their intended use.

This guidance applies the principles of GMP and ISO 9001 to the construction of production quality management system of pharmaceutical packaging material manufacture, and refers to the specific requirements of ISO15378. At present, most pharmaceutical packaging materials manufacture comply with the requirements of ISO 15378 to establish relevant production quality management system. As a customer, pharmaceutical company establish their production quality management system in accordance with GMP. There are some differences in the contents and requirements of the two systems, which cause unnecessary errors in the communication between the two sides. This guidance is based on the requirements of ISO 15378, and uses GMP language to describe relevant contents, so that pharmaceutical packaging material manufacture and pharmaceutical company can fully understand the requirements of this guidance, and can correctly implement it. This guidance is to standardize the production management of pharmaceutical packaging material, establish the production quality management system of pharmaceutical packaging material, and ensure the product quality of pharmaceutical packaging material and their intended applicability (including protection, functionality, safety and compatibility). This guidance encourages the adoption of Process Analytical Technologies in the establishment, implementation and improvement of the effectiveness of the production quality management system to enhance customer satisfaction by meeting customer requirements.

This guidance can be used for internal or external inspection of pharmaceutical packaging material manufacturers and for contract purposes with customers, as well as for reference of supplier audit. In this guidance, the regular typeface is the basic requirement, and the italics is the practice of some manufactures for reference.

This guidance is applicable to the design, manufacture and supply of pharmaceutical packaging materials. It mentioned in this guidance refer to the packaging system (including functional secondary packaging materials), components, drug delivery devices and printed packaging materials in direct contact with drugs. The requirements are applicable to pharmaceutical packaging material manufactures and their main suppliers.

Guidance of Good Manufacturing Practice for Packaging Materials for Medicinal Products

1 Scope

This standard specifies the establishment of quality management system, institutional responsibilities and personnel requirements, plant and facilities, equipment, procurement control and materials management, validation and verification, production management, product design and development, quality control and quality assurance, customer management and after-sales services and other content.

This standard applies to the design, manufacture and supply of pharmaceutical packaging materials.

2 Terms and definitions

The following terms and definitions apply to this document.

2.1 batch

Defined quantity of primary packaging material manufactured in one process or series of processes intended to have uniform characteristics with consistent, homogeneous quality.

2.2 batch record

Documents and records that provide a history of the batch, including information relating to its production and control, and which facilitate its traceability.

2.3 batch number

Unique identifier to identify a batch. A batch number can be a combination of numbers, letters and/or symbols which identifies a batch and from which the production and distribution history can be determined.

2.4 calibration

Process of checking or adjusting (by comparison with a reference standard) the accuracy of a measuring instrument

2.5 clean room
Room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room, and in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary.

2.6 contamination
Introduction of any unwanted material into the primary packaging material.

2.7 finished product
Primary packaging material which has completed all stages of production.

2.8 intermediate product
Primary packaging material which has completed some but not all production stages.

2.9 starting material

Raw material/components/substances used in order to produce primary packaging materials.

2.10 approved

Confirmed conformity status.

Note Conformity can be confirmed for any stage of the process (starting materials, process aids, packaging material or finished product).

2.11 batch release
Decision to release the batch for sale or supply, following a formal review of the batch document performed by the quality unit or a person authorized by the quality unit(s).

2.12 change control

Documented control of changes.

Note Changes may include, e.g. changes in raw materials, specifications, facilities, equipment, production processes and test methods.

2.13 customer complaint

Customer information about deficiencies and/or nonconformities.

Note1 The information may be verbally orally communicated or written.

Note2 The subject of a complaint can include primary packaging material quality, quantity or supply.

2.14 date of manufacture
Date on which one of the first stages in the process of manufacture of the primary packaging material, or the packaging, or the final release, occurs, and which may be subject to customer agreement.

2.15 deviation

Departure from an approved standard operating procedure (SOP) or established standard.

2.16 in-process control
Actions taken during the production process to test product conformity to its specification.

Note1 Monitoring processes and adjusting the means of production can be necessary to meet product requirements.

Note2 The control of the environment or equipment can also be regarded as a part of in-process control.

2.17 medicinal product
Any substance or combination of substances presented for treating or preventing disease in human beings or animals.

Note1 Any substance or combination of substances that may be administrated to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product.

Note2 Medicinal product may also be referred to as the pharmaceutical or drug product including clinical trial products.

2.18 out of specification/OOS

Test results that do not comply with the specification.

2.19 packaging materials for medicinal products

Packaging system (including functional secondary packaging material) ,

components, drug delivery devices and printed packaging material in direct contact with drugs.

2.20 process aids
Material used to facilitate process realization.

Note The material is not include in the products specification and can be removed at or before the final processing stage.

Examples Mould release agents, compressed air, rolling lubricants.

2.21 production

Processes resulting in packaging material.

Note The processes form the full production cycle from receipt of starting materials through processing and packaging, to completion as a finished product.

2.22 quality control

Part of quality management focused on fulfilling quality requirements.

Note Quality control includes checking or testing that specifications are met.

2.23 quality unit
Organizational unit which fulfils both quality assurance (QA) and quality control (QC) responsibilities.

Note The quality unit(s) may consist of separate QA and QC units or a single individual (group), depending upon the size and structure of the organization.

2.24 reconciliation
Comparison between the amount of finished product theoretically and actually produced or used, making allowance for normal variation.

Note The comparison considers waste, samples or other losses inherent in the process.

2.25 rejected
Status of starting materials, process aids, intermediate products or finished products whose test results do not comply with one or more of the requirements of the specification, and which have been deemed, usually by the quality unit(s), as not suitable for use.

2.26 rejection
Process whereby starting materials, process aids, intermediate products or finished products which have been deemed, usually by the quality unit(s), as not suitable for use.

2.27 reprocessing

Repeating part of a production process

Note Continuation of part of a process after an in-process control test has shown that the part is incomplete, is considered to be part of the normal process, and is not reprocessing.

2.28 rework

Action on a nonconforming product to make it conform to the requirements.

2.29 retained samples

Materials or finished products stored for future reference

Note These samples are generally taken in a sufficient amount and stored under recommended conditions for reference during a defined period of time.

2.30 return

Process for sending back primary packaging material(s) to the organization.

2.31 risk management
Systematic application of management policies, procedures and practices to the task of analyzing, evaluating and controlling risk.

2.32 standard Operating Procedure

Authorized, documented procedures, work instructions and test instructions for production and control.

2.33 sterile

State of being free from viable microorganisms.

2.34 validation
Confirmation, through the provision of objective evidence that the requirements for the specific intended use or application have been fulfilled.

2.35 verification
Confirmation, through the provision of objective evidence that specified requirements have been fulfilled.

Note1 The term “verified” is used to designate the corresponding status.

Note2 In development and design, verification is the process of examining the results of an activity under consideration in order to establish whether said activity conforms to the specified requirements.

3 General provisions

The content of this standard covers the basic scope and key points of the implementation of production quality management in pharmaceutical packaging materials enterprises to ensure the applicability of the pharmaceutical packaging materials. It is the basic requirement for the production management and quality management of pharmaceutical packaging materials, aiming to minimize the risk of contamination, cross-contamination, errors and confusion during the process of production and transfer process of packaging materials. The management of quality risk is a forward-looking or retrospective approach throughout the product lifecycle and a systematic process of assessing, controlling, communicating, and audit. The methods, measures, forms and documents taken in the quality risk management process should be compatible with the level of risk. Ensure the continuous and stable production of pharmaceutical packaging materials in accordance with the intended use and use requirements, and continue to meet customer requirements including the legal requirements and quality management system requirements of the location.

