Guideline for the Manufacturing Quality Management of of Pharmaceutical Packaging Materials

（draft for public opinion collection）

Chapter 1 Objective, Scope and Principles

1.1 In order to improve the manufacture management of pharmaceutical packaging materials, establish a quality management system for the manufacture of pharmaceutical packaging materials, and ensure product quality and intended suitability (including protection, safety, compatibility and functionality) of the pharmaceutical packaging materials, according to the current *Drug Administration Law of the People's Republic of China, Good Manufacturing Practices for Drugs* and *Specific Requirement of Primary Pharmaceutical Packaging Materials ISO9001*, including *Good Manufacturing Practice (ISO 15378),* the guideline is formulated. Meanwhile, this guideline is intended to be a reference to pharmaceutical companies when auditing pharmaceutical packaging material suppliers.

1.2 This guideline is an application guideline for the design, manufacturing and distribution of pharmaceutical packaging materials. The pharmaceutical packaging materials mentioned in this guideline refer to packaging systems (or components), drug delivery devices and printed packaging materials that are in direct contact with the drug, excluding secondary packaging material or beyond. The requirements involved are universally applicable to pharmaceutical packaging companies.

1.3 The quality management system for pharmaceutical packaging materials should be established. The system should cover all factors affecting the quality of the package, including all organized, planned activities that ensure the quality of the package shall meet its intended use.

1.4 This guideline is part of the quality management system for pharmaceutical packaging materials. It covers the basic scope and key points of the implementation of manufacturing quality management for pharmaceutical packaging material manufacturers to ensure that the pharmaceutical packaging materials carry protection, safety, compatibility and functionality. It is the baseline requirement for the management and quality control of pharmaceutical packaging materials. This guideline aims to minimize the risk of

contamination, cross-contamination, errors and mixture during the manufacturing and transportation of pharmaceutical packaging materials.

1.5 The clean room requirement of the corresponding level shall be set up according to the intended use of the pharmaceutical packaging material for the control over the level of microorganisms and dust particles. The manufacturing environment of the pharmaceutical packaging material and the packaged drug shall be comparable. Or it shall be ensured that drug to be packaged and its manufacturing environment can be protected from contamination of the packaging material. The management of clean room is in principle based on the requirements in the Good Manufacturing Practices. If there are special requirements, it can be carried out without potential of affecting the quality of the drug after quality risk assessment.

1.6 Quality risk management is a prospective or retrospective approach throughout the product life cycle. It is also a systematic process for assessing, controlling, communicating, and reviewing quality risks. The methods, measures, forms and documents developed in the quality risk management process should be adaptive to the level of risk. Ensure sustainable and stable manufacturing of pharmaceutical packaging materials that meet the intended use and use requirements, and continue to meet customer requirements including statutory requirements and quality management system requirements.

1.7 This guideline is formulated in accordance with the requirements of current laws and regulations. When the statutory requirements are updated, this guideline will be updated and revised in a timely manner.

Chapter 2: Quality Management System

2.1 General Principles

2.1.1 The quality management system shall be established in accordance with relevant technical standards and applicable statutory requirements, and documented, implemented and maintained, while continuously improving its effectiveness to achieve the objectives of fulfilling quality standards and meeting customer requirements.

2.1.2 The processes, sequences and interactions involved in the quality management system will be described in the quality manual and the corresponding procedure documents, and standard management procedures and related standard operating procedures shall be developed. The relevant procedures shall be approved to quality standards and methods for the effective operation of these processes and control.

2.1.3 Controlled documents shall be circulated to the quality event scene to ensure that the operator has the necessary information.

2.1.4 Procedure documents from continuous improvement of the quality of products and services shall be formulated.

2.2 Document system

2.2.1 General requirements

The quality management system document is a detailed description of the quality management system and objective evidence of its operation, including: quality policy, quality objectives and quality records.

2.2.2 Quality Policy

It is the officially released quality-related requirement and commitment which are consistent with the aim and operation principle. It is also a framework for the detailed quality objectives;

2.2.3 Quality objectives

Quality objectives are derived from the quality policy with detailing and quantitification. Quality objectives shall be defined according to the responsibilities. Quantity objectives should be measurable, consider the applicable requirements, andshould be related to product and service specification and customer satisfaction.

2.2.4 Quality record

It is the objective record and evidence for the effective implementation of the management documents and operation document of the system operation.

