Ministry of Public Health Announcement

Subject: Specifying details regarding criteria and methods for producing modern medicines.

and amending the rules and methods for producing traditional medicines According to the law on drugs

2016

By virtue of Section 5, Section 6 (9) and (10), and Section 7 (4) of the Ministerial Regulations.

Establishing criteria, methods and conditions for the production of modern medicine, B.E. 2003, issued in accordance with

Drug Act B.E. 2510 and Article 6, Article 7 (8), (9) and (10) and Article 12 (4) of the Ministerial Regulations.

Requesting permission and issuance of a license to produce, sell, bring or order into the Kingdom traditional medicines, B.E.

2012, issued in accordance with the Drug Act, B.E. 2510, as amended by the Drugs Act (No. 3) 1979 and the Drug Act (No.

5) B.E. 2530, Minister of Public Health

Announcement has been issued as follows.

clause 1 This announcement of the Ministry of Public Health shall apply to

1.1 Licensee to produce modern medicine and those responsible for operating the production site

modern medicine From the day following the date of the announcement in the Royal

Gazette 1.2 Licensees to produce traditional medicine and those responsible for operating the production site

Traditional medicine as specified in Section 4 and Section 5 of this announcement from

(1) Date 24 August 2016 for those who have received a production license.

Traditional medicine according to the announcement of the Ministry of Public Health on specifying the details of the criteria

and methods for producing traditional medicine According to the Law on Medicines B.E. 2016, dated 8 February.

2016

(2) October 1, 2017 for those who have received a traditional medicine production license.

and those requesting permission to produce traditional medicines according to items 7 and 8 of the Ministry of Public Health

Announcement regarding the determination of details regarding the criteria. and methods for producing traditional medicine

According to the Law on Medicines B.E. 2016, dated February 8, 2016, as the case may be.

Section 2 shall be cancelled.

2.1 Announcement of the Ministry of Public Health regarding the determination of details regarding

Principles and methods for producing modern medicines For biological drugs According to the Drug Law, B.E. 2006

2.2 Announcement of the Ministry of Public Health regarding the determination of details regarding the criteria.

and methods for producing modern medicine According to the Drug Law, B.E. 2011

Clause 3 allows licensees to produce modern medicine. and those responsible for operating the production site modern medicine Must proceed and comply with the rules and methods for producing drugs attached to this announcement.

Clause 4: The contents of Clause 3 of the Announcement of the Ministry of Public Health regarding the determination of Details about the criteria and methods for producing traditional medicines According to the Law on Medicines B.E. 2016, dated February 8, 2016, and use the following instead.

"Clause 3 allows the licensee to produce traditional medicine. And those with operating duties of the following traditional medicine production sites must operate and comply with the rules and procedures for producing medicines only in the relevant sections. As specified in the announcement of the Ministry of Public Health regarding the determination of details regarding the criteria. and methods for producing modern medicine and amending the rules and methods for producing traditional medicine. According to the Drug Law, B.E. 2016

(1) Licensee to produce traditional medicine which is an oral medicine that produces the medicine in the form or use the following production methods

(a) Film Coated Tablet

(b) Soft Capsule (c) Sugar Coated Tablet (d) Medicine using the Spray Dry or Freeze Dry production process (e) Extracted medicine that uses extracts that are not Water or alcohol (f) Medicines produced using pharmaceutical chemicals of the type specified by the Food and Drug Administration. It is a substance that helps in the production process.

(2) Licensee to produce traditional medicines that are oral medicines. In addition to those mentioned in (1) and producing in large quantities with an annual production value of 20 million baht or more." Item 5:

The content of item 6, first paragraph of the announcement of the Ministry of Public Health regarding the determination of Details about the criteria and methods for producing traditional medicines According to the Law on Medicines B.E. 2016, dated February 8, 2016, and use the following instead.

"Item 6: In the case where a traditional drug production location has drug production according to item 3 together with drug production according to item 4 or item 5, the licensee shall produce traditional medicine. and the person responsible for operating the traditional medicine production site Must proceed and comply with the rules and procedures for drug production in the relevant parts. As stated in Announcement of the Ministry of Public Health on specifying details of criteria and methods for production Modern medicine and amendments to the rules and methods for producing traditional medicine. According to the law on drugs 2016"

Announced on 18 May 2016

Piyasakon Sakolsatayadorn

Minister of Public Health

Main Criteria and w Methods for producing medicine

Attached to the announcement of the Ministry of Public Health regarding specifying details regarding and w Methods for producing drugs criteria, current plans, and amending additional criteria and methods. Methods for producing traditional medicine according to the law on medicines 2016

Criteria and methods for producing medicine include:

Definition of producing drugs Part 2: Criteria and methods for drugs. for producing

Appendix

Appendix 1 Production of medicines without chemicals

Appendix 2 Production Biological pharmaceutical materials for use in humans,

Appendix 3 Fertilizer production radiological medicines

Appendix 4 Production Animal drug products that are not immune stimulating

Appendix 5 Production drugs. Immune stimulating products for animals.

Appendix 6 Production Medicinal products from medicinal plants

Appendix 7 Sampling of raw materials and packaging materials

Appendix 8 Produce ointments, creams

Appendix 9 Productivity and ointments, aerosol inhalation lozenges, prescribed doses

Appendix 10 Systems that use computers,

Appendix 11 use ionizing radiation (Ionising radiation) in the production of pharmaceutical

Appendix 12 Production products, research

Appendix 13 Production pharmaceutical products, and pharmaceutical products prepared from metals. Human plasma or plasma. Appendix 14 Verification and validation.

Appendix 15 Parametric release. The samples are collected Reference and sample samples. in Appendix 16.

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Attached to the Ministry of Public Health announcement

is the determination of details regarding the criteria and procedures. Method of production and ÿ

Current traditional medicine and amendments Wow! **to add criteria for** ÿ **methods of production**

traditional medicine according to the law. This **Wow ya**

2016

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term definition

Action limit means a specified threshold or boundary which, if it is beyond this threshold, must be monitored and corrective action taken immediately. **Air lock** means a closed area with a door. 2 way or

more which separates between rooms or areas with different levels of cleanliness for the purpose of controlling air flow Between these rooms or areas when the door is opened, this airlock is designed and used for the entrance and exit of people and things.

Alert limit means a threshold or limit established to warn of A trend in which values show changes from normal conditions that do not require corrective action. But there must be an investigation. Follow up to find the cause. **Authorized person** means a

person who has basic scientific and technical knowledge and experience assigned by the organization. This shall include those with operational duties. As specified in the law on medicines, **production batch or time received/manufactured (Batch or lot)** means a specified quantity

of the starting material. Packing material or products which are produced in one process or continuous process, therefore it is expected that Uniformity Note: To complete some steps in production, it may be necessary to divide production batches into smaller

batches, which will later be combined together into one batch. that is consistent in the final stage or in the case of continuous production A production lot designation is a part of production that is scheduled to have uniform characteristics.

For controlling finished products The manufactured version of a medicinal product will consist of all units of the pharmaceutical product. produced from the same raw materials and go through the same production process or has been sterilized same time In the case of continuous production processes Every unit of product produced during a specified period. will be considered the

same model **Production model number or number of times received/produced (Batch number or lot number)** means numbers or letters or a combination of both which is a clear indication of the model or time of receipt/production.

Biomass cultivation machine (Biogenerator) means a storage system such as a fermentation tank that brings biological substances. along with other materials to increase the number of biological substances or to produce other substances by reacting with other materials. A typical biomass grower is equipped with equipment for monitoring, controlling, connecting, filling, or removing mate

Biological agents mean microorganisms, including microbes from genetic engineering. cultured cells and endoparasites (endoparasites) both causing and not causing disease **Products waiting to be**

packed (Bulk product) means products that have gone through every step of the production process. completely, but does not include final loading into containers

Calibration means an operation that is carried out under specified conditions.

To find the relationship between the values obtained from the measuring device. or measurement system with reference standard values

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Cell bank

Cell bank system means a system in which multiple product models are produced. Continue by cultivating cells from the master cell bank. (Fully verified in identity and free from contamination). Bulk containers from the master cell bank are used to prepare the deployed cell bank. The master cell bank must be validated for passivity or population multiplicity. that exceeds that obtained from regular production

Master cell bank means cell culture that is monitored. Completely distributed in containers in a single operation. and go through a confident process in consistency and storage that ensures stability Normally stored at -70 degrees Celsius or lower. *Working cell bank* means cell culture that comes from the

master cell bank and is intended to be used for the production of cultured cells. Normally stored at -70 degrees Celsius or below.

Cell culture means the result of the growth of external cells. A body that has been separated from a multicellular organism. **Clean area** means an

area where particle contamination and Microorganisms in the environment must be within specified criteria. Construction and use must be done in a way that minimizes contamination. to bring into existence or who are confined in that area

Note: Different levels of environmental control are specified in Supplementary Guidelines for the Manufacture of Sterile Medicinal Products

Clean/Contained area means an area that is built and used.

in a way to achieve the objective of being both a clean area and a storage area at the same time

Containment means limiting biological substances or other substances within a specified area.