4 Establishment of Quality Management System

4.1 General

4.1.1 The quality management system shall be established in accordance with relevant technical standards and applicable regulatory requirements, documented, implemented and maintained, while continuously improving its effectiveness to meet quality standards and customer requirements.

4.1.2 The processes, sequences and interactions involved in the quality management system will be described in the quality manual and the

corresponding procedure documents. Standard management procedures and related standard operating procedures shall be developed and documented. Documents shall be approved to make sure all processes are under control and in an effective operation.

4.1.3 Controlled documents shall be released on site to assure necessary information sharing to operators.

4.1.4 Procedure documents for continuous improvement of both product quality and services shall be developed.

4.2 Documentation

4.2.1 General

The quality management system documentation is a detailed description and objective operational evidence of the quality management system. It shall include: quality policy, quality objectives, standard operation procedures and records.

4.2.2 Quality Policy

It is a quality commitment, officially released and consistent with the organization mission and business policy, further providing the framework of specific quality objectives.

4.2.3 Quality Objectives

The quality objectives are derived from the quality policy and responsibility allocation. It shall be measurable and consistent with the specification of product, services and customer satisfaction.

4.2.4 Standard Operation Procedures

Approved, documented procedures or series of procedures, work instructions and test instructions for production and control purposes.

4.2.5 Records

Record established to provide evidence of compliance with the effective operation of the quality management system.

4.3 Control of Documents

4.3.1 Scope

SOPs regarding document management shall be developed and implemented to control all documents, including technical documents, quality management system documents, appropriate documents of external origin

and applicable regulatory documents.

4.3.2 Content

4.3.2.1 All documents shall be reviewed and approved by authorized personnel before they are released; if necessary, the documents should be reviewed and re-approved after any modification or update.

4.3.2.2 The method to identify current revision status and changes of documents shall be developed, and to ensure its implementation.

4.3.2.3 Current version of applicable documents (including electronic form) shall be available at points of use, accompanied by the document release list.

4.3.2.4 Documents shall be in a uniform format, remain legible and identifiable. Referenced documents of external origin, such as specifications, drawings etc., shall be identified and released under control. Invalid or obsolete documents shall be withdrawn in time to prevent their unintended use.

4.3.2.5 Save and archive documents by document type.

4.4 Control of Records

4.4.1 Records management shall follow the following principles: records are traceable, data is clear and visible, records and operations are generated / entered synchronously, first-hand data and records are not transferred, records are consistent with actual operations, and there is no subjective fraud or objective input error4.4.2 The company shall establish a documented procedure to define the detailed controls needed for the filling, reviewing and archiving of records.

4.4.3 In some procedure documents, standard operational procedures and technical documents, evidence for the results obtained or the quality activities performed is required. These documents usually provide blank forms as a vehicle for recording results and process parameters.

4.4.4 Various process records include: manufacturing, packaging, engineering, maintenance, calibration, testing, storage, training, auditing, purchasing, inventory, etc. All these records must be correctly filled and archived as evidence of the effective operation of the quality system. All manufacturing, control, inspection, sales, and investigation records shall be retained for at least five years after the date of manufacture of the primary

packaging material, or until the shelf-life of the medicinal product as specified by the customer.

4.4.5 Computerized systems and data management shall ensure that network and files are secure and that only authorized personnel have access to systems and files. The file integrity shall be ensured when they are stored in a shared area.

4.5 Internal Review

4.5.1 The company shall conduct internal review at least once a year to check the effectiveness of the quality management system and the implementation and maintenance of this guideline.

4.5.2 The internal review system shall be established, including the review planning, the criteria and scope for the review, the trained review team, the review procedures and subsequent corrective actions, to ensure that the review outputs are reported to the relevant management, and the written documents regarding the review shall be retained.

4.6 Management Review

4.6.1 Top management shall review the organization's quality management system, at least once a year, to ensure its continuing suitability, adequacy and effectiveness， and also the consistency with the strategic direction of the organization.

4.6.2 During the management review, it is necessary to combine the measures taken in the past management review and the changes of internal and external factors related to the quality management system; it is necessary to take into account the performance and effectiveness information of the quality management system, such as customer satisfaction and product service feedback, the process of achieving quality objectives, process performance and product qualification, nonconformity and corrective and preventive measures, audit results, and The performance of the Department supplier, etc.; the sufficiency of resources shall be considered; the effectiveness of training shall be considered.4.6.3 The output from the management review shall include opportunities for improvement, changes required for the quality management system, resource needs, and training needs, etc.

4.6.4 Documented information shall be retained as the evidence of management review results.

5 Organization, responsibility, and personnel requirements

5.1 The company should be set up in accordance with the manufacturing of primary packaging materials, and the job responsibilities of the quality, manufacturing, materials, equipment and engineering departments and personnel that affect the product requirements should be clearly defined in written form.

5.2 The quality department shall be independent of the manufacturing department, and the person in charge of quality department shall not be the same person in charge of manufacturing department. The quality department shall independently perform the duties of finished product release and exercise the power to approve or reject the raw materials or finished products. It enjoys the right to participate in the review and approval of all quality-related activities such as manufacturing processes, quality standards, changes in procedures and testing methods, deviations and complaint investigations; regular reporting to the top management on the operation of the quality system and the changes of customer specifications and relevant statutory requirements is required. Top management shall provide enough resources, rational planning, organization and coordination to ensure the independent performing of quality management duties. The persons in charge of quality and manufacturing departments shall have at least a relevant professional background or a certain number of years of experience in the manufacturing and quality management of primary packaging materials, at least one year of quality management experience in pharmaceutical industry and has received professional knowledge training related to the products to be manufactured.

5.3 There should be a certain number of managers and technicians who are compatible with the production of pharmaceutical packaging materials. Key personnel should be full-time employees of the company. Personnel at all levels who are engaged in the production, quality management and equipment maintenance of pharmaceutical packaging materials shall have the education level appropriate to their responsibilities and undergo training and assessment to meet the needs of pharmaceutical packaging materials production.

5.4 Training procedures shall be established and implemented. The comprehensiveness, adaptability, effectiveness and sustainability of the training should meet the needs of the work.
Training shall cover related technical knowledge, operation procedures, health knowledge, relevant laws and regulations, and this guideline. Training

shall be conducted in sufficient frequency by qualified personnel to ensure employees are familiar with the requirements of this guideline. Training records shall be retained.

5.5 Pharmaceutical packaging companies should manage the health of personnel involved in quality activities and establish health records. Thereafter, at least one physical examination is taken each year. When an employee has a higher risk of microbial contamination due to health reasons, appropriate measures shall be taken by designated personnel.

5.6 Staff entering clean manufacturing areas should add additional training on microbial and particulate contamination to understand the potential risks of such contamination.

5.7 Anyone entering the production area shall change clothes according to the regulations. The selection, style and wearing method of the overalls shall be compatible with the work and the specific clean area requirements.

5.8 Personnel entering the clean production area shall not wear makeup and wear accessories.

5.9 Smoking and eating should be prohibited in production areas and storage areas, and non-productive items such as food, beverages, cigarettes and personal medicines are also prohibited.