2.3 Document control

2.3.1 Scope of control

SOPs regarding document management should be developed and implemented to control all required documents, including technical documentation, quality management system documentation, and appropriate range of external documentation and applicable laws and regulations.

2.3.2 Content of control

All documents are subject to approval by authorized personnel for their suitability and adequacy before they are issued; when necessary, the documents must be reviewed and revised and updated to be approved again.

Indication rules should be developed to identify the status of use and change status of the document, and to ensure that document changes and use status are label;

The current version of the documents used (including electronic documents) are available at all locations where the quality management system operates, and the circulated documents should be accompanied by a circulation list;

Documents should be kept clear and in a uniform designing and format that is easy to identify and inspect;

External documents (such as standards, drawings, etc.) as references should be identified and controlled to be circulated within the relevant scope; invalid or obsolete documents should be withdrawn from all circulation or use areas in time to prevent their unintended use.

Save and archive documents by document type.

2.4 Record control

2.4.1 Records management should follow the ALCOA principle, that is,

Attributable A, record be traceable;

Legible L; data is clearly visible

Contemporaneous C ; records and operations generated / entered in synchronization

Original O; first-hand data and records, no transfer

Accurate A; the record is consistent with the actual operation, no subjective fraud or objective input error

2.4.2 SOPs on record management should be established to control the planning, filling, reviewing, and archiving of records with detailed description.

2.4.3 In some procedure documents, standard operating 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.

2.4.4 Various process records include: manufacturing, packaging, engineering, repair and maintenance, calibration, testing, storage, training, auditing, procurement, inventory, etc. All these records must be correctly filled out and be archived as evidence of the operation of the quality system and its validity. All manufacturing, control, inspection, sales, and investigation records should be kept for at least five years after the date of manufacture, or until the end of the drug's shelf life in consultation with the client.

2.4.5 Computerized systems and data management should ensure that the network and documents are secure. Only authorized personnel may access the

system and documents. The document integrity should be ensured when they are stored in the shared area.

2.5 Internal Review

2.5.1 A company shall conduct internal review at least once a year to check whether it meets the requirements of its own quality management system, whether it meets the requirements of this guideline, and whether it is effectively implemented and maintained.

2.5.2 The internal review system shall be established, including the planning and review plan, the criteria and scope for the audit, the trained audit team, the review implementation and subsequent improvement, to ensure that the review outputs are reported to the relevant management, and the written documents regarding the review shall be retained.

2.6 Management Review

2.6.1 The top management of the enterprise shall review the quality management system of the enterprise at least once a year to ensure the enterprise maintains suitability, adequacy and effectiveness, and be consistent with the strategic direction of the enterprise.

2.6.2 Management of review input should be combined with the measures taken in the past management review and the changes in internal and external factors related to the quality management system; information on the performance and effectiveness of the quality management system, such as customer satisfaction and feedback on products and services, the extent to which quality objectives are achieved, process performance and product quality control, product failure and corrective actions, audit results, performance of external suppliers, etc. should be considered; sufficiency of resources should be

considered; effectiveness of training should be considered.

2.6.3 Management of review output should include opportunities for improvement, changes required for the quality management system, resources demand, training demand, etc.

2.6.4 Management review should retain documented information as evidence of management review results.

Chapter 3. Organization, responsibility, and personnel requirements

3.1 The organization should be set up in accordance with the manufacturing of pharmaceutical 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.

3.2 The quality management department shall be independent of the manufacturing management department, and the person in charge of the quality management department and the person in charge of the manufacturing management department shall not be one person.

3.2.1 The Quality Management Department shall independently perform the duties of finished product release and exercise the power to approve or reject the semi-finished products of raw materials and pharmaceutical packaging materials. 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. The quality person is responsible for the implementation of this guideline, and regularly reports to the person in charge of the company on the

operation of the quality system, customer requirements and changes in relevant statutory requirements.

3.2.2 The person in charge of the company shall periodically review the quality system to ensure compliance with the requirements of this guideline.

3.2.3 The quality management department shall be independent of the manufacturing management department. The person in charge of quality management shall have at least relevant professional experience or a certain number of years of experience in the manufacturing and quality management of pharmaceutical packaging materials. The person should have at least one year of experience in quality management of pharmaceutical packaging materials and has received professional knowledge training related to the products to be manufactured.