Primary containment means a containment system which prevents escape. of biological substances entering the operating environment By using closed containers or biosafety cabinets together with methods Work safely

Secondary containment means a containment system that prevents escape. of biological substances entering the external environment or enter the work area By using an air handling room that has been Specially designed There is an air lock system. and/or sterilizing tools at the exit of the object together with There are safe ways to work. In many cases, it may be added to increase the effectiveness of primary storage.

Contained area means an area where appropriate air and air filtration systems are built and installed. and used in such a way as to achieve the objective of protecting the environment. outside from contamination by biological substances from within that area

Controlled area means an area that is built and used in such a way as to Controlling the introduction of contaminants The appropriate air intake should be approximately at a good level (D) and control the release of live microorganisms. The level of control depends on the type of microorganisms used in the process. At a minimum, this area must maintain a lower pressure in the room than the adjacent outdoor environment and be effective in removing contaminants. Even though there is a small amount in the air **computer based system (Computerised system)** means a

system that includes data entry, electronic processing and output of data for reporting. or control type

automatic

Cross contamination means contamination of raw materials or products. with other types of raw materials or products.

Medicinal plants (Crude plant (vegetable drug)) means medicinal plants or parts of plants, fresh or dried.

Cryogenic vessel means a container designed to store liquid gas at very low temperatures.

Cylindrical tank (Cylinder) means a container designed to store high pressure gas. **Exotic**

organism means a biological substance which has no disease in the country. or geographic area or has a disease that is the subject of preventive measures or eradication plans currently in place in the country. or geographic area **Finished product** means a drug

product that has passed all stages of processing.

Proceed with production Including loading into the final container.

Herbal medicinal products means medicinal products that contain The main medicine is only plant material. and/or medicinal preparations made from plants. **Infected** means contamination with unwanted

biological substances. and cause spread of infection

Control during the production process (In-process control) means inspection during production operations. To monitor and adjust the process if necessary. To ensure that you get the product Correct and according to requirements

Controlling the environment or equipment may be considered part of control.
during the process

Products in process (Intermediate product) means raw materials that have gone through a process. Some of it must go through further production steps before it becomes a ready-to-pack product. **Liquifiable**

gases means gases that are still liquid in the cylinder when filled. Under normal temperature and pressure **Multi-tank gas filling tool (Manifold)**

means a tool or device designed to be able More than one container can be filled with gas from the same source at the same time.

Production means all operations related to purchasing raw materials. Packaging materials and products, production operations Quality control, release, storage and delivery of medicinal products and other related controls. **Manufacturer** means a person

licensed to produce drugs. According to the law on medicine, **media fill** means a

method for evaluating sterile processes using food.

Culture, which is a word that has the same meaning as Simulated product fills, broth trials, broth fills, etc.

Medicinal plant means all or part of a plant used for medicinal purposes. **Medicinal products** means medicine according to the law on medicines. **Packaging**

means all operations. Since the product is waiting to be packed Put in primary containers and label. Until it becomes a finished product. Note: Packing

sterile drugs into primary containers is not considered part of the packaging but is considered. It is part of the production process.

Packaging material means the material used to package the drug product. It may be primary or secondary depending on whether there is direct contact with the product or not. But does not include packing materials. externally used for moving or transporting

Procedures (Procedures) means a description of the operations that must be followed. Precautions and measures related to the direct or indirect production of medicinal products. is a document showing Work methods, for example, cleaning, dressing, and controlling the environment. Sampling, testing, instrumentation

Production means all operations involved in the preparation of a medicinal product, starting with receiving raw materials. The filling material passes to the manufacturing process. and packaging until complete has become a finished product.

Verification (Qualification) means verification and preparation of documents to confirm that Various tools work correctly and produce results as expected. The word verification in some cases has the meaning of including verification.

Quality control means part of the criteria and methods of production. This involves sampling, specification and testing, working in collaboration with other departments within the organization. In processing documents and procedures for letting go This is to ensure that there is no release through the raw materials. Packaging materials intended to be used or not released through the product for sale or delivery. Until it is decided that The quality is satisfactory.

Quarantine means the status of raw materials or product packaging materials during production. Products waiting to be packed or finished products that are separated by physical means. or other effective methods while waiting for the decision to pass or fail.

Radiopharmaceuticals (Radiopharmaceutical) means a ready-to-use drug product containing a nuclide One or more radioactive substances (radioactive isotopes) used for medicinal purposes.

Checking the consistency of the quantity (Reconciliation) means comparing between the amount of theoretical products and those actually produced or quantity of raw materials Theoretical packing material with the actual use that is within the range of normal, acceptable variation.

Record means a document showing the history of each product model. including delivery that product and all information related to product quality **Recovery** means taking all or part of

a previous batch of a product that meets quality requirements and combining it with another batch of the same product in a specified process of manufacture **Repeating the same process (Reprocessing)** means taking products

during the production process. or products waiting to be packed or finished products of the model or production time that do not meet the requirements in any step To repeat with the same process as specified in the recipe registration in order to have acceptable quality.

Product return (Return) means returning a product that may or may not have a defect. Quality is returned to the producer or distributor. **Seed lot** *system .*

Seed lot system means a

system in which many generations of product production are obtained from the seed lot system. the same host germ at the specified pass level For routine production A working germline version was prepared. From the mother germline generation The final product obtained from the active germline model and there is no number of passes from generation to generation The parent strain is rather than a vaccine that has been shown in clinical trials to be satisfactory in terms of safety. and effectiveness The origin and passing history of the parent strain and the used strain must be recorded.

Master seed lot means microbial cultivation distributed from a single source. In a single operation, in a manner stability The liquid version to ensure consistency, to enter small containers, prevent contamination. and to ensure of the parent strain is stored at The temperature is lower than –70 degrees Celsius, but the master germline version in the form of freeze-dried powder is stored at a temperature that Confident in stability

Working seed lot means the cultivation of microorganisms obtained from the seed lot. template for use in production Active strains should be stored in containers for distribution or storage as described in Master germline version .

Specification

means a document showing details of product requirements or raw materials or packing materials used or obtained during production. are accurate and consistent with those specified, these terms will be used It is a criterion for evaluating quality. **Starting material**

means substances used in the production of pharmaceutical products. But does not include materials Packing

Sterility means the absence of living microorganisms. Test conditions

Sterility is as specified in the drug textbook. The methods and precautions used must ensure that the product

Ready-made products that contain no more than one in 106 units of living microorganisms according to theory.

Verification (Validation) means verifying and preparing documents to confirm that

How to perform a process, tool, activity object, or system will have the expected results and be in accordance with

Principles of criteria and methods for producing drugs (see the topic of certification)

Furthermore, if it appears that there is the same vocabulary as provided in Part 2 or the Appendix as well. Adhere to the definition of the term

that are primarily provided in Part 2 or the Appendix.

MainCriteria and w Methods for producing medicine

The part

Attached to the Ministry of Public Health announcement
is the determination of details regarding the criteria and procedures. Method of production and
Current traditional medicine and amendmetts add criteria for methods of production
traditional medicine according to the law. Wow ya

2016

Category 1

Quality management

Principle

The production licensee must produce the drug product to ensure that The products produced are It is suitable for its intended use, meets the requirements of the drug registration and does not pose a risk. to consumers due to products having insufficient quality, effectiveness, or safety Quality objectives are the responsibility of senior management. which requires participation and commitment from attainment Personnel in every department at every level of the organization Including suppliers and distributors to achieve quality objectives. reliable success A system of quality assurance including criteria and methods for drug production and quality control must be designed with complete details. Coverage is understood and implemented correctly. It is fully documented and monitored effectively. Every part of the quality assurance system should have adequate resources and competent personnel. There are appropriate and adequate buildings, equipment, and facilities. Including legal responsibilities for production licensees. and for those assigned Basic principles of quality assurance Criteria and methods for production and quality control will There is a relationship between them. This section is described to emphasize their relationship and importance to production operations. and control of pharmaceutical products In addition to following the rules and procedures for producing drugs, part

ÿ After this, follow

Related appendices as well

Quality Assurance 1

clause Quality Assurance is a concept that covers everything that affects the quality of a product. The sum of management actions aimed at ensuring that a medicinal product meets the required quality for The purpose of use, therefore, quality assurance is a combination of principles and methods for drug production and other factors. together

The production licensee must establish an appropriate quality assurance system for the production of medicinal products.

As follows:

ÿ.ÿ Drug products are designed and developed taking into account the requirements of the criteria and methods for drug production and the criteria and methods in the laboratory.

1.2 Production operations and controls are clearly defined by applying criteria and Methods for producing drugs

ÿ.ÿ Clearly define management responsibilities.

1.4 There is proper management of production, procurement, and use of starting materials and packaging materials.

1.5 There are necessary controls for products during production. There is control during production and There is a check for accuracy.

1.6 Finished products go through the production process and are inspected correctly according to the established procedures. specified

1.7 Drug products cannot be sold or delivered if they have not been certified by the person receiving the certification. Assign that the production batch is produced and controlled correctly according to the drug registration and other regulations related to the production, control and release

of drug products. 1.8 There is good management to ensure that drug products are Continuous storage, delivery, and management to ensure quality

throughout its lifespan. 1.9 There are procedures for self-inspection and quality monitoring which are Regularly to evaluate the efficiency and ability to comply with the quality assurance system.

Principles and methods for producing drugs

Article 2: Rules and methods for producing drugs are part of quality assurance. which ensures that the product Go through the production process and are regularly controlled. To have appropriate quality for the intended use. and complies with the drug registration or product specifications.