6 Plants and Facilities

6.1 Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process. The manufacturer should have a neat manufacturing environment. The ground, roads, and transportation in plant area should not introduce contamination to the manufacturing. Premises and facilities used for production, packaging, inspection and storage of pharmaceutical packaging materials should facilitate cleaning, repair and maintenance to maintain in good condition. Interior surfaces (walls, floors, ceilings and windows) 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.

6.2 The cleanliness level of the premises and facilities shall be determined according to the applications and characteristics of the pharmaceutical packaging materials. The production area for the pharmaceutical packaging

material can be divided into the controlled-not-classified (CNC) area and clean area, and the design of the cleanliness level of the clean area should follow the principle that the cleanliness level be suitable with that of the clean area where the drug to be packaged with the material. When there are multiple processes in the clean area, different cleanliness levels should be employed according to different requirements of the processes. The following italics are just for examples. Different enterprises have different situations and may take different approaches.

Practical example: as shown in Table 1, for glass pharmaceutical packaging materials mostly of which are not ready-to-use products, an enclosed controlled-not-classified (CNC) area and be employed. For ready-to-use packaging materials (e.g. prefillable products) a clean area should be set as the cleanliness level which is suitable with that of the drug manufacturer.
Process steps of rubber stopper production like weighing, milling, preforming, vulcanization, and trimming may be carried out in the controlled-not-classified (CNC) area and washing process in an area of Class D. Discharging primary packages which are not ready-to-use may be performed in Class-C and discharging ready-to-use primary packages in Class A with a Class C background.

The forming process of the prefillable syringe is carried out in the non-clean area, the injection molding process and needle assembly process in Class D, and washing and nesting are in Class A with a Class C background.

Table 1 Example of cleanliness level

Cleanliness level	*Examples of operations*
Class A with B background	*Blowing extrusion, molding and sealing of plastic containers for aseptic eye drops*
Class A with Class C background	*Primary packages discharging zone (rubber stopper)*
Class B	*Primary packaging and air lock of plastic containers for aseptic eye drops*
Class C	*Non-discharging zone of primary package (rubber stopper); manufacturing process of terminally sterilized products, such as membrane of transfusion bags, plastic infusion bottle, aluminum-plastic composite cap, aerosol valve, etc.*
Class D	*Manufacturing process of non-high-risk pharmaceutical packaging materials; such as washing (rubber stopper), printing (medical*

	aluminum foil), coating (medical aluminum foil), cutting (medical aluminum foil), compositing (medical composite film),curing (medical composite film), bag making (medical composite bag)
CNC (controlled-not-classified)	*Ingredients weighing (rubber stopper), preforming (rubber stopper), vulcanization (rubber stopper), trimming (rubber stopper), secondary packaging of finished products (aluminum foil), PVC hard disk mixing*

6.3 The area and space for production and storage should be suitable for the scale the manufacturing operations, to properly place equipment, utensils and materials, facilitate the manufacturing operation and minimize the errors and cross-contamination. In particular, attention should be given to the occurrence of cross-contamination and errors in the ingredients weighing room.

6.4 The air handling system shall be designed to prevent cross-contamination, and return air shall not be used in areas prone to cross contamination. Individual ventilation shall be used for area with particular properties as possible.

6.5 The temperature and relative humidity of the manufacturing area shall be set and controlled according to the nature of the product and the requirement of the process.
Practical example: The storage and transportation of glass pharmaceutical packaging materials shall avoid moisture resulting in alkali dissolution.

The storage condition for rubber stopper is room temperature and protection from light, and the temperature and humidity of primary packaging during manufacturing are controlled according to the requirements of the corresponding clean area.

6.6 The garment and its quality shall be appropriate for the production operations and the cleanliness of the working area. Its design and wearing shall be in such a way as to protect the products and personnel.

The description of gowning requirement for each clean area is given below: Class D: hair, beard and relevant parts should be covered. Appropriate garments and shoes or overshoes should be worn. Appropriate measures should be taken to avoid introducing any contamination from outside the clean area.

Class C: hair, beard and relevant parts should be covered. A face mask should

be worn. A jump suit or two-piece trouser suit with sleeves gathered at the wrists and appropriate shoes or overshoes should be worn. They should be virtually free of fibers or particulate matter.

Class A/B: hair, beard and relevant parts should be covered by a headcover thoroughly. The hood cover should be tucked inside the collar. A face mask should be worn to prevent shedding of droplets, and if necessary, safety goggles should be worn. Appropriate sterilized, particle (such as talc powder)-free rubber or plastic gloves and sterilized or disinfected foot covers should be worn. Trouser-legs should be tucked inside the foot covers and garment sleeves into the gloves. The garments should be sterilized jump suit without shedding fibres or particulate matter, and retaining particles shed by the body.

6.7 The workshop should effectively prevent rodents, birds, insects and other animals from infesting. The CNC area should be enclosed, and equips with necessary insect prevention and mousetrap facilities according to technological requirements.

6.8 Lighting shall be appropriate in all areas, and emergency lighting should be equipped as required.

6.9 The setting of the floor drain in the manufacturing operation area should be suitable with the manufacturing requirements, and use air break, liquid break or other devices to prevent backflow and contamination.

6.10 There should be appropriate measures to prevent cross-contamination caused by personnel and materials in and out of the workshop. Changing rooms and material buffer rooms leading to areas of class D or higher cleanliness level shall be designed as airlock. There shall be pressure difference between clean area and non-clean area, or clean areas of different levels as positive. When necessary, appropriate pressure difference shall also be kept between different areas (operation room) of the same cleanliness level.

6.11 Laboratory that meets the requirements shall be set up, and equipped with testing and experimental instruments and equipment suitable for the testing items specified by the state. The design of laboratory shall be ensured to be applicable to its intended use, and prevent confusion and cross-contamination. There shall be enough area for sample handling, retention, stability test samples storage and records keeping. When necessary, a dedicated instrument room should be set to protect instrument with high sensitivity from static, shaking, humidity or other outside interferences.

7 Equipment

7.1 The equipment for the manufacturing, packaging, testing and storage of pharmaceutical packaging materials shall be designed and installed to facilitate operation, cleaning and maintenance. The equipment should be designed to minimize contamination from direct contact with the operator. Enclosed equipment and piping can be installed outdoors.

7.2 The surface of the equipment used for manufacturing shall be smooth and even, and shall not chemically react with the material, no effect on quality and easy to clean or disinfect.

7.3 Measures should be taken to avoid direct contact between the lubricants or coolants required for the operation of the equipment and the raw materials of pharmaceutical packaging materials, semi-finished products for pharmaceutical packaging materials or finished pharmaceutical packaging materials. When contact is inevitable, the lubricant or coolant used should at least be of food grade.

7.4 The name and flow direction of the materials in the material pipeline shall be indicated.

7.5 Calibration for critical metrology and monitoring equipment, including laboratory test equipment and intermediate control equipment, shall be performed in accordance with plans and procedures. Instruments and equipment that do not meet the set standards shall not be used.

Calibration standards should be traceable to statutory standards and provide measurement uncertainty. Calibration and inspection of scales, gauges, meters, recording and control equipment and instruments for the manufacturing and inspection of pharmaceutical packaging materials should be carried out on a regular basis in accordance with the operating procedures and calibration plans, and relevant records should be archived.