3.2.4 The person in charge of manufacturing management shall have at least relevant professional experience or a certain number of years of experience in the manufacturing and quality management of pharmaceutical packaging materials, including at least one year of experience in the manufacturing and management of pharmaceutical packaging materials, and have received professional knowledge training related to the products to be manufactured.

3.3 A certain number of management personnel and technicians appropriate to the manufacturing of pharmaceutical packaging materials should be equipped. Key personnel should be full-time employees of the company. Personnel at all levels engaged in the manufacturing of pharmaceutical packaging materials, quality management and equipment maintenance should have the education appropriate to their responsibilities and have received training and assessment to meet the needs of pharmaceutical packaging materials manufacturing.

3.4 Training procedures should be established and implemented. The comprehensiveness, adaptability, effectiveness and sustainability of the training should meet the needs of the work.

Training should cover related technical knowdedge, operation procedures, safety knowledge, health knowledge, relevant laws and regulations, and this guideline. Training should be conducted in sufficient frequency by appropriately qualified personnel to ensure employees are familiar with the requirements of this guideline. Training should have a corresponding record.

3.5 Pharmaceutical packaging manufacturers should manage the health of personnel and establish a health archive. Thereafter, at least one health examination should be taken each year.

Pharmaceutical packaging manufacturers should establish voluntary reporting procedures to ensure that personnel who are in direct contact with pharmaceutical packaging materials are entitled to report any abnormal conditions that may cause pollution, including the type and extent of pollution. When an employee may increase the risk of microbial contamination due to health reasons, appropriate measures should be taken by the designated person.

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

Chapter 4 Plants and Facilities

4.1 Site selection should be considered comprehensively based on plant and manufacturing protection measures. Enterprises should have a tidy manufacturing environment, while the ground, road surface and transportation

of the plant should not cause contamination to the manufacturing of pharmaceutical packaging materials. Plants and facilities used in the manufacture, packaging, inspection and storage of pharmaceutical packaging materials should be easy to clean, repair and maintain in order to maintain good condition. The inner surface (walls, ceilings, floors, doors and windows) of the clean area should be even and smooth, free of cracks, tightly connected, free of shredded particulate, resistant to dust accumulation, easy to effectively clean, and disinfection if necessary.

4.2 The cleanliness level of the manufacturing plant and facilities should be determined according to the objective and characteristics of the pharmaceutical packaging materials. The manufacturing area of the pharmaceutical packaging material can be divided into the controlled manufacturing area and clean area, and the clean room requirement of the clean area should in principle follow the same cleanliness level of the drug to be packaged by this material. When there are multiple processes in the clean area, different cleanliness levels should be used according to different requirements of the process.

Glass pharmaceutical packaging materials are mostly not ready-to-use products, thus controlled-not-classified (CNC) area can be used for manufacturing. Ready-to-use packaging materials (such as packaging materials for pre-filled drug products) should be manufactured in clean areas that are compatible with the cleanliness level of the drug manufacturer.

The process of dispensing, rubberizing, preforming, vulcanization, and edge-cutting of rubber stoppers can be carried out in an controlled-not-classified (CNC) area. The cleaning process is carried out in the Class-D area. The non-ready-to-use primary package discharge area is carried out in the Class-C area. The ready-

to-use primary package discharge is carried out in the Class C+A area.

The molding process of the prefilled syringe is carried out in a general area, the injection molding process and the needle staking process are carried out in Class-D area and cleaning and nesting are carried out in a local Class A zone in a Class C area.

Cleanliness level	Example of manufacturing operation

Class A in Class B	Extrusion, molding and sealing of non-terminally sterilized eye drops plastic containers
Class A in Class C	primary packaging discharge zone (rubber stoppers)
Class B	primary packaging of non-terminally sterilized eye drops plastic container, and air lock
Class C	non-discharge area of primary package (rubber stoppers); 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 vulcanization (rubber stoppers), punching (rubber stoppers), washing (rubber stoppers), printing (aluminum foil), composition (aluminum foil), cutting (aluminum foil), bag making (aluminum foil), curing (aluminum foil)
CNC (controlled-not-classifed)	dispensing of ingredients (rubber stoppers), preforms (rubber stoppers), secondary package of raw materials and finished products (aluminum foil), PVC hard sheet mixing

4.3 The manufacturing area and storage area should have an area and space suitable for the manufacturing scale to properly place equipments, utensils and materials to facilitate manufacturing operations and minimize errors and cross-contamination. In particular, attention should be paid to the occurrence of cross-contamination and errors in the ingredient weighing and dispensing room.