Principles and methods for producing drugs relate to production operations and quality control. The basic requirements of the criteria and methods for producing drugs are as

follows: 2.1 All production processes are clearly defined. There was a systematic review by Considering past information and experience and has shown that it has the ability to produce pharmaceutical products with Quality as specified and is consistent with the requirements. 2.2 The accuracy of

critical steps of the production process is checked and when Significantly change the process

2.3 Provide adequate necessary facilities, consisting of:

(1) appropriately qualified and trained personnel (2) adequate location

and space (3) appropriate tools and

services

(4) Objects, containers and labels are correct.

(5) Certified procedures and instructions. (6) Proper

storage and transportation. 2.4 There are

instructions and procedures written by Use language that practitioners can easily understand, not ambiguous, and It is specific and can be used with existing facilities.

2.5 Operators receive training on how to operate correctly. 2.6 Records are

kept during production to show that every step specified in the operating method and The recommendations listed have actually been implemented. and the quantity and quality of the product are as expected in the case of Significant deviation The cause must be recorded and investigated. 2.7 Production

records and sales records must be traceable to the complete history of the production batch. They must be kept in a format that is understandable and retrievable.

2.8 Product delivery must minimize risk to quality.

2.9 There is a system for collecting back products from sales or deliveries.

2.10 There is a system for investigating complaints about products in the market. investigation into causes of products with quality defects and have appropriate measures in place to deal with defective products and measures to prevent recurrence.

Quality control

Item 3: Quality control is part of the rules and methods for pharmaceutical production, which involves sampling, specifications, and testing. It is done in collaboration with other departments within the organization. In processing documents and How to practice letting go To ensure that there is no release through objects or packaging materials for use or not. The product is released for sale or delivery. Until it is judged that it is of satisfactory quality. Basic quality control

requirements include: having adequate facilities; There

ÿ.ÿ are trained operators. And there are ways to practice that. Qualified for sampling Inspection and testing of starting materials Product packing materials During product production, waiting for finished product packaging and monitoring environmental conditions as appropriate To meet the objectives of the rules and methods for drug production 3.2 Sampling of starting materials. Product packaging materials during production

Products waiting to be packed and
Finished products It must be performed by the operator and by methods approved by the Quality Control Department.

3.3 The accuracy of the testing methods is checked. 3.4

There is a record to show that Sampling, inspection and testing procedures There has been actual practice as specified. If any deviation occurs Must be recorded and investigated. 3.5 The finished product has

the correct amount of active ingredients. and has quality consistent with the drug registration Have purity according to requirements, packaged in appropriate containers and correctly labeled. 3.6

The results of inspection and testing of product packaging materials during production are recorded. Products waiting to be packed and finished products as well as being evaluated and compared with the assessment requirements
The product includes a review and evaluation of production documentation operations including an evaluation.
Deviation from established procedures

3.7 No version of this product may be released for sale or delivered before it has been certified by The head of quality control or the person responsible for releasing finished products confirms that the products are correct. According to the drug registration

3.8 A sufficient number of starting material and product samples are maintained for reference in order to inspect the product in the future if necessary. and must be stored in containers for export and distribution In addition to being the case of production in large containers

Product Quality Review Item 4: There

is a review of the quality of all medicinal products that are registered, including medicinal products. also for export This must be done at regular intervals or in rotation. The purpose of the review must be Covers the consistency of production processes and controls. Suitability of the terms used in Current regulations for starting materials and finished pharmaceutical products To consider trends and to develop products and To improve the process, these reviews must be in writing on an annual basis based on the results. The previous review consisted of and must at least consist of

4.1 Review of starting materials and packaging materials used for specific products in In the case of new starting materials and packaging materials 4.2 Review of the

results of inter-process control at critical points and Ready-made pharmaceutical products 4.3 Review of all batches found to not

pass specifications and investigation of causes. 4.4 Review of all deviations. or significant non-

compliance with requirements. investigation into causes Effectiveness of corrective actions and prevention operations. 4.5 Review of all changes related to processes or analytical methods. 4.6

Review of changes in the application for permission, permission, refusal, documentation for drug

registration. Including documents for registration of drug formulas for 3rd countries in the case of export.

4.7 Review of the results of stability monitoring and undesirable trends Review of all drug product returns,

ÿ.ÿ complaints and recalls.

Relevant to product quality, including immediate investigation to find the

cause. 4.9 Review of the adequacy of previous corrective actions of processes or equipment. In the

ÿ.ÿÿ case of newly registered drugs or has been changed from the recipe registration must Conduct a review of conditions or assurances made regarding post-market inspections of medicinal products.

4.11 Status of certification of equipment and related production support systems, such as air systems, water systems, compressed gas, and others.

4.12 Review of technical agreements to ensure that Always up to date The production licensee must evaluate

the results of this review and assess whether corrective and preventive actions are required. Or is there a double check for accuracy? The reason for the corrective action Must be in writing. Agreed corrective and preventive actions must be completed on time. Effectively prescribed There must be procedures for management. both in terms of continuous management and reviewing those solutions Including the efficiency of such practices must be verified in During self-check Product quality reviews may be grouped according to product type, e.g. solid dosage form liquid form medicine Sterile products, etc. in cases where the owner of the registration of the drug formula is

not the licensee for production. There must be a technical agreement between the parties that defines the responsibilities involved in conducting quality reviews. assigned person For certification of the final batch, the drug registration holder must work together to ensure that there is a review. quality in a timely manner and correctly

Quality risk management No. 5 Quality risk

management is A systematic process for evaluating, controlling, communicating, and reviewing risks to the quality of medicinal products. It can be applied both
Advance preparation and retrospective review

Section 6: Quality risk management system 6.1

Quality risk assessment must be based on scientific knowledge and experience. about the process And finally, it must be linked to patient protection.

6.2 Level of management formality and documentation of administrative processes Quality risk management must be related to the level of risk.

Examples of processes and applications of quality risk management At least this can be found in Appendix 20 of the document Guide to Good Manufacturing Practices for
Medicinal Products PE009-12, issued date 1 October 2015

Category 2

personnel

Principle

Establishing and maintaining a quality assurance system and producing pharmaceutical products correctly depends on with operators, therefore, it is the responsibility of the production licensee to provide qualified personnel. in an amount sufficient for operations Each person must clearly understand their responsibilities and have them recorded. All personnel must be aware of the principles, principles and methods of production and receive training before working. There is continuous training. Including advice on hygiene related to the work being done.

General requirements

Section 1: The production licensee must provide personnel with appropriate qualifications and experience in the number specified in Adequate. The duties assigned to each person must not be excessive to the point of risking quality.

Section 2: The production licensee must have an organization chart. Personnel in positions of responsibility must have their responsibilities clearly defined. Written in job descriptions and having sufficient authority in the job responsibilities. There may be people with qualifications at the level who can perform the duties on behalf of the personnel involved in the rules and procedures. In the production of medicines, there must be no overlapping duties or gaps in which responsible persons cannot be found.

Key Personnel

No. 3 Key personnel consisting of the head of production and the head of quality control must be independent and independent of each other. The head of quality control is responsible for releasing finished products. If any organization has the head The quality control department is not responsible for releasing finished products. The organization must appoint a person responsible for

clearance. Finished products The head of production Head of Quality Control Department and those responsible for releasing the pro
The finished product must be a pharmacist with a pharmacy license. and must be a full-time permanent position

The production head generally has the following responsibilities: Item 4.

4.1 Ensure that products are produced and stored correctly as specified in the documents. in order to achieve the quality as specified. 4.2 Certify all procedures

related to production operations. and must ensure that there is Strictly implemented. 4.3 Ensure that production records are evaluated and signed by those

who receive them. Assigned before sending to the quality control department. 4.4 Check the maintenance of premises and equipment in the production department.

4.5 Ensure that accuracy is properly verified. 4.6 Ensure that personnel in

the production department undergo training before working and have training. continuously as specified By adjusting it appropriately according to your needs.

Item 5: The head of the quality control department generally has the following responsibilities:

5.1 Certify or not certify the results of inspection of the starting material. Product packaging materials during production Products waiting to be packed and finished products

5.2 Evaluate production records

5.3 Ensure that all necessary tests are carried out. 5.4

Ensure sampling method requirements. Testing methods and practices for quality control. 5.5 Certify

and monitor analytical contractors according to analytical contract. 5.6 Check

maintenance of premises and equipment in the Quality Control Department. 5.7

Ensure that Accuracy is properly checked. 5.8 Ensure that personnel in

the quality control department undergo training before working and There is continuous training as specified. By adjusting it appropriately according to your needs.

Article 6: The production head and the quality control head have joint responsibility for work related to the following: Quality.

6.1 Approve procedures and other documents. Including the

correction of 6.2 Monitoring and controlling the production

environment. 6.3 Hygiene of the

production site. 6.4 Checking the accuracy of the process.