The range of calibration should cover the scope of actual manufacturing and testing. Calibration should be carried out using a standard instrument and the standard instrument used should comply with the relevant national regulations.

The calibration record shall indicate the name, number, Calibration validity period and measurement certificate number of the standard instrument used to ensure traceability of the record.

Scales, gauges, meters, equipment and instruments used for recording and control should be clearly marked to indicate the validity period of their calibration. Do not use scales, gauges, and meters that are not calibrated, that exceed the calibration validity period, or are no more accurate. This rule also applies for equipment and instruments for recording and control.

7.6 Maintenance and repair procedures for key equipment used in the manufacturing, packaging, inspection and storage of pharmaceutical packaging materials (including molds used in the manufacturing of pharmaceutical packaging materials) shall be established and implemented.

The mold should be coded for management. The monitoring plan should be implemented and whether to replace the mold should be decided based on the judgment of the monitoring results of the mold.

The using times and replacement cycle should be determined according to the characteristics of the mold material and the process requirements.

7.7 Process water treatment and its associated systems shall be designed, installed and maintained to ensure that the water supply meets the set standards. The final cleaning water for the disposable drug package for sterile drugs should be water for injection, and the final gas to be blown should be degreased, water-free and sterilized.

8 Procurement Control and Material Management

8.1 Procurement Control

8.1.1The supply channels (suppliers, manufacturers) of materials for manufacturing shall have legal qualifications. The comprehensive capabilities of the suppliers shall be assessed to ensure that the materials and services meet the contract requirements.

8.1.2 Raw materials, processing aids for quality-critical processes and suppliers of packaging materials used in clean rooms must be approved by the quality management department. Materials must be sourced from approved suppliers and ideally purchased directly from the manufacturer. Quality audits or assessments of major material producers should be conducted to ensure that the specifications and quality of the materials meet the quality requirements for the manufacturing of pharmaceutical packaging materials.

8.1.3 The list of qualified suppliers approved by the quality management department shall be controlled and circulated as documents and updated in a timely manner as the basis for confirming the suppliers during material procurement and warehouse acceptance.

8.1.4 The material suppliers shall relatively remain stable. A separate quality agreement shall be signed when signing the supply contract, and the quality terms shall be stipulated, such as packaging and transportation, acceptance plan, specification, disqualification of inspection and acceptance, notification of change, and responsibilities of both parties. But the quality agreement does not involve commercial terms.

8.1.5 The supplier's changes shall be subject to the change control procedures and the necessary assessment audit, validation and stability checks. If necessary, changes of the major raw material suppliers are subject to additional regulatory submission in accordance with relevant statutory requirements.

8.1.6 The risk of any outsourced services that affect product quality, including printing and formatting, laboratory services, sterilization, calibration services, cleaning, transportation, pest control, etc., should be controlled.

8.2 Receipt

8.2.1 The procedures and records for the acceptance of materials and finished products shall be formulated. When receiving materials, the receiving batch numbers shall be assigned in time and relevant information be registered.

8.2.2 All incoming materials should be inspected to ensure that they are consistent with the order, confirmed that they are from the supplier approved by the quality management department, and have the supplier's inspection report. The outer packaging of the material should be labeled. If necessary, it should also be cleaned.

8.2.3 Each time the goods are received, the integrity and closure of the outer packaging of the container shall be checked, and the delivery note shall be consistent with the contents of the supplier's identification. The inspection should result in a record.

8.2.4 If the same material received in one time is composed of several batches, it shall be stored, sampled, tested and released for use in batches. If effective measures can be taken to ensure that the quality is uniform, it can

be mixed, stored, sampled, tested and released for use.

8.2.5 Appropriate measures such as verification or testing should be taken to ensure that the materials in each package are correct.

8.2.6 If damage to the outer packaging or other problems that may affect the quality of the material are found, it shall be investigated and recorded and reported to the quality management department.

8.2.7 All materials and finished products should be labeled immediately after receipt or manufacturing, and stored according to the requirements as testing articles, until release for use or release for market.

8.3 Storage Management

8.3.1 Materials and products should be stored according to the storage conditions, nature and characteristics and management requirements, and placed in the designated warehouse area. The enterprise shall clearly specify the correspondence between the materials and the reservoir area in written documents to avoid placing errors.

8.3.2 All materials and products should be stored and turned over by batch under the appropriate conditions.

8.3.3 The storage process should be regularly inspected and maintained and storage conditions be monitored.

8.3.4 Non-conforming materials should have separate areas, with obvious labeling or other effective means to avoid being released to the manufacturing process.

8.4 Material release

8.4.1 Only materials approved by the quality management department and with shelf life can be used.

8.4.2 All materials and products should be released in accordance with the principle of first-in-first-out and close-to-shelf life-first-out.

8.4.3 The materials used for manufacturing shall be released by special personnel in accordance with the approved written procedures. Measures shall be taken to avoid mixture and errors to ensure the materials used for the manufacturing of pharmaceutical packaging materials are correct.

8.5 Weighing and dispensing

8.5.1 The ingredients shall be dispensed by specially designated personnel in accordance with written procedures to ensure that the qualified materials are accurately weighed or measured, then placed in a clean container and properly labeled.

8.5.2 Each material prepared and its weight or volume, ideally, should be independently reviewed by others and have a review record.

8.5.3 The changeover between materials shall be controlled by measures to avoid cross-contamination. The storage conditions of the weighed and dispensed materials shall meet the storage requirements of the materials.

8.5.4 When weighing materials, instruments with appropriate accuracy and precision level should be selected according to the quantity of materials in the formula and the process requirements.

8.5.5 The ingredients to be dispensed should ideally be single package based to make it possible to determine that the quantity difference is due to dispensing error or the original packaging error.

8.5.6 Essential measures shall be taken to ensure the uniform mixing.

8.6 Reuse of materials in the manufacturing process

Practical example: According to the characteristics of products and materials in different industries, different enterprises can formulate management measures for material reuse that are in line with their own, and carry out risk assessment, process confirmation and verification, product quality inspection, user confirmation and verification for material recycling and reuse.

9 Qualification and Validation

9.1 Qualification or validation to be performed should be determined to demonstrate that key elements of the operation are effectively controlled. The scope, extent and frequency of qualification or validation should be determined by a risk assessment.

9.2 Plants, facilities, equipment and testing instruments shall be qualified. Production, operation and testing shall be conducted using validated manufacturing processes, operating procedures and testing methods, and maintained in a continuous validation state.

9.3 Validation Master Plan (VMP) should be developed to describe the sequence of qualification and validation activities and execution in a document format, while listing the overall validation method. Validation Master Plan should be reviewed and updated periodically, such as annually. In general, VMP includes validation plans and timelines, organizational structure of validation activity, functions and responsibilities, overview of key equipment, processes and products, existing documentation for reference. For large projects, it is recommended to create a separate VMP.