4.4 The air handling system shall be designed to prevent cross-contamination, and areas prone to cross-contamination (eg, dispensing areas) should not utilize return air. Areas with significant dust production (such as vulcanization areas) should be exhausted seperately as much as possible.

4.5 The temperature and humidity of the manufacturing area should be set and controlled according to the nature of the product and the process requirements.

Glass package materials should be stored and transported at room temperature and in dry contition, avoiding alkali forming, and it is not necessary to set special temperature and humidity requirements. The temperature and humidity conditions of the rubber stoppers are in-door, room temperature and light-proof, and the temperature and

humidity of primary packaging during manufacturing are controlled according to the requirements of the corresponding clean area.

4.6 Working uniforms and their quality should be compatible with the requirements of manufacturing operations and the level of cleanliness of the operation area. The style and way to wear should meet the requirements of protecting products and personnel.

The dress code requirements for each clean area are as follows: Class D clean area: The hair, beard and other relevant parts should be covered. Appropriate uniform and shoes or shoe covers should be worn. Appropriate measures should be taken to avoid the introduction of contaminants outside the clean area.

Class C clean area: The hair, beard and other relevant parts should be covered and a mask should be worn. One should wear a coverall that can be tightened at the wrist or uniform with a separate top and pants, and wear appropriate shoes or shoe covers. Work clothes should not generate fiber or particle.

Class A/B clean area: All hair and beard and other relevant parts should be covered with a hood. The hood should be inserted into the collar. Masks should be worn to prevent droplets from being emitted. Wear protective eyepieces if necessary. Rubber or plastic gloves that are sterilized and free of particulate matter (such as talc) should be worn and sterilized or disinfected foot cover should be worn. The leg sleeves should be tucked into the foot cover and the cuff should be inserted into the glove. The uniform should be sterilized one-piece overalls, without production of fibers or particles, and can retain particles shredded from the body.

4.7 The plant should be effective in preventing rodents, birds, insects and other animals from infesting. The CNC area should be enclosed and the necessary dust prevention and dust collection facilities should be equipped according to the process requirements.

4.8 All areas should be appropriately lightened and emergency lighting should be equipped as required.

4.7 The setting of the floor sink in the manufacturing operation area should be compatible with the manufacturing requirements, and use air lock, liquid lock or other

devices to prevent back suction and contamination.

4.10 Manufacturing personnel and materials entering and leaving the manufacturing workshop should have measures to prevent cross-contamination. The locker room and material buffer room that open into Class D or above area should be designed according to the airlock principle. The pressure difference between clean and non-clean areas and between different cleanliness levels should be greater than 10 Pa. Appropriate differential pressure gradients should also be maintained between different zones of the same cleanliness level (operating room) if necessary.

4.11 Laboratory that meets the requirements shall be set up, equipped with testing and experimental equipment suitable for the in-house testing items specified by the state. The laboratory should be designed to ensure that it is suitable for the intended use and to avoid mixture and cross-contamination. Sufficient areas should be used for sample handling, sample retention and storage for stability study samples and record storage. If necessary, a special instrument room should be set up to protect sensitive instruments from static electricity, vibration, humidity or other external factors.

Chapter 5 Equipment

5.1 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.

5.2 The surface of the equipment used for manufacturing shall be smooth and even, and shall not chemically react with the material, shall be quality-neutral fand easy to clean or disinfect.

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

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

5.5 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.

5.6 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, and use times and replacement cycle should be determined according to the characteristics of the mold material and the process requirements.

5.7 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.

Chapter 6: Procurement Control and Material Management

6.1 Procurement Control

6.1.1 The 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.

6.1.2 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.

6.1.3 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.

6.1.4 The base of material suppliers shall relatively remain stable. A seperate 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.

6.1.5 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.

6.1.6 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.

6.2 Warehouse acceptance

6.2.1 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.

6.2.2 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.

6.2.3 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.

6.2.4 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

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

6.2.6 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.

6.2.7 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.

6.3 Storage Management

6.3.1 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.

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

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

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

6.4 Material release

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

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

6.4.3 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.