6.5 Training

6.6 Certify and monitor suppliers of raw materials and packaging

materials. 6.7 Certify and monitor contract manufacturers according to

production contracts. 6.8 Determine and monitor raw material storage conditions. Packaging materials

and products 6.9 Keep records

6.10 Monitor compliance with the requirements of the criteria and methods for drug production.

6.11 Inspect, investigate, and collect samples. To monitor factors that may affect the quality of product

Training

Clause 7: The production licensee must provide training for all personnel whose duty is to enter the processing area. Production or quality control laboratory and other personnel whose activities affect product quality, including technical staff Maintenance staff and cleaning staff as well. Clause 8: New personnel must be

trained in the principles and methods of drug production. Both theoretical and They must also receive training in their assigned duties. There must be continuous training and performance evaluations on a regular basis. A training schedule approved by the supervisor must be provided. Production department or quality control department head, whichever is appropriate. and training records must be kept.

Article 9: Personnel working in contaminated areas that cause danger, such as clean areas or areas with high levels of active substances. Toxic substances Substances that cause infection or allergic reactions must be treated.
Specialized training

10 Visitors or untrained personnel must not enter the production operations area and quality control area. But if it is unavoidable, information must be given in advance, especially regarding personal hygiene. and advice on wearing clothing to prevent contamination. and must be closely monitored

clause 11 concepts of quality assurance and all measures that promote understanding and implementation
Practice requires extensive discussion during training.

personal hygiene

Article 12: Details regarding hygiene must be prepared and adjusted to suit different needs within the factory, which includes health-related procedures. Hygiene practices and dress of personnel. These procedures must be followed by everyone whose duties require entering the production and control areas. Understand and strictly follow Hygiene details It must be promoted by management and encouraged to have extensive discussion during training.

Article 13 All personnel must undergo a health examination before being hired for work. It is the responsibility of the recipient. Authorize the manufacturer to provide health advice that affects the quality of the product after receiving it. First health check Examinations must be repeated as necessary, appropriate to the work performed and the health of the personnel. Article 14

There must be procedures to ensure that people with infectious diseases or open wounds on the skin of the body are not involved.
in the production of pharmaceutical products

Article 15: Everyone entering the production area must wear clothing appropriate to the work performed. Article 16:

Eating is prohibited. Do not drink beverages. Do not chew snacks. No smoking or store food, beverages, cigarettes, or personal medicines in the production area and the storage area of products in process. There must be no unhygienic practices in the production area or other areas. This may have an adverse effect on the product.

Article 17: Workers are prohibited from using their hands to come into direct contact with medicinal products. Including the primary packaging materials. and areas of tools that have contact with the product

Item 18 Personnel must receive instructions on the use of hand washing facilities. Item 19 In cases where there are

specific requirements for the production of specific product groups, such as the preparation of sterile medicines. Also follow the specific requirements.

Section 3
Premises and tools

Principle

Buildings, premises, and equipment must be in appropriate locations and designed, constructed, modified, and maintained to suit their use. Planning and design must aim to minimize risks. To minimize errors, cleaning and maintenance must be done effectively to avoid cross-contamination. Accumulation of dust and anything else that will have an adverse effect on the quality of the product.

building

General requirements

clause 1 The building must be located in an environment which, when considered together with other measures to protect production, has the least risk of causing contamination of objects and packaging materials. or products

Item 2: Buildings and premises must be carefully maintained. Repair and maintenance must ensure that does not cause harm to the quality of the product. The place must be cleaned and disinfected as appropriate according to the details of the procedures written in Section 3. There must be light. temperature humidity

and proper ventilation Does not produce any results Direct and indirect adverse effects on medicinal products during production and storage. or affect the accuracy of tools

Section 4: Buildings and premises must be designed Install equipment to prevent insects and other animals from

entering. Item 5: There must be a procedure to prevent people without duties from entering the production area, warehouse. and quality control area Including, it must not be a passing path for personnel who do not work in that area.

Production operation area

Item 6: Drugs that are seriously dangerous, such as drugs that cause high allergic reactions. Including the penicillin group, cephalosporin group or Biological preparation: Products made from living microorganisms. Products of antibiotics, hormones, cytotoxic drugs, strong drugs as classified by the Food and Drug Administration must be separated. A dedicated area with complete facilities for the production of such medicinal products. To reduce the risk of Cross contamination occurs. In some cases, these products may be accepted for production in production areas. Production can be done in the same way as other drugs by using the principle of separating production times (Campaign) and must provide Specific precautions that must be taken include verification of accuracy with the approval of the employee. Authorizing officials for the production of toxic substances such as animal killers.

(Pesticides) herbicide

(Herbicides) Production is not allowed in the same building as the production of pharmaceutical products.

Clause 7: The building and premises must be planned so that production continues according to the sequence of operations steps. and the specified level of cleanliness

Item 8: There must be sufficient space for working and storing during the process so that tools and various objects can be placed orderly in appropriate positions. In order to create the least risk of mixing between Different drug products or different ingredients Including to avoid cross-contamination. and create risks Minimum skipping of steps or errors in the production or control process. Clause 9: In areas where starting materials and primary packaging materials of products during production or products waiting to be packed Is exposed to

environmental conditions Surfaces within the premises (walls, floors and ceilings) must be smooth and free from cracks. or joints that are not completely welded Including not releasing particles It must be easy and efficient to clean. In cases where it is necessary to be able to disinfect pipes, light bulbs, ventilation points. and other service work Design and installation that cause

clause ÿÿ

There are nooks and crannies that are difficult to clean. Where possible, maintenance must be carried out outside the production area.

clause ÿÿ Make the drainage pipe the appropriate size. And there is a trap to prevent going back. If possible, it must not be The drainage system is an open system. But if necessary It must be shallow so that it is easy to clean and disinfect.

Article 12: The production area must have effective ventilation. There are facilities. To control air such as temperature and humidity and air filtration to be suitable for both the product and the operation that is carried out within that area and to the external environment. 13 Weighing of the starting material must be done in a separate weighing room specifically

clause designed for weighing. 14 In processes where dust is generated, such as during sampling and mixing. Carry out production

and product packaging.

Dry types require special attention to avoid cross-contamination and ensure easy cleaning.

Clause 15 Buildings and facilities for packing pharmaceutical products. Must be designed and laid out to avoid mixing or cross-contamination.

Article 16: The production area must have adequate lighting. Especially in controlled areas.
Eyes on the production line

Article 17 Control during the process may be carried out within the production area, provided that Must not introduce risk into production operations.

Storage area

Article 18: The storage area must have sufficient space to store the initial objects. Product packaging materials during production Products waiting to be packaged as finished products Products in quarantine status Let it pass or not? Returned products or recalled products in an orderly manner

Article 19: Storage areas must be designed or adapted to provide good conditions for storage. In particular, they must be clean and dry and maintain temperatures within acceptable limits. Especially in cases where special storage conditions are required, such as temperature and humidity. A location must be provided and there must be inspection and monitoring.

Article 20: The receiving and delivering area must be able to protect the product from weather conditions. The product receiving area must Design and install cleaning equipment for incoming containers, objects, and packing materials. before putting it into storage

Article 21 Goods in quarantine status shall be stored in a separate area. This area must be clearly identified and only authorized personnel may enter this area. Alternative systems for physical containment must provide a level of protection. equal protection

Item 22: There must be a separate area for sampling the starting materials. If sampling is carried out in storage areas, this must be done with protection from contamination and cross-contamination.

Article 23 There must be a separate area for storing objects and packing materials. or products that do not pass Requirements for recalled products or product returned

Article 24 Objects or products that have a strong effect must be stored in a safe and secure area.

Article 25 Packaging materials that have a message printed on them. Must be accurate and consistent with the drug product. and stored in The area has tight security.

Quality control area No.

26 The quality control laboratory must be separated from the production area. especially Microbiology Biomaterial Quality Control Laboratory and radioactive isotopes, which each room must be separated from. Item 27: Quality control

laboratories must be designed to be suitable for operations. There is enough space to Does not cause mixing and cross-contamination. There is an area for storing samples and keeping records easily. appropriate enough

Item 28: Tools that are sensitive to vibration. electrical current disturbances Humidity etc. requires a separate room.

Article 29 There must be specific requirements for the laboratory used in treating samples of certain substances, such as biological samples. or radioactive samples

in other areas.

Item 30: The rest room must be separated from other areas.

clause ÿÿ Changing rooms, sinks and toilets must be easily accessible and available in sufficient numbers. Restroom users must not be adjacent to production processing or storage areas.

Article 32 Rooms for maintenance work must be separated from production areas. If you keep spare parts or equipment Maintenance in the production area must be kept in a specially designated room or locker. Item 33:

Animal holding areas must be separated from other areas. Including the entrance of animals and systems. separate air

Tools No.

34 Production tools must be designed Arrange and maintain to suit the intended use. Article 35 Repair and

maintenance must not cause harm to the quality of the product.

Article 36 Production tools must be designed to be easily washed and thoroughly cleaned. Cleaning must Follow the written instructions. After cleaning, store in clean and dry conditions.

Item 37: Equipment for washing and cleaning must be selected that is not a source of contamination. Item 38: Equipment must be installed in a way that prevents the risk of contamination or damage. contamination

Article 39 Production tools must not cause harm to the product, including the parts of the tools used in it. Production that comes into contact with the product must not react, release substances, or absorb substances that affect product quality. or cause danger

Article 40 Scales and measuring devices must have a suitable operating range and accuracy for production operations. and control

Item 41: Scales and measuring instruments recorder and the control device must be calibrated and checked at intervals. specified in an appropriate manner, test records shall be maintained.