9.4 Equipment qualification

9.4.1 The prerequisites for equipment qualification and identification are as follows:

- Approved equipment requirements

- the functions and responsibilities of the parties are clear

- Specify key process parameters

- Training in GMP and qualification as minimal requirement

9.4.2 If quality-critical equipment has potential impact on product quality, this critical equipment should be qualified and included in the VMP. The quality-critical equipment can be pinpointed according to the following judgments. If the answer is yes, it is regarded as quality-critical equipment:
-Whether equipment failure directly affects product quality

- Whether the equipment is used for product sterilization

-Whether the equipment is used for the control or measurement of quality-critical process steps or parameter

- Whether the device generates data or records that are received or rejected

- Whether the equipment is in direct contact with the product

- Whether it is part of contamination prevention or elimination equipment, or cleaning equipment
Non-critical equipment don’t need to be in the VMP.

9.4.3 The process of equipment validation must include risk assessment, design qualification (DQ), installation qualification (IQ), operation qualification (OQ), performance qualification (PQ) and equipment release, where:

- Design Qualification (DQ), to prove the equipment is designed to meet the intended use and the requirements of this guideline;

- Installation Qualification (IQ), to prove that the equipment installation complies with the technical guideline and if calibration is done as appropriate;

- Operation Qualification (OQ), to prove whether the equipment is operated between the desired upper and lower limits;

- Performance Qualification (PQ) is a challenging test of the entire manufacturing line performance to ensure that it is stable according to the required quality standards. The test process and results of continuous manufacturing batches (usually three batches) are formally documented and approved. If the manufacturing process is very long and a batch of material needs to be continuously produced for several weeks, the company may have a waiver from three consecutive batches. The work can be carried out in three sub-batches in one days minimally.

9.5 Process and product validation

9.5.1 The prerequisites for process/product verification are as follows:

- Approved/agreed process specifications

- Complete equipment qualification

- Validate that the functions and responsibilities of the parties are clear

- Specify key process parameters

- Trained operators, quality personnel

9.5.2 Process validation includes multiple continuous manufacturing batches (usually three) under commercial batch conditions with higher sampling levels and additional testing compared to conventional manufacturing. It should be demonstrated that a manufacturing process can produce products that meet the requirements of product quality standards in accordance with the specified process parameters continuously.

9.5.3 Product validation is the same as process validation, but may add specific customer needs.

9.6 Documents of qualification and validation

9.6.1 Documents and records for validation and verification shall be established and all documents shall be reviewed and approved prior to qualification/validation release. The quality department is responsible for the approval of all documents. Any revisions to the document should be tracked through version control.

9.6.2 The qualification/validation plan should be written and include the following: project scope description, responsibilities and task, rationale of the method used, test methods and test conditions used, the detailed acceptance criteria for each test, sampling plans, key process parameters, referenced procedures, change control and technical standard requirements, and other necessary conditions.

9.6.3 The validation report shall include the following: summary of test results, raw data, observed deviations and corrective actions, conclusions, and appropriate changes to the plan specified in the protocol. When the test passes, it should be approved for qualification/validation in the next step.

9.6.4 The qualification/validation record shall be archived at least five years after the date of manufacturing of the product.

9.7 Specific measures should be taken to control the changes in the qualification/validation process. Documented change controls which cover the entire equipment, process, and product life cycle should be established after release.

9.8 When changes or deviations occur, the equipment/process should be reviewed and evaluated, and requalified or revalidated as appropriate. The clean room and sterilization process should be periodically qualified and validated.

9.9 As long as the equipment/process is operating under controlled conditions and there is no change to the equipment/process or product being produced, the equipment does not need to be requalified and the process does not need to be re-validated. Whether the equipment/process is under control is determined by routine process control data and analysis of compliance and variability of all product test results, as well as by product quality review.

9.10 Process procedures and operating procedures should be qualified based on the results of the qualification/validation.

10 Manufacturing Management

10.1 An operational procedure for dividing the manufacturing batch of the product should be established, and the division of the manufacturing batch should ensure the uniformity and consistency of the quality and characteristics in the same batch of product.
Procedures for formulating the batch number of the package material and the date of manufacture should be established. A unique batch number should be assigned for each batch of products. Given the uniformity and consistency of the batch is ensured, the commercial batch provided to the customer can be composed of multiple manufacturing batches, but the rule of determining batch size must be clarified.

Pharmaceutical packaging materials are produced on a continuous and scaled style, and products and processes have diversity and continuity. There are many ways to divide the batches. For example,:

The rubber stop batch can be defined as a batch of a certain quantity of products produced in the same continuous manufacturing cycle within the specified limit with the same formula and the same raw material. The specific recommendations are as follows:

Quantity in one order of the same specification: ≤ ¢ 13 series products, 300,000 - 3 million pcs, that is, one sales order corresponds to one manufacturing batch number; > ¢ 13 series products, 100,000 - 3 million pcs, that is, one sales order corresponds to a manufacturing batch number.

Quantity in one order of the same specification:>3 million pcs, the manufacturing batch number corresponding to this order should be divided into 2 or more manufacturing batch numbers.

Quantity in one order of the same specification: >3 million pcs, if the client of this order requires a single batch number, then the batch could be established according to user requirement.

>¢13 series products, quantity in one order of the same specification <100,000, this order is not produced as a scaled batch for production.

≤¢13 series products, quantity in one order of the same specification <300,000, this order is not produced as a scaled batch for production.

Under the premise that the construction material and excipients are not changed and the equipment of each process is running well, the key to affect the quality of the rubber

stopper is the cleaning process of the rubber stopper. Whether the cleaning process is validated is the key to evaluate the uniformity within the batch and the consistency between the batches. It is recommended that rubber stopper manufacturer should internally define the internal batch as the minimally-sized cleaning batch, and at the same time, consider the actual situation of the customer order to define the delivery batch, so as to trace the quality of the commercially available rubber stoppers.

The batch division of products such as PVC/PE/PVDC can be defined as products produced with the same formula, the same material, the same manufacturing line, the same thickness, and the continuous manufacturing of the same process. When continuous manufacturing of PVC sheet for pharmaceutical use exceeds100t, the batch should be divided every 100t. Different widths are distinguished with a general batch number followed by a sub batch number such as "-1, 2, 3...". PVC/PVDC batch shall not exceed 30t, and the PVC/PE/PVDC batch shall not exceed 15t.

Manufacture batch of glass vials can be defined as at the same time by one or more vials production machines of the same model, with the same supplier of the vial, and with the same specification in a continuous manufacturing cycle.

Definition of non-continuous manufacturing cycle: continuous unplanned downtime by more than 24 hours, continuous planned downtime for more than 120 hours.

Aluminum foil batch is defined as：per customer order (in m2 or kg), products produced continuously with the same formula and same process condition. All orders, recipes and processes are managed through the system to achieve traceability.

Batch range: According to the batch division principle, the number of products produced in the continuous manufacturing period.

10.2 Identification and traceability

10.2.1 A document system should be established and maintained to track the process from source to product realization of all materials. Batch manufacturing records should be developed per batch.

10.2.2 All used materials, intermediate products or containers of the products to be packaged, main equipment and necessary operating rooms shall be labeled or otherwise marked with the name, specification and batch number of the product or material in manufacturing. It should be possible to trace the material, equipment and process information used in the product by the product batch number.

10.2.3 Ensure that the returned pharmaceutical packaging material to the

manufacturer (such as products to be reprocessed to meet the specified requirements) is identified and always distinguished from the normally produced product.

10.3 Clean manufacturing and contamination control management

10.3.1 Documented procedures for the cleanliness of pharmaceutical packaging materials and the prevention of contamination of equipment or products should be established and maintained.