6.5 Weighing and dispensing

6.5.1 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.

6.5.2 Each material prepared and its weight or volume, ideally, should be independently reviewed by others and have a review record. All ingredients used in the manufacturing of the same batch of pharmaceutical packaging materials should be stored centrally and clearly labeled accordingly.

6.5.3 Only one material is allowed to be weighed and dispensed at the same time. 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.

6.5.4 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.

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

6.5.6 Essential measures shall be taken to ensure the uniform mixing of large materials and small materials.

6.6 Reuse of materials in the manufacturing process

6.6.1 Materials that affect product quality, such as polymer and rubber trims, shall not be recycled and reused in the manufacturing of pharmaceutical packaging materials.

6.6.2 In the pharmaceutical glass formula, a certain proportion of fragmented glass (clinker) of the same class can be reused according to the process requirements. Specification should be established for the fragmented glass and controls should be planced according to requirements.

Chapter 7 Qualification and Validation

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

7.2 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. The validity shall be continuously maintained.

Equipment qualification and manufacturing process validation can be implemented independently of each other, for example new process validation does not require requalification of the existing equipments.

7.3 Validation Master Plan (VMP) should be developed to describe the sequence of qualification and validation activities and their execution in a document format, while listing the overall validation method. Validation Master Plan should be reviewed and updated periodically, such as annually.

VMP typically includes validation plans and timelines, organizational structure of validation activity, functions and responsibilities, overview of quality-critical equipments, processes and products, existing documentation for reference. For large projects, it is recommended to create a separate VMP.

7.4 It is recommended to take prospective validation and in some cases may be simultaneous validation or retrospective validation. Prospective validation should be performed prior to marketing, and simultaneous validation is only applicable to performance qualification and process validation; simultaneous validation should be conducted in accordance with the principles and procedures for prospective

valication; retrospective validation means that the product has been released prior to the end of the validation activity. Retrospective review may include maintenance and engineering records, quality records, and customer complaints. Prospective validation is the only option for sterilization process.

7.5 Equipment qualification :

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

- Approved equipment requirements

- Clear functions and responsibilities of the parties envolved in validation

- Specify key process parameters

- Training in GMP and qualification as minimal requirement

7.5.2 If quality-critical equipments have a potential impact on product quality, these critical equipments 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 quality control or process control or measurement of parameters of a quality-critical process parameter

- Whether the device generates data or records associated with release/rejection

- 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 equipments need not be included in the VMP.

7.5.3 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 guidelinelines and if calibration is done as appropriate;

- Operational 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 performance of the entire manufacturing line 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 three days minimally.

7.6 Process and product validation

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

- Approved/approved process specifications

- complete device confirmation

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

- Specify key process parameters

- Trained operators, quality personnel

7.6.2 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 continue to produce products that meet the requirements of product quality standards in accordance with the specified process

parameters.

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

7.7 Documents associated with qualification and validation

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

7.7.2 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.

7.7.3 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 qualificaiton/validation in the next step.

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

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

7.9 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.

7.10 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 analysis.

7.11 Process procedures and operating procedures should be qualifed based on the results of the qualification/validation.

Chapter 8: Manufacturing Management

8.1 Batch division and batch number formulating

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. Batch size affects the testing cost of pharmaceutical packaging materials manufacturers and pharmaceutical manufacturers. 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 continuaty. 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 units, that is, one sales order corresponds to one manufacturing batch number; > ¢ 13 series products, 100,000 - 3 million units, that is, one sales order corresponds to a manufacturing lot number.

Quantity in one order of the same specification: >3 million units, 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 units, 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 products producted 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, changeover in the middle.

Delivery batch: delivery batch number is assigned for products produced with glass tube of the same supplier, the same specification, composed of one or several different manufacturing batch numbers and delivered to the same customer's products at the same time.

Aluminum foil batch is defined as： per customer order (in m^2 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.

8.2 Identification and traceability

8.2.1 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.

8.2.2 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.

8.2.3 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.

8.3 Clean manufacturing and contamination control management

8.3.1 Documented procedures for the cleanliness of pharmaceutical packaging materials and the prevention of contamination of equipment or products should be established and maintained. Personnel health should be managed and a health record should be established.

8.3.2 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.

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

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

8.3.5 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.