Article 42 The installed pipe must have an indication of what is inside. and the direction of flow clearly.

Article 43 Distilled water pipes, pure water pipes, and other types of water pipes Disinfection must be done according to written instructions. This must include details of the operating limits for microbial contamination and the measures to be taken.

Article 44 Broken tools It must be removed from production processing and quality control areas. Or at least have to clearly label it as damaged.

Section 4
Document operations

Principle

Good documentation practices are an important component of a quality assurance system and are key to compliance with pharmaceutical manufacturing rules and procedures. The various types of documents and media used must be specified. fully included in the manufacturer's quality management system It may be in different formats. This includes publications. electronic media or photography The main purpose of the document system is to create, control, monitor and record. All activities This directly or indirectly affects the quality of drug products in every aspect. In a quality management system, in addition to recording the various processes and evaluating the results of any observations, there must also be adequate detail of the instructions. To help understand the needs or requirements together. and may reflect continued operations according to those needs or requirements.

Documents used to manage and record compliance with rules and procedures for pharmaceutical production can be divided into two main types: recommendations (guidelines, specifications) and records/reports. which must use criteria and methods in Processing documents according to document type as appropriate

Appropriate controls must be in place to ensure that documents are accurate. completely clear and ready to use Recommendation type documents There must be no mistakes. prepared in writing and ready for use The word "written" means to record or record on any medium in which information may be displayed in a readable form.

Necessary documents related to criteria and methods for producing medicines (divided by type)

Pharmaceutical manufacturing site master information: A document that details activities related to pharmaceutical manufacturing. Principles and methods for producing drugs

Type of advice (Guidelines or requirements) :

Requirements: Describe in detail the requirements that the product materializes. or packing materials used or received during production must be followed These requirements form the basis for evaluating quality.

Production formula, production process instructions Packaging and testing methods: Describe details of all starting materials, tools and computer systems (if any) used. and specify the method Carry out all the production processes. packing, sampling and testing, if there is control between Production process and the use of analytical technology shall be specified as appropriate. including acceptance criteria

Procedures: (or Standards of Procedures or SOPs) provide an explanation of how to proceed in each operation

Protocol: Provides instructions for performing work and careful recording of each task. Operation

Technical contract: is a contract between the employer and the contractor for the performance of activities by outsider

Type of record/report:

Records: They are evidence of actions taken to show that recommendations were followed, such as activities, events, investigations. Includes records of production and sales of each batch of the product. Records include raw data used to create or create other records. For recordings by means of The electronic record must specify what raw data was used to make the record. At least all the information used to make decisions Quality must be established for raw data.

Certificate of Analysis: This is the summary of the analysis of a sample of a product or object. Packing material Along with an assessment of conformity to specified requirements, or alternatively, certification may be based on the results of a real time assessment, either in whole or in part (summaries or exception reports).) that comes from production models related to process analysis technology. parameters or Matrix based on approved pharmaceutical registration documents. **Reports:** Documents related to activities, projects, or investigations. together with results of

operations, conclusions and recommendations

Document preparation and control

clause 1 All types of documents must be clearly defined and must comply with the requirements. which is enforced equally in all document formats and media types In the case of using a complex system Must be understood, recorded and checked for accuracy. and have an appropriate control system Many types of documents Instructions (instructions and/or notes) may be in a variety of formats, for example some in electronic form and others in printed form. Relationships and control measures of master documents Official copy Data management and recording must be specified for a single media document system. and documents that use many types of media together Appropriate controls over electronic documents, such as document templates, forms, prototype documents, must be in place. Appropriate controls are in place to ensure the integrity of records throughout their retention period.

Article 2: Documents must be designed, prepared, and reviewed. and distributed carefully to be accurate or consistent with documents related to product specifications, production and registration of pharmaceutical formulas according to Occurs in the documents used in work must not contain any errors from the original document. copying process. Proper preparation of

Article 3 Documents related to procedures must be certified, signed and dated by the designated person. Documents must not contain ambiguous statements. Content must be clearly stated. and must specify an effective date.

Item 4. Documents related to operating instructions must be formatted in an orderly manner and can be easily inspected. The language and format of the document must be consistent with its intended use. Standards, procedures, recommendations and methods must be written in a regulatory manner.

Item 5: Documents in the quality management system must be regularly reviewed and updated when available. Document updates must have a system in place to prevent obsolete documents from being used.

Article 6 Documents must not be handwritten. If the document requires recording information Must leave space for Keeping adequate records

Good practices for handling documents

Item 7. Recording information by writing using permanent ink to write clearly and easily to

read. Item 8. Records must be completed when each step of work is completed. Recording important related activities. With the production of pharmaceutical products, they must be traceable.

Article 9: Editing records must be signed and dated after the changes have been made. Must read information If previously made, the reasons for the correction must be recorded as appropriate.

Document retention 10 must

clause be clearly stated. What records are related to each production activity, including where the records are kept? And there must be a document security control system to ensure that records are safe. Completely accurate throughout the retention period and verified. as appropriate

clause 11 There are specific requirements for documents related to production batches that must be preserved1. years after the expiration date of The production version of the product or at least 5 years after the person assigned to certify the production model This longer period of time should be maintained. Documents pertaining to the production batch of the investigational medicinal product must be kept for at least 5 years after the clinical trial. The latest clinic using the manufactured version of the drug has been completed or has officially ended. Other requirements related to Document retention period This may be defined in legislation relevant to a particular type of product, such as Advanced Therapy Medicinal Products, and is defined.
The retention period for some types of documents is longer.

Article 12 The document retention period for other types of documents depends on the business activity. about those documents Important documents including raw data (e.g. documents related to verification, accuracy or stability) which support the pharmaceutical registration must be maintained if the pharmacopoeia is registered. Still in effect Consideration may be given to eliminating certain documents (e.g., raw data to support reporting). validate or stability) if those data are replaced with the entire set of new data Cancellation of documents Must give reasons and do so in writing. And consideration must be given to the preservation of documents related to the production batch, such as in the case of raw data for process validation. Data must be retained for a period of time. It is at least equal to the record of every production model released on the basis of that verification.

The following are examples of some of the required documents a quality management system must specify. All types of necessary documents This is to ensure product quality and patient safety.

Requirements

clause 13 There must be approved and dated specifications for starting materials. Packing material
Products in process Products waiting to be packed and finished products

Requirements for starting materials and packaging materials

Article 14 Requirements for starting materials and primary packaging materials or printed packaging materials.
Must at least consist of or provide reference documents (if any)

14.1 Information on objects and packaging materials includes:

(1) Designated name and reference code.

(2) Reference documents such as topics (monographs) in drug textbooks.

certification or (3) Supplier (meaning the seller or service provider of the product and packaging) that has passed initial object
materials as appropriate or the manufacturer of the product

(4) Examples of packaging materials with printed messages.

14.2 Sample and testing methods

14.3 Qualitative and quantitative requirements with acceptance limits.

14.4 Storage conditions and precautions

14.5 The longest period of retention before re-examination.

Requirements for products during production and products waiting to be

packed. Clause 15. Requirements for products during production and products waiting to be packed must be established for the steps.
Important or in the case of import or export, these requirements must be similar to the requirements of the original material or
Finished products as appropriate **Requirements**

for finished products

Clause 16 Requirements for finished products must at least include or have reference documents.
as follows

ÿÿ.ÿ Product name as registered and reference code (if any)

16.2 Recipe

16.3 Information on the form of pharmaceuticals and details of the packaging.

16.4 Sampling and testing methods

16.5 Qualitative and quantitative requirements along with acceptance limits

16.6 Storage conditions and special precautions (if any)

16.7 Period of use

Production formula and production process recommendations

Production formula and production process recommendations Must be prepared for each product and size.
Model that will be produced It is a document that requires official approval. These documents are often packaged together.
same

Clause 17: The production formula must at least include:

17.1 Product name as registered in the drug formula. and the reference code of the product with which it is related
with the specifications of this product.

17.2 Form and characteristics of pharmaceuticals, product strength and batch size.

17.3 List of all starting materials used along with the quantity of each type. Write using the name
Define and reference code that is unique to that initial object. and must also specify which substances may be lost during
Production process

17.4 Determine expected output along with acceptance limits. and output during production
(if any)

Article 18: Production process recommendations Must at least consist of

18.1 Specify the location of the production process and the main tools used in production.

18.2 Methods or references to methods used for preparing important tools such as cleaning.
Assembling the sterilization calibration equipment

18.3 Verifying that tools and production locations are free from products, documents, and objects from
Previous production and those that are not required to plan this production process and appropriate clean tools
with use

ÿÿ.ÿ Details of the production process such as Inspection of preliminary preparation objects, sequence
Adding critical process parameter objects (e.g. time, temperature) 18.5 Control during

the process together with the specified limits

18.6 Storage requirements for products awaiting packaging, including containers, labels, and special conditions.
Storage (if any)

18.7 Special precautions

Packaging

recommendations No. 19 There must be packing recommendations for each type of product in terms of size. and container type
Packaging that has been approved Must include or have the following reference documents:

19.1 The name of the product as registered in the drug formula, including the production version of the product awaiting packaging and
Finished products

19.2 Form and characteristics of pharmaceuticals and strength (if any)

19.3 The package size is expressed as the quantity, weight, or volume of the product in the final container. 19.4 A

list of all packaging materials required for the batch size. including quantity Size and type together with the code or reference number that relates to the specifications of each type of packaging material. 19.5 Samples or copies of printed packaging

materials. and an example indicating the location of printing model numbers and expiration dates. 19.6 Inspection of tools and workplaces to ensure that they are free

from products, documents or objects or packing materials from previous work and that are not required in the process of Packing this time (line clearance) and motor It must be clean and suitable for use.