10.3.2 Manufacturers in the following situations shall establish documented cleanliness requirements for pharmaceutical packaging materials:

- The pharmaceutical packaging material is cleaned by the manufacture before sterilization and/or before use, and the pharmaceutical packaging material is released as a ready-to-sterilize or ready-to-use product;

- The pharmaceutical packaging material is supplied as a non-sterile product, but the cleanliness is important in use;

- When the processing aid is removed from the product during the manufacturing process.

10.3.3 Personnel entering the clean manufacturing area shall change to the corresponding clean uniform in accordance with the dressing procedure;

10.3.4 The manufacturing materials and pharmaceutical packaging materials entering the clean manufacturing area shall go through air lock with surface cleaning;

10.3.5 Storage containers and associated branch pipes and inlet-outlet management should be identified. Packaging materials that come into direct contact with the product should be covered or properly sealed. The container and equipment cleaning procedures shall be established, and the state of the cleaned containers and equipment shall be marked, indicating the cleaning status, expiration date and operator, and the cleaning records shall be retained.

10.3.6 In different batch manufacturing, size clearing and inspection procedures shall be established. Materials, documents and articles related to the previous batch shall be cleaned up, and the clearing process and inspection results shall be recorded; and the cleaning status of the manufacturing area and the room area shall be marked, indicating its clean

status.

10.3.7 If multiple batches, multi-specs and multi-customer products are required to be produced simultaneously in the same area, strict management procedures and isolation measures should be established.
10.3.8 When sterilization is required, the establishment shall establish a recording procedure to verify the sterilization process. The process should be validated prior to release to use and periodically re-validated. If sterilization is outsourced, ensure that the process complies with the requirements of this document.

10.3.9 The process parameters of the sterilization process used for each sterilization batch shall be maintained and the sterilization record shall be traced back to each batch of pharmaceutical packaging material.

10.3.10 Products should be clearly identified, isolated, and stored intact to prevent contamination or cross-contamination of foreign materials. The packaging used to produce and store the product should be clean and suitable. Delivery should be accompanied by appropriate documentation specific to the batch.

10.4 Process Specification

10.4.1 Each pharmaceutical package material shall have corresponding manufacturing process specification. Its basic content shall cover: the manufacturing formulation and manufacturing process flow of the pharmaceutical packaging material consistent with information submitted during connected review, SOPs of key equipment, and in-process methods and acceptance criteria, as well as calculation methods for mass balance and limits.
Glass pharmaceutical packaging materials are not required to calculate mass balance.

Needle caps and stainless-steel needles of pre-filled syringes require only theoretical mass balance.

10.4.2 The manufacturing and packaging of pharmaceutical packaging materials shall be carried out in accordance with the approved process specifications and operating procedures and relevant records shall be in place to ensure that the pharmaceutical packaging materials meet the specified quality standards and meet the requirements for information provided in the connected review.
The primary packaging of glass pharmaceutical packaging material is

generally in the form of carton or PP thermoplastic box, and also in the form of a box-free heat shrinkable film.

Following the customer's requirements for the cleanliness level of the rubber stopper, ready-to-sterilize/use rubber stoppers should be is packaged in breathing bag plus a PE bag and secondary carton. Rubber stopper not washed should be packaged with a two-layer PE bag and secondary carton.

Laminated film as pharmaceutical package materials should be packaged with a PE bag plus a buffer and a secondary carton.

Barrels of pre-filled syringe should be placed in a nest, placed in a nest box, and covered with Tyvek (without glue) to prevent foreign matter entry, and apply Tyvek (with glue) and heat sealed. Dust-proof bags with Tyvek is used to further pack and finally placed in a double-layer corrugated cardboard box.

If wood pallet is used for packaging, contamination from the chemicals used in pallet treatment should be considered.

10.4.3 The manufacturing process specification shall not be randomly changed. If changes are required, they should be revised, reviewed, and approved in accordance with the relevant operating procedures.

10.4.4 The content of the process specification shall at least include:

10.4.4.1 Formula of the pharmaceutical packaging material, product name and product code; list of construction materials of excipients, with name, code, and amount of each material.

10.4.4.2 Manufacturing operation requirements:

Description of the manufacturing site and equipment used (such as the location and number of the operation room, the cleanliness level, the essetial temperature and humidity requirements, equipment model and number, etc.);

The method or corresponding operating procedure number used for the preparation of key equipment (e.g. cleaning, assembly, calibration, sterilization, etc.);

Detailed manufacturing steps and process parameters (such as material check, pretreatment, order of material addition, mixing time, temperature, etc.);

All in-process control methods and standards;

The expected maximum output. If necessary, output limit of the intermediate should also be indicated, as well as the calculation method and limits of the mass balance;

Storage requirements for the products to be packaged, including containers, labels and special storage conditions.

10.5 Manufacturing Process Control

10.5.1The control procedures for the manufacturing process of pharmaceutical packaging materials should be established to ensure that the product quality meets the standard requirements and controls various factors affecting product quality during the manufacturing process.

10.5.2 Process control during and after the manufacturing of pharmaceutical packaging materials shall be carried out by means of in-process testing or by setting in-process control points.

10.5.3 If any deviation from the control requirements is found during the manufacturing of the pharmaceutical packaging material, actions shall be carried out. Change control should be carried out when changes are made to the process, equipment, standards, environment, etc. that have been determined.

10.5.4 Some special manufacturing process for pharmaceutical packaging materials should be operated by operators with corresponding qualifications. The equipment needs to be qualified, and the process parameters are monitored and controlled throughout the manufacturing process. All process control records should be archived.

10.5.5 Manufacturing equipment should be qualified to ensure manufacturing process capability.

The key processes of rubber stoppers include: rubber mixing, preforming, vulcanization, edge punching, cleaning, and packaging

Rubber mixing: affecting yield and process of preforming and vulcanization.

Pre-forming: affects the size and appearance of vulcanized products, affecting the yield

Vulcanization: The control of size and appearance affects the transfer, filling and visible foreign matter of drug:

Edgepunching：the quality of the edge affects the particles, visible foreign matter, etc.

Cleaning: Cleaning and silicidation-drying affect the product particles, foreign bodies, smoothness of transferrin machine, moisture, etc., directly affecting drug quality.

The key operating processes of PVC/PE/PVDC including calendering process (control of product thickness) and PVDC coating amount (control PVDC weight by gram), oven temperature (control solvent residue), laminating process, cutting, printing and patterning.

The key process of tubing glass include mainly in the two processes of vial making and annealing. The control of the flame temperature of the vial-making process is basically judged by visually observing the change of the shape of the flame and the state of melting of the glass, and the temperature parameter is only a range. The key operating processes for manufacturing pharmaceutical glass tubes are mainly melting and forming. The quality of the melt will affect the appearance defects, physical and chemical properties of the glass, and the quality of the molding will affect the size.

The key operating processes of medicinal aluminum foil are: printing, patterning, coating, cutting, etc.

10.6 Batch record management

10.6.1 Each batch of products shall have a corresponding batch record, which traces the manufacturing history of the batch of products and the conditions related to the quality of the batch of products. Key parameters in the manufacturing process should be recorded.

10.6.2 Batch records shall be based on the relevant content of the current approved process specifications. Records should be designed to avoid mistakes as much as possible. Each page of the batch record should be labeled with the product name, specification, and lot number.