8.3.6 Inbetween 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.

8.3.7 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.
Unless the customer agrees, pharmaceutical packaging materials should not be produced with thermoplastic materials that are re-pulverized and reused.

8.3.8 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.

8.3.9 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.
8.3.10 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.

8.4 Process Specification

8.4.1 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.

8.4.2 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 an 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.

8.4.3 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.

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

8.4.4.1 formula of the pharmaceutical packaging material: product name and product code;
A list of construction materials of excipients, with name, code, and amount of each material.
8.4.4.2 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 (eg 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;。

8.5 Manufacturing Process Control

8.5.1 The 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.
8.5.2 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.
8.5.3 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.

8.5.4 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.

8.5.5 Personnel engaged in manufacturing process control must be trained and have corresponding hands-on assessment records.

8.5.6 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:

Edge punching： 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 transfer in 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.

8.6 Batch manufacturing record management

8.6.1 Each batch of products shall have a corresponding batch manufacturing 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.

8.6.2 Batch manufacturing 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.

8.6.3 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.

8.6.4 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.

8.7 Product Protection

8.7.1 The 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.

8.7.2 The 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. Ready-to-use/sterilize drug package has at least two layers of sealed package.

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

8.7.4 The storage conditions of materials and products shall be consistent with the requirements in the materials submitted for connect review. 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. The life cycle of the drug

package should cover the shelf life of the drug.

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

8.8 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 apprearance. 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.

Chapter 9: Product Design and Development

9.1 Determination of technical standards for products

9.1.1 It is necessary to establish management procedures for the determination of technical standards for pharmaceutical packaging materials, as well as the establishment, review, approval, and change control of regulatory standards.

9.1.2 The technical standards of pharmaceutical packaging materials shall meet the functionality, protection, compatibility, safety requirements and preset quality standards for pharmaceutical packaging products.

9.1.3 The establishment of technical standards for pharmaceutical packaging materials should involve the manufacturing technology, quality management, regulatory affairs, design and development personnel and other departments to participate in the full technical review, and should be approved or confirmed by the customer if necessary.

9.2 Product Design and Development Management

9.2.1 SOPs regarding design and development for pharmaceutical packaging materials shall be established and the records of this process shall be kept. These procedures should be specific to product design and development workflow, job responsibilities, work content and work standards, design and development strategies, input, review, verification, validation and output requirements and implementation methods, technology transfer, design changes management requirements such as control and authorization. Records of this process should be kept.

9.2.2 When designing and developing products, the product technical standards associated with product development should be determined first and approved in advance.

9.2.3 Planning. A manufacturer should consider the nature, duration and complexity of the design and development activities, the review, verification, validation activities required for the entire process, as well as internal and external resources. The responsibilities and authority of the relevant department in the activity should be clarified, and the customer or user should be involved in the design and development process if necessary.

9.2.4 Product design and development input. A manufacturer should consider the functionality and performance requirements of pharmaceutical packaging materials, legal and regulatory requirements, industry norms, and the potential failure consequences caused by pharmaceutical packaging materials. Regarding design and

development purposes, input should be sufficient and appropriate and should be complete and clear.

9.2.5 Product design and development control. Necessary review activities, verification activities, validation activities should be regularly carried out. Project information communication should be carried out according to the project work plan, and conduct project summary to ensure product design and development projects are executed in an orderly manner.

9.2.6 Product design and development output, design and development personnel should transfer relevant technical development technical standards, process specifications, material quality standards and other related technical documents to the product manufacturing department and quality management department. Technical review of manufacturing process regulations, batch manufacturing records, manufacturing process control standards, and quality standards in the formal manufacturing stage.

9.3 Product design and development validation and verification (V&V)

9.3.1 The verification and verification management procedures for product design and development shall be established. The principles of validation content, validation method and acceptance criteria for different design and development phases shall be determined, and relevant records shall be kept.

9.3.2 A V&V plan shall be established based on the object of V&V, and shall be reviewed and approved. V&V protocol should clarify responsibilities, while V&V should be carried out in accordance with pre-determined and approved protocol and documented. After V&V work is completed, the report should be written and reviewed and approved. The results and conclusions of V&V (including evaluations and recommendations) should be documented and documented.

9.3.3 Product should not be delivered to client or released for commercial manufacturing before V&V for product designing or development is completed.