19.7 Premises and equipment must be carefully inspected before starting work. that there is no residue or residue from previous production

19.8 Description of packaging methods, including significant sub-operation steps and tools.
will be used

19.9 Details of controls during packing including recommendations for sampling. and accepted limits

Production process record

Article 20 Production process records must be kept for each batch of products produced which must contain information. related according to the most recently approved formula and production process instructions. and must consist of The following information: 20.1 Name of the product

as registered in the drug formula and production lot. 20.2 Date and time

from the start of production, important steps during production until production. Completed. 20.3 Signatures of workers at each

important step of the production process. and has signature
of those reviewing these procedures as appropriate

20.4 The lot number or analytical control number and the quantity of each starting material actually weighed, as well as the lot number and quantity of any recycled or reprocessed starting material mixed.
Come in too.

20.5 Any related production processes and the main tools used. 20.6 Records

of controls during the production process and signatures of operators and results. Control obtained 20.7 Quantity of output obtained in

each step of the production process 20.8 Record problems that occur along with

details. and the signature of the person approving the deviation from the production formula and production process recommendations if acceptable.

20.9 Approved by the person responsible for each step of the production process . **Note:**

Where validated processes are continuously monitored and controlled, automatic reports may be limited to only chapter reports. Summary of compliance with the requirements and exceptions or failure to meet the requirements. (out-of-specification)

Record of packing

version. Article 21. Records of the packing version of each product lot or part of the lot must be kept in the event that there is Packed non-continuously according to relevant packing instructions. The

packing version record for each batch of product must contain the following information: 21.1 Name of

the product as registered in the drug formula and production lot. 21.2 Date and

time of packing. 21.3 Signature of the

operator at each step. Important stages of packing operations and The signature of the person reviewing these steps, as appropriate.

21.4 Records of verification of identity and accuracy match packing instructions, including Results of control during packing. 21.5 Details of packing methods, equipment, and

packing lines used. 21.6 Examples of printed packing materials. which indicates the model

number Expiration date and other additional information

21.7 Record problems that occur along with details. and the signature of the person approving the deviation From packing instructions 21.8 Quantity and

reference number or identification of all types of printed packaging materials and products awaiting packaging that are used for destruction or returned to the warehouse To check the consistency of the quantity All the quantities of product contained in the case use a completely reliable electronic control system. Packaging may have reasons not to include this information.

21.9 Approved by the person responsible for placement.

How to practice and record

Receiving

Article 22: There must be procedures and a written record for each receipt of the starting material. (Including products waiting to be packed, products during production and finished products), primary packaging materials, packaging materials Secondary packaging and printed packaging materials

Article 23: The receipt record must at least include:

23.1 Name of the packing material on the delivery note. and on the container

23.2 Name given and/or the code of the packaging material object (If different from item 23.1)

23.3 Date of receipt

23.4 Name of the deliverer and the name

of the manufacturer 23.5 the manufacturer's model number or

reference number 23.6 total quantity and the number of

containers received. 23.7 Model number assigned

after receipt. 23.8 Related remarks.

Article 24: There must be written procedures for labeling, quarantine and storage.
Starting materials, packaging materials and other materials

as appropriate

Sampling Article 25: There must be written procedures for sampling. This includes sampling methods and equipment used to collect sample quantities. and precautions that must be observed to avoid contamination. or deterioration of the quality of objects and packaging materials

Test

Article 26 There must be a written procedure for testing materials, packaging and products.
at each stage of production It describes the methods and tools used and must record test results.

Others No. 27 There must be a written procedure for passing and not passing for objects and materials. Packaging includes products, especially issuing documents for the sale of finished products. Must be issued by the person receiving it. Assigned to perform this duty, all records must be kept for use by those assigned to them. A system must be established to show results when abnormal observations and any changes in important information are

found. Article 28 Records must be kept. of the sales of each product model for information in case of necessity
The product of that model must

be recalled. Article 29 There must be a policy, procedures, protocols (protocols), reports, and records of operations that related matters or conclusions obtained in writing as appropriate As in the following example

29.1 Validation and verification of the process Instruments and systems 29.2 Instrument assembly and calibration

29.3 Technology transfer

29.4 Maintenance of cleaning and hygiene

29.5 Personnel matters including signature lists Training regarding criteria and Methods of pharmaceutical production and technical matters of dress, hygiene, and verification of training effectiveness.

29.6 Monitoring environmental conditions

29.7 Animal and insect control

29.8 Complaints

29.9 Product recall

29.10 Product return

29.11 Control of change 29.12

Investigation when deviations are found and inconsistent results

29.13 Internal quality audit or auditing compliance with the criteria and

Methods for producing medicine

29.14 Summary of relevant records (such as product quality reviews) 29.15

Manufacturer/distributor assessment.

Article 30: There must be clear procedures regarding the use of main production and testing equipment.

clause 31 Must provide and maintain a logbook for main tools. or important tools used for Production analysis and work area The logbook must record, in order of use, as appropriate, any use of the area, equipment or methods of calibration, maintenance, cleaning or Repairs must be recorded with the operator's signature and date. Section 32. A list of documents in the quality management system must be maintained.

Section 5

Production operations

Principle

Production operations must follow clearly specified procedures. and must be correct according to the principles of Principles and methods for producing drugs in order to obtain quality products as specified and in accordance with the drug registration.

General requirements

clause 1 The production process must be carried out and controlled by a person with knowledge and ability.

2 All management of objects, materials, packaging and products such as Quarantine receipt, sampling, storage, labeling, disbursement, manufacturing processes Packaging and distribution must be done correctly according to the procedures or instructions written and must be recorded. Section 3: Objects and packing materials received every time must be ensured that they are

correct and consistent with the Ordered Containers must be clean and labeled with the required information. Section 4: Damaged containers and other problems that may have an undesirable effect on the quality of the materials.

Packaging must be investigated, recorded and reported to the quality control department. Section 5. Packing materials and finished products received. Must be quarantined immediately after receiving it?

Production is completed until it is released for use or sale.

Article 6: Products in process of production (Intermediates) and products awaiting packaging (Bulk products) that are purchased must be managed in the same way as the original materials.

Clause 7. All types of materials, packaging and products. Must be stored in appropriate conditions as specified by the manufacturer. and keep it in order Separate each model and convenient to circulate for use

Article 8: Product must be inspected and quantity consistency checked when necessary. to make sure that there are no differences beyond acceptable limits

Article 9: Do not produce different types of products in the same room at the same time or continuously. In addition, there is no risk of mix-up or cross-contamination 10 at every step of the process. Products and objects must

be protected from microbial contamination.
joints and other contaminants

of 11 when working with dry objects or products Special care must be taken to prevent the generation and spread dust. Especially starting materials that have strong effects or cause allergic reactions.

Article 12. At all times during the production process, all objects, containers that hold products in various stages, main tools. and production rooms must be labeled or have identification signs of the products or objects currently in the process. The strength, model number, and steps of production must also be specified.

13 labels attached to containers Equipment or locations must be clear, not ambiguous, and have the format specified by the organization. Labels, in addition to having text, Color may be used to indicate status, such as quarantined, released, or failed.

clean

14 Inspections must be made to ensure that pipes and other parts of equipment used for transporting No. products from one area to another. There is connection in the correct manner. Article 15.

Deviation from instructions or procedures must be avoided. If there is deviation, Certified in writing by a person with knowledge and ability along with the participation of the quality control department according to suitability

Article 16 Entering the production area Must be limited to only those who are assigned.

Clause 17: Avoid manufacturing non-drug products in the same area used for production. pharmaceutical products and do not use equipment used for the production of pharmaceutical products

Preventing cross-contamination in production operations.

Item 18. Contamination of the starting material or contamination of the product by other materials or products must be avoided. The risk of accidental cross-contamination arises. from not controlling the release of dust, gas, vapor, spray, or microorganisms from objects and products during production from residue on tools and clothes of Workers risk cross-contamination. Its importance varies according to the type of contaminant and Products that are contaminated with highly hazardous contaminants are highly allergenic substances. Biological products that have living microorganisms certain hormones Cytotoxic substances and strong active substances are the most dangerous products. When there is contamination, that is, injections, drugs used in large quantities at a time. or medicines used continuously for a long period of time

as item 19Cross-contamination must be avoided by appropriate techniques. or have management measures such

19.1 Carry out production in a separate area. This is a requirement for products such as penicillin and live vaccines. Live bacteria products and some biological products Or produce by separating production times. After that, clean appropriately.

19.2 Provide an airlock. and air removal as appropriate

19.3 There must be filtration of recirculating air or recycled air to reduce the risk of Contamination from the air 19.4 Keep clothing

for work within the area where products are produced.
Special risk of cross-contamination

19.5 Use effective cleaning and decontamination methods. Because of doing Ineffective tool cleanliness is often a source of cross-contamination.

19.6 Use a “closed system” in production operations.

19.7 Residues are tested and clean status labels are used on the tools that have been treated. It's clean.

Article 20 Measures and their effectiveness in preventing cross-contamination must be inspected periodically in accordance with Prescribed procedures

Validation Item 21 Validation study.

Must act correctly according to the prescribed procedures, including The results of the study must be recorded and summarized. Section 22: When there is a new production

formula or production method, there must be steps to show that the process is correct. The routine is appropriate. Including must show that the specified process Use of specified objects and tools It will yield products that are consistent and have the desired quality.

Article 23 In the case of important changes in the production process including tool changes Objects which may affect the quality of the product and/or the reproducible production process must be verified.

Article 24 The correctness of the process and procedures must be periodically checked in order to Make sure you still have the ability to achieve the desired results.

Starting Materials (Starting Materials) No. 25

Purchasing starting materials is an important operation that requires workers with specific knowledge and skills. Details of the delivery person

Article 26 Starting materials must be purchased from certified suppliers listed in the starting materials specifications. That type is provided by the pharmaceutical manufacturer and must be considered in conjunction with the supplier only. and must be purchased directly from the object manufacturer The production and control of questionable precursors should be jointly considered between drug manufacturers and suppliers. Contains requirements for management. Labeling and packaging requirements include procedures for Deal with complaints and non-acceptance of initial objects.

Article 27 Every delivery must check the completeness and sealing of the container, including checking the correctness of the match between the delivery note and the label of the delivery person. Article 28 Each

delivery of the starting material if the starting material is The same has many models produced. Must separate random Example testing and release of each release

Item 29. Starting materials stored in storage areas must be appropriately labeled (see Section 5, Item 13). The label must contain at least the following information:

29.1 Designated name and reference code (if any).

29.2 Model number assigned upon receipt. 29.3

Status of the initial object such as quarantined, waiting for testing, released, passed, failed.

29.4 Expiration date or due date for retesting.

If a computer-controlled system is used to store the starting materials, all information does not need to be in the form of labels.

Item 30: There must

be appropriate procedures or measures to ensure the identity of the starting materials in each container, including The sample container must be identified.

31 Only starting materials that have been released by the quality control department and are still within their useful life will be Items can be used

Article 32. Initial items must be paid for by the designated person only. and follow the procedures as written. This ensures that the correct starting material is dispensed. There is accurate weighing or measuring. Packed in clean containers and correctly labeled. Item 33: The type and weight or volume

of the dispensed starting material must be checked by a second person. Repeat the inspection. and the results are recorded

Article 34 Starting materials supplied for the production of each batch must be kept together and clearly labeled.

Carrying out the production process for products during production and products waiting to be packed.

Item 35 Before starting the production process, make sure that the work area and tools are clean and free of starting materials. Products, residual products, or documents not related to operations This production process remains. Article 36. Products in

process of production and final products. Products awaiting packaging must be stored under

appropriate conditions. Item 37. Critical processes must be verified as specified in Appendix 14. Verification. and verification of accuracy, item

38. Control must be carried out during the production process. and controlling the production environment, including recording

Article 39 If the output has significant deviations from the specified amount, it must be recorded and investigated.

Find the cause

Packaging materials

Article 40 Procurement, management and control of primary packaging materials and printed packaging materials. Must be treated in the same way as the original object. Clause 41:

Packaging material with printed text. Must be kept in a sufficiently safe condition, such as prohibiting unrelated people from accessing it. Finished cut labels or printed packaging materials that have been separated into pieces must be stored and transported in separate closed containers to avoid mixing. Packaging materials to be used must be approved. Pay only by the designated person. and follow the approved operating procedures document. Clause 42. Packing materials with printed messages and primary packing materials delivered every time

or every batch must

Provide a unique reference number or unique identification mark.

Article 43 Primary packaging materials that are outdated or old models that are no longer in use. or packing materials left from Applications where the production model number is printed It must be destroyed and there must be a record of destruction.

Packing operation

Article 44: In setting up a schedule for packing operations, the risk of cross-contamination, mixing, or alternation must be minimized. Do not pack different types of products in close proximity to each other. In addition to the separation Physically as appropriate, such as having a partition wall in proportion

Article 45 Before starting the packing process, the work area, packing line, printer, and other equipment must be clean and free from any other products. Packing material or documents of Remains of previous packing This must be inspected according to the appropriate checklist.

Item 46 The name and production model number of products being packed must be displayed in each location or production line. contain

Item 47 All products and packing materials to be used must be inspected when they are sent to the packing department to ensure that the quantity, identity and correctness correspond to the packing instructions. Item 48

The containers before packing must be clean. and remove contaminants such as broken glass and metal, No. 49, when

packed into containers and sealed. Labeling must be done as soon as possible. If this cannot be done, there must be Appropriate procedures to ensure that there is no mix-up or mislabeling. Item 50. Printing accuracy must be

inspected and recorded, e.g. Production model, expiration date, whether
Printed separately or printed during packing in the case of manual printing must be rechecked periodically.

No. 51 In the case of using labels that have already been cut and are printed outside the packing line, they must be prevented from Mixing up Where possible, use roll labels.

Article 52 There must be an inspection to ensure that the electronic equipment for reading the code Label counters or similar devices are functioning properly. Item 53. Information printed

or embossed on the packaging material must be clearly visible and durable and not fadeable. Item 54 Online product

control during packaging must be checked as follows. 54.1 General characteristics of the container. 54.2 Integrity of the

container. 54.3 Accuracy of the product and

packaging materials used. 54.4 Accuracy of

printing. 54.5 Accuracy in making. The work of monitoring equipment at

the packaging line Samples removed from

the packaging line must not be reused.

Article 55 Products involved in abnormal events can be returned in the process after There is a special inspection, investigation and certification by only those who have been assigned and must be kept.
Record the details of the operation.

Article 56 Checking the consistency of the quantity of products waiting to be packed and the printed packaging materials with the number of products that can be packed. If it is found that there are significant differences or abnormalities, it must be done. Investigate the cause and obtain a satisfactory reason before

allowing it to pass. Article 57 After the filling process has been completed. Packaging material with the production model number printed on it. Must be destroyed and recorded. If it is not yet printed, return it to the warehouse by following the written instructions.

Finished products. Item

58. Finished products must be quarantined until released under conditions specified by the manufacturer. Item 59.

Finished products and documentation must be evaluated before the product is released for storage. Disappointment

No. 60 after release Finished products must be stored in the warehouse under conditions specified by

manufacturer

Objects that do not pass specifications Recycled objects and returned objects. Article 61

Objects and products that do not meet the requirements must be clearly marked and stored separately in a controlled area. They may need to be returned to the supplier or may also be reworked. The original process or destruction, whichever is appropriate, regardless of the method of operation, must be certified and recorded by the designated person.

Item 62 Re-processing products that do not pass the specifications using the same process as a special case can be done if it does not affect the quality of the final product. Is accurate and consistent with product specifications and Prescribed procedures approved after an assessment of the relevant risks. Including the need to preserve
Record the results of such operations.

Article 63 Reusing all or part of products of past generations that meet quality requirements. By mixing with another lot of the same product at a specified stage of production. Must be correct according to the method Prescribed practices which are approved after an assessment of the relevant risks. Including the effects that may occur on The lifespan of the product and the results of such operations must be recorded.

Article 64 The quality control department must arrange additional testing for finished products that have been used. Repeat with the same process. or products are reused and mixed together.

Article 65 Products returned from the market which are not under the control of the manufacturer must be destroyed. Except in the case where the manufacturer considers that re-sale Put it on a new label. or reused together with The next generation has undergone rigorous evaluation by the quality control department according to established procedures and has been found to be free of Doubts in the quality of this assessment must take into account the type of product, the special conditions of storage required, its condition and history, and the time elapsed after its sale. If there is doubt in the quality of the product, it must not be taken into account.

returned for sale or recycled, even though important drugs can be reused. All operations It must be properly recorded.

Section 6
Quality control

Principle

Quality control is an operation that involves sampling. testing requirements and collaborate with other departments within the organization to manage the documentation system and procedures for release. To ensure that the packaging material has been released for use or the finished product has been released. passed for sale Only when it is determined that it has passed the necessary tests and is of quality can it not be controlled. Limited to laboratory operations. But it is involved in every decision that may be related to quality. The independence of quality control from production operations is an important basis for Implementation of quality control

General requirements

1 The licensee to produce drugs must have a quality control department that is independent from other departments. Managed by people with appropriate qualifications and experience working in quality control laboratories. Including having to have resources like Adequate, quality control management is efficient and reliable.

In addition to section 2, the main duties of the head of quality control are set out in section 2. Quality control personnel also have other duties, such as creating all quality control procedures, checking the correctness of the procedures. These and the implementation of reference sampling of objects, packaging materials and products, controlling the correctness of labeling of containers, objects, packaging materials and products, Control the accuracy of product stability monitoring and participate in complaint investigations. related to product quality, etc. All these operations must be carried out correctly according to the methods. Follow the instructions in writing and record them.

Item 3: Evaluation of finished products must include all relevant factors. which consists of conditions In carrying out the production of the results of tests during the production process, a review of production process documents is performed. and packing records, compliance with finished product specifications, and inspection of containers. of the finished product

Item 4: Quality control personnel can enter the production area to carry out sampling. and check as appropriate

Criteria and methods for quality control laboratories, Section 5: Quality

control laboratories and equipment must comply with general and specific requirements. For the quality control area

Item 6: Personnel, places, and equipment in the laboratory must be suitable for the work being done. The nature and scale of production and the use of outside laboratories must be carried out in accordance with the principles set out in Section 7, hiring production and Analysis. Hiring an analysis may be acceptable in some cases with approval. Approved by the Food and Drug Administration and must be specified in the quality control record.

Document operations

Item 7: Preparation of documents related to quality control for the laboratory must have the following details:

7.1 Requirements

7.2 Sampling procedures 7.3 Testing and

recording procedures Contains analysis notes and notebooks.

7.4 Analysis report and analysis certificate

7.5 Data from monitoring of environmental conditions as specified. 7.6

Record of verification of the correctness of testing methods as relevant. 7.7

Procedures, records of calibration and maintenance of equipment. Item 8: Quality

control documents related to production records must be kept for at least 1 year after the expiration date of that product lot. Item 9: Some types of information,

such as results of analysis and testing, yield, and environmental control, must be recorded in a manner. that can assess trends

clause 10 In addition to information that is part of the production record Other original information, such as work diaries Operations and/or operation records They must be preserved and available for inspection.

Sampling 11

Sampling shall be carried out according to approved procedures that describe

11.1 Sampling method 11.2

Tools used

11.3 Random sample quantity

11.4 Recommendations for sample division

11.5 Type and condition of sample containers. 11.6

Identification of sample containers. 11.7 Special

precautions to be observed. especially sampling of sterile objects or dangerous

11.8 Storage conditions

11.9 Recommendations for cleaning and collecting tools used for sampling, item 12, reference samples

Must represent the version of the packing material object. or sampled products Additional samples may be collected. To monitor important steps of the process, such as the beginning or the At the end of the production process, 13 sample containers must be labeled with the contents inside.

clause including model number, random date
Samples and containers from which the samples were

taken. Article 14. Samples based on each batch of finished products must be stored in the final containers and 1 year after least the recommended conditions. Starting materials the expiration date of the finished product. Samples of objects Store under at (except solvents, gases and water) if they are in good condition must be stored for at least 2 years after release. through finished products If the stability results specified in the specifications are shorter than The storage period may be shorter. Reference samples of materials, packaging and finished products shall be available in sufficient quantity to carry out thorough inspection. Can be completed at least twice

Test

Article 15 Analysis methods must be checked for accuracy. All tests described in the register Medication preparations must be prepared according to approved methods.

Item 16: The test results obtained in the calculation must be recorded and inspected. They must be carefully checked.

Article 17: There must be a recording of the test. The record must at least contain the following information:

17.1 Name of the packaging material. or product and form of pharmaceutical product 17.2

Model number, name of manufacturer and supplier As appropriate

17.3 References to relevant regulations and procedures.

17.4 Test results include observations, calculations and references to the results certificate.
analyze

17.5 Test date

17.6 Signature of the person performing the

test. 17.7 Signature of the person verifying the test and calculations as appropriate. 17.8 Statement clearly indicating pass or fail. or other decision status
and the signature with date of the assigned responsible person. Clause

18 Control during all production processes carried out in the production area by personnel. The production department must operate according to methods approved by the quality control department. and the test results are recorded.

Item 19: Quality of chemicals used in the laboratory. Glassware for measuring and measuring solutions and substances. Reference standard and culture media must be prepared correctly according to the written procedures.

Item 20: Chemicals used in the laboratory that will be stored for long periods of time. There must be a label indicating the date of preparation and Signature of the person who prepared Unstable laboratory chemicals and culture media Must specify expiration date and Storage conditions on the label are also available for solutions of known exact concentration. The search date must be specified. last concentration and latest factor value. Item

21. Specify the date of receipt and opening of the substance used for testing on the container, such as chemicals used in laboratory Reference standard substance And the instructions for use and storage must be followed in some cases. Chemicals Items used in the laboratory may require identification and/or other testing after receipt or
Before use

Article 22 Laboratory animals used for testing must be quarantined before use as appropriate. These laboratory animals must be cared for and controlled to be suitable for the purpose for which they will be used. In addition, they must be identified and recorded. sufficient to show the history of the use of these laboratory animals.

Continuous monitoring of stability

Article 23 After releasing the product to the market Product stability must be monitored. Medication as prescribed in the plan on an ongoing basis To be able to detect problems related to the stability of the formula. in the containers sold, such as changes in the level of contaminants or dissolution information

Article 24 Objectives of continuous stability studies To monitor the shelf life of medicinal products and to determine whether the product is of quality and is expected to still meet the quality requirements under Storage conditions specified on the label, Section 25:

Continuous monitoring of stability. To be used with medicinal products packaged in distribution containers. For products waiting to be packed, there must also be a plan to monitor their stability. For example, when products waiting to be packed are kept A long time before packing or waiting for transfer from the production site to the packing site requires evaluation and study. Impact on the stability of the product under normal conditions, including the need to continuously monitor its stability. of products during production that are stored and waiting to be used for a long time if the stability of products mixed with water is studied or other solvents before use is studied after mixing at various times during product development in the continuous monitoring of the stability of such products. It is not necessary to check at different intervals after mixing. However, it is still recommended that, wherever possible, the stability of the product be continuously monitored. The product should be mixed with water or other solvents before use at various times.

Article 26 There must be a written protocol and a report on the results of continuous monitoring of stability according to the principles set out in Section 4. Documentation operations include verification and maintenance. Tools used to continuously monitor stability, such as cabinets for monitoring stability at specified conditions. Principles specified in Chapter 3, Buildings, Facilities and Equipment, and Appendix 14, Verification and Certification. validate

Article 27 Protocol for continuous monitoring of stability. Must cover the expiration date.
of that drug product and must at least consist of

27.1 Number of production models for each strength. and production model size (if

any). 27.2 Physical testing methods Chemistry, Microbiology and Biology

27.3 Acceptance criteria

27.4 Reference to the testing methods used.

27.5 Details of the container and sealing system. 27.6 Test periods at

various times.

27.7 Details of storage conditions Especially the testing conditions must be used according to the announcement of Food and Drug Administration

27.8 Parameters specific to each medicinal product (if any) 28. Continuous stability

monitoring protocols may differ from stability studies. Long-term medicines that have been applied for registration are provided that reasonable reasons are provided and specified in the protocol, such as the frequency of testing. or updated according to the announcement of the Office of the Commission.
food and medicine

Article 29: Number of production models and frequency of testing. Sufficient information must be provided for trend analysis. In addition to having sufficient reason Follow up on the stability of at least 1 model produced per year in every strength and every type. Type of primary packaging material used unless no production was produced during the year for the product being monitored. Continuous stability, which is normally tested using laboratory animals and no other suitable, validated methods. After validation, the frequency of testing may be determined by the risks and benefits being monitored. Continuous stability may be achieved using the principles of bracing and matrixing design. If a scientific basis is included in the protocol.

Article 30 In some situations, continuous stability monitoring may increase the number of batches studied, for example when there are significant changes or deviations in the process or packaging materials. Including repetition with a new process, repetition with the same process. or recycling

clause ÿÿ Results of continuous monitoring of stability Must be presented to key personnel Especially those who Assigned to continuous stability monitoring at a location other than the product manufacturing facility. Packaging or finished products There must be a written agreement between the relevant agencies. Reports of the results and continuous monitoring of stability must be kept at the premises that are authorized to produce the drug. To be able to check

Article 32 Failure to pass the requirements or trends that are significantly abnormal There must be an investigation. Confirmed reasons for non-conformity or significant negative trends must be reported to the office. The Food and Drug Administration. The possible effects on each marketed version must be considered as stated in
Section 8 Complaints and product recalls and must be notified to the Food and Drug Administration.

Article 33 Summary of all data including results for each period of the monitoring plan. Must be written written and preserved. This summary must be reviewed periodically.

Section 7

Outsourcing production and analysis

Principle

Outsourcing production and analysis requires clear conditions, agreements, and controls to Avoid misunderstandings that will result in products or work being of unsatisfactory quality. You must make an employment contract. It is in writing between the employer and the contractor that clearly defines the duties of each party. The contract must specify the methods and responsibilities of the person assigned to release each model of product.

Clearly distributed

Note: The content in this section concerns the responsibilities of the production licensee to the Office. The Food and Drug Administration, which authorizes the production and registration of drug formulas It does not cover liability. of contractors and employers towards consumers

General requirements

1. There must be a written employment contract covering the production, analysis, clauses, and related technical agreements under the said

contract. 2. All agreements of the production and analysis contract including the clauses. Propose to change Other techniques or agreements It must be in accordance with the drug registration of the product.

Employer

No. 3 Employer is responsible for evaluating the ability of the contractor. To complete the work successfully as desired and comply with the principles of the rules and procedures for producing drugs as specified in the announcement. Ministry of Public Health, this issue. Clause 4: The employer

must provide all information necessary for the contractor to efficiently carry out the contract. Correct according to the drug registration and other specified rules. The employer must ensure that the contractor is careful about problems. Everything related to products or work performed that may cause danger to buildings, premises, tools, personnel, other objects, or other products of the contractor. Clause