10.6.3 The blank template of batch manufacturing record shall be reviewed and approved by the person in charge of manufacturing management and the person in charge of quality management.

10.6.4 During the manufacturing process, each operation shall be recorded in a timely manner. After the operation is completed, the manufacturing operator should confirm, sign and date.

10.7 Product Protection

10.7.1The package for material and products, storage conditions, transportation conditions, expiration date or storage period, and materials to be re-tested and testing items shall be determined in the form of documents. This document should be immediately available at the execution site.

10.7.2The packaging materials that are in direct contact with the pharmaceutical packaging materials shall not adversely affect the quality of the pharmaceutical packaging materials. Pharmaceutical packaging materials should use sealed package.

10.7.3 Reusable containers, before use, should have the original packaging label removed and clean and keep the container dry. Check the cleaning status before use.

10.7.4 If there is no specific requirement of shelf life, a storage period should be established. If the material needs to be re-tested, the re-inspection cycle and testing items shall be formulated according to the stability and use requirements of the material.

10.7.5 The transportation of materials and products should meet the quality assurance requirements, and the storage conditions and transportation conditions should be validated.

10.8 Material recycle and mass balance

Mass balance standards for each process should be specified. And after the end of manufacturing, the output (yield) and mass balance check are carried out per batch. If there is a difference, the cause must be identified and no potential quality risk is identified before it can be handled as normal.

The glass pharmaceutical packaging materials can be reworked for unqualified size or appearance. Broken glass, if it is clinker, can be used as an aid with a validated proportion.

Laminated film packaging materials allows rework if not affecting product quality and use.

11 Product design and development

11.1 Management procedures for determination of technical standards, establishment of standards, review, approval, change control and other management procedures shall be established.

Practical example: the content of technical standards for drug packaging products should meet the requirements of functionality, protection, compatibility, safety and the determined quality standards. The establishment of technical standards for drug packaging products shall be subject to the full technical review with the participation of departments such as production process technology, quality management, design and development personnel involved in various laws and regulations, and shall be approved or confirmed by customers if necessary.

11.2 The design and development management documents of drug packaging materials and corresponding records shall be established, and the records of the process shall be kept.

Practice example: the design and development procedures of drug packaging materials should be established, and the records of this process should be kept. The product design and development procedures shall specify the workflow, responsibilities, work contents and standards, design and development strategies, input review, verification, confirmation and output requirements and implementation methods, technology transfer, design change control and authorization management requirements of product design and development.

In product design and development, the product technical standards for product development shall be determined first and approved in advance.

For planning, the enterprise shall consider the nature, duration and complexity of design and development activities, review, verification and validation activities required for the whole process, as well as internal and external resources. The responsibilities and authorities of relevant departments in the activities shall be clarified, and customers or users shall be allowed to participate in the design and development process if necessary.

For the input of product design and development, the enterprise shall consider the functional and performance requirements of drug packaging materials, the requirements of laws and regulations, industry specifications, and the potential failure consequences of drug packaging materials. For the

purpose of design and development, the input shall be sufficient and appropriate, and shall be complete and clear.

For product design and development control, necessary review activities, verification activities and confirmation activities shall be carried out, information communication for project implementation shall be carried out regularly according to the project work plan, and project summary shall be carried out to ensure the orderly development of product design and development projects.

For product design and development output, design and development personnel shall transfer relevant technical documents such as product development technical standards, process procedures, material quality standards, etc. to product production department and quality management department. In addition, technical audit shall be conducted for production process procedures, batch production records, production process control standards and quality standards in the formal production stage.

11.3 The confirmation and verification management procedures for product design and development shall be established, the confirmation items, confirmation methods and principles of acceptable standards at different design and development stages shall be defined, and relevant records shall be kept.

Practice example: the validation or validation scheme shall be formulated according to the objects of validation or validation, and shall be reviewed and approved. The responsibilities of the validation or validation scheme shall be clear, and the validation or validation shall be implemented in accordance with the pre-determined and approved scheme, with records. After the confirmation or verification work is completed, a report shall be written and approved. The results and conclusions (including evaluation and suggestions) of confirmation or verification shall be recorded and archived. Before the confirmation and verification of product design and development are finally completed, products shall not be delivered to customers or commercial batch production.

11.4 Management procedures for product design and development review shall be established to specify the timing of design and development review, qualification of reviewers, review contents and standards, review follow-up management and other management requirements. And keep relevant design and development review records.

Practice example: the participants in the review shall include representatives

of functional departments related to the reviewed design and development stage. The participants in the product design and development review shall have a sufficient understanding of the product quality characteristics, production methods and process control required for use, and quality control knowledge of pharmaceutical packaging materials, so as to ensure the fairness, systematicness and accuracy of the review results.

The timing of product design and development review can be determined according to the project scope and project plan of design and development. Product design and development review shall be carried out before product technical standards are determined and products are submitted for related review. The review contents at different stages of drug packaging product design and development shall include the following contents:

The quality characteristics of the product meet the pre-determined product quality standards; the effectiveness and suitability of the production process, quality standards and testing methods of the product; the completion effectiveness of the change measures in the design and development stage; whether the improvement measures are needed.

11.5 Change of product design and development shall be controlled.

Practice example: when the design and development changes, the design and development changes shall be analyzed and evaluated, the corresponding change control plan shall be formulated, and measures such as review, verification and confirmation of changes shall be taken if necessary. The scope of review shall include the evaluation of the impact of changes on product components and delivered drug packaging materials, so as to ensure that the changes meet the requirements and will not have adverse effects. All change control measures shall be authorized and approved before implementation. All design and development related change control records shall be kept.

Any change of data provided to customers shall be informed to customers, and explanation shall be made in the registration data provided to the regulatory department when necessary.

12 Quality Control and Quality Assurance

12.1 The quality management department shall be responsible for the quality management and inspection of the whole process of pharmaceutical packaging materials manufacturing. The quality management department

shall be equipped with a certain number of quality management personnel and testing lab staff, and shall have places, instruments and equipment that are compatible with the manufacturing scale, variety and testing requirements of the pharmaceutical packaging materials.

12.2 The test responsibility of the quality management department is to sample, test and review the raw materials, manufacturing excipient materials and finished pharmaceutical products in accordance with the statutory requirements and the methods and procedures stipulated by the internal quality control standards of the enterprise to determine whether these materials and products meet the preset specification. Lab staff should receive special operation training.

12.3 The quality control laboratory shall have written procedures for the procurement and preparation of reagents and test solutions and strictly implement them. The purchased reagents and test solutions should be labeled with the name, concentration, and expiration date. Records of test solution preparation shall be kept, including the product name, preparation time and the amount of materials used. The test solution for volume analysis shall be standardized according to legal standards, and the standardized records shall be retained.

12.4 The laboratory shall be equipped with necessary reference books such as Chinese Pharmacopoeia, standard profile, and drug packaging materials standards, as well as related standard materials such as reference standards or reference materials. The testing protocol should include quality standards, sampling procedures, and testing procedures. The quality management department shall have a complete record of tests performed to ensure that the products meet statutory or internal quality standards. The sampling method should be science based and reasonable to ensure the representativeness of the sample and detailed sampling procedure is required. If the sample is moved to a separate test site, it should not be returned to the manufacturing area. The sampling protocol is recommended to comply with GB/T 2828 “Sampling Procedure for Inspection by Attributes”.

12.5 The operational procedures for the approval of release of materials and products shall be established separately, the standards and responsibilities for approval of release shall be clearly defined, and corresponding records shall be made.

The final testing shall be completed before the finished batch is released. All batch documents and records, including testing data, should be reviewed by the quality management department and meet the requirements. Unqualified

products shall not be released.

12.6 If the test results do not meet the requirements of the specification, a complete investigation must be conducted and recorded in accordance with written procedures. The quality control laboratory shall establish procedures for the OOS investigation.

12.7 The retained sample should be representative of the sampled batch of product or material; the sample container should be labeled with the name of the sample, the batch number, the date of sampling, the packaging container, the sampler, etc.; the sample should be retained until one year after the expiration of the drug. The retained sample mass should be no less than twice the total amount to complete a test.

12.8 The stability of the pharmaceutical packaging materials should be documented and recorded, and should be tested regularly according to the stability study protocol.

The stability of glass pharmaceutical packaging materials is generally not conducted, and the pharmaceutical packaging materials made from polymer materials should be subject to stability study based on material study.

12.9 A change control system shall be established in accordance with the requirements of the relevant technical guidelines regarding pharmaceutical packaging materials changes, and all changes affecting the quality of the products shall be evaluated and managed in order to identify, classify, record, review, and approve changes regarding raw materials purchase, quality standards/specifications, equipment and facilities, and manufacturing processes. The quality management department and the relevant departments are responsible for final approval of the change. The necessary communication should be made within the company and between the company and the user regarding the impact of the change.

12.10 The operating procedures for deviation handling shall be established, and the reporting, recording, investigation, processing, and corrective actions taken shall be specified, and corresponding records shall be documented.

12.11 Any deviation should be assessed for its potential impact on product quality. Enterprises may classify deviations (such as major and minor deviations) according to the nature and scope of deviations, and the degree of potential impact on product quality. The assessment of major deviations should also consider whether additional product testing is required and the impact on product shelf life. When necessary, stability investigations should

be conducted on products involving significant deviations.

12.12 Any deviation from the manufacturing process, mass balance limits, quality standards, inspection methods, operating procedures, etc. shall be recorded and immediately reported to the personnel in charge and the quality management department. The deviation shall be clearly descripted. Major deviations shall be thoroughly investigated by the quality management department together with other departments and an investigation report shall be issued. The deviation investigation report shall be reviewed and signed by the designated personnel of the quality management department.

12.13 A system of corrective and preventive measures should be established to investigate complaints, recalls, deviations, self-test or external test results, process performance and quality monitoring trends, and to take corrective and preventive actions. The depth and form of the investigation should be commensurate with the level of risk. All customer complaints should be investigated in a timely manner, and the identified corrective and preventive measures should be communicated to the manufacturing and manufacturing related departments. The measures should be implemented according to the timetable. When necessary, the company should promptly feedback the status of the implementation of the measures to the customer.

12.14 Control procedures for rejected product should be established. Rejected raw materials, intermediate products and finished products should be clearly labled and controlled to prevent inadvertent use or inflow to the market. The enterprise shall keep records of the disposal of rejected materials, and shall have subsequent procedures for evaluating rejected products to determine whether rejected materials should be disposed by:

- Reprocessing/rework to meet regulatory requirements

- Accepted by customer consent

- Re-rating for other purposes

- destruction

Reprocessing, which is not a normal part of the manufacturing process, can only be carried out with the approval of the quality department, and the quality department maintains a written record of the risk assessment, and the reprocessing should be carried out under the same conditions.

Reprocessing must consider:

- new impurities that may be introduced by rework

- Additional testing for rework control

- Relevant records and traceability of the original batch

- Acceptance criteria applicable to products of rework

Rework, which is a normal part of the manufacturing process, should be implemented in accordance with the rework procedures.

This guideline does not accept the mixing of rejected batches with qualified batches to reduce the number of failed units below acceptable or detectable limits.

12.15 Rejected products shall be isolated and identified before corrective or other measures are taken.

12.16 Recall procedures for pharmaceutical packaging materials should be established. The entire process of the recall should be recorded, the customer notified and the record kept. Products recalled should be labeled and isolated. The effectiveness of the recall system should be assessed on a regular basis。

13 Customer Management and Service

13.1 Quality Agreement

13.1.1 The quality management department must sign a quality agreement with the customer. In the agreement, name and specification the purchased materials, and responsibility of the quality department of both parties should be specified.

13.1.2 Quality agreements generally include the following: supply requirements, transportation requirements, technology transfer, requirements of raw materials and pharmaceutical packaging materials, manufacturing facilities and equipment requirements, definition of batch of pharmaceutical packaging materials, batch size, customer testing items and sampling principles, packaging methods, acceptance criteria, disposal of the rejected, quality traceability, change control requirements, etc., and precautions for using pharmaceutical packaging materials, etc.

13.2 Contract review

13.2.1 Contract review procedures should be established, and the sales department should take the lead and organize relevant departments to conduct a comprehensive review of the contract.

13.2.2 The content of the contract review shall cover relevant issues related to quality, manufacturing technology and finance. For example: product specification, product acceptance and release methods, way to handle quality issue and liability of the two parties, manufacturing timetable, quality control and manufacturing capability (such as support of personnel, equipment, process, etc.) and product pricing and so on. The quality agreement shall be included in the contract review, and the relevant product quality execution clause shall be implemented in accordance with the quality agreement of both parties.

13.2.3 The contract review shall be conducted after initial drafting of the contract and a preliminary agreement with the customer, but before the main contract is signed.

13.2.4 Discuss with the customer regarding contract revision, the contract must be formed in writing.

13.3 Customer complaint

13.3.1 Customer complaint procedures should be established, procedures for registration, evaluation, investigation and handling of complaints should be established, and measures should be taken for complaints arising from possible product defects, including consideration of whether it is necessary to recall products from the market.

13.3.2 All complaints should be registered and reviewed. Complaints related to product quality defects should be detailed in document and investigated.

13.3.3 If the pharmaceutical packaging material is found or suspected to be defective, the necessity of investigating other batches should be considered to determine whether it is affected.

13.3.4 The investigation and handling of complaints shall be recorded and the information of the relevant batches of products investigated shall be indicated.

13.3.5 The complaints record should be reviewed periodically to identify issues that are red flags, recurrent, and the need to recall products from the market and take appropriate action.

13.4 Customer Service

13.4.1 Relevant customer service department and services should be deployed to ensure service capabilities and resources.

13.4.2 A customer satisfaction system should be established to collect and analyze information feedback from customers about products and services, including customer surveys, customer feedback on delivered products or services, customer interviews, market share analysis, and more. Companies should use the results of collection and analysis to assess product and service compliance, customer satisfaction, the performance and effectiveness of the quality management system, the effectiveness of measures taken to address risks and opportunities, and the need for improved quality management systems.

13.4.3 The company should actively cooperate with the audit requirements of customers. In addition to the first audit for the purpose of adding new suppliers, the manufacturer should prepare the information and analysis of the pharmaceutical packaging materials used by the customers during the period being audited, including customer complaints and other concerns. With the full communication with the customer site, the manufacturer should be committed to solving the reasonable needs of our customers and continuously improve the quality and application of the pharmaceutical packaging materials.