9.4 Product Design and Development Review

9.4.1 SOPs for design and development review management procedures shall be established, and the timing of design and development review, the qualification of the reviewer, the content of the review and the criteria for review, and the subsequent management of the review shall be specified. Relevant design and development review records should be archived.

9.4.2 Participants in the review shall include representatives of the functional departments related to the design and development stages being reviewed, and the reviewers for product design and development shall have product quality characteristics, user requirements, manufacturing methods and process controls for the pharmaceutical packaging materials, sufficient understanding of quality control to ensure the fairness, systemicity and accuracy of its review results.

9.4.3 Timing of product design and development review. The timing of the review can be determined based on the project scope and project plan of the design and development. Product design and development review should be conducted before product technical standards are determined and products are submitted for connected review.

9.4.4 The content of the review at the different stages of design and development of pharmaceutical packaging materials shall include the following contents: if the quality characteristics of the product meet the pre-determined product specification; the manufacturing process methods, quality standards and effectiveness and suitability of testing methods; the effectiveness of the execution of change control that occurred during the design and development phase; whether improvements are needed and details.

9.5 Change Control of Product Design and Development

9.5.1 When design and development experience changes, the changes should be

analyzed and evaluated, the corresponding change control plan should be formulated, and if necessary, review, V&V of changes should be taken. The review should cover the evaluation on the impact of changes on the product composition and pharmaceutical packaging products already delivered to ensure that the changes meet the requirements without adverse effects. All change control measures should be authorized and approved prior to execution. All change control records related to design and development should be kept.

Any changes to the data provided to the customer should be communicated to the customer and, if necessary, in the submission information provided to the regulatory authority.

Chapter 10 Quality Control and Quality Assurance

10.1 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.

10.2 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. ,

10.3 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.

10.4 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”.

10.5 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 from the factory.

10.6 If the test results do not meet the requirements of the standard, a complete investigation must be conducted and recorded in accordance with written procedures.

The quality control laboratory shall establish procedures for the OOS investigation.

10.7 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.

10.8 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 investigated, and the pharmaceutical packaging materials made from polymer materials should be subject to stability study based on material study.

10.9 A change control system shall be established in accordance with the requirements of the relevant technical guidelinelines 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.

10.10 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.

10.11 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 are required and the impact on product shelf life. When necessary, stability investigations should be conducted on products involving significant deviations.

10.12 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 a investigation report shall be issued. The deviation investigation report shall be reviewed and signed by the designated personnel of the quality management department.

10.13 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.

10.14 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.

10.15 Rejected products shall be isolated and identified before corrective or other measures are taken. Any compromised release plan for rejected products shall be approved by the customer's authorized documents.

10.16 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。

Chapter 11: Customer Management and After Service

11.1 Quality Agreement

11.1.1 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.

11.1.2 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.

11.2 Contract review

11.2.1 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.

11.2.2 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.

11.2.3 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.

11.2.4 Dicuss with the customer regarding contract revision, the contract must be formed in writing.

11.3 Customer complaint handling

11.3.1 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.

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

11.3.3 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.

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

11.3.5 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.

11.4 Customer Service Management

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

11.4.2 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.

11.4.3 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.

Chapter 12: Definition

Key personnel: The key personnel in this guideline include at least: the person in charge of the company, the person in charge of quality, and the person in charge of manufacturing.

Batch: A group of primary packaging materials manufactured in a process or series of processes that is expected to have uniformity and consistency in quality.

Batch document, batch record: Documents and records that provide batch history, including information about products and controls, with traceability.

Batch Number: A unique designation number used to identify a batch of products. A batch number can be a combination of numbers, letters, and/or symbols that identifies a batch of products and determines the manufacturing and distribution history of the product.

Calibration: The process of calibrating or standardizing (compared to a reference standard) the accuracy of a measuring instrument.

Clean room: A room that controls the concentration of indoor airborne particulates. Its construction and utilization minimizes the introduction, generation, and maintenance of indoor particulates, and controls other relevant parameters such as temperature, humidity, and pressure.

Contamination: Any unwanted material entering into the packaging material.

Finish product: packaging materials completed for all stages of manufacturing.

Intermediate product: packaging materials completed for some, but not all, manufacturing stages.

Raw material: construction materials/components/substances used in the manufacturing of packaging materials.

Materials used in manufacturing: construction materials, processing aids for key quality processes, and packaging materials used in clean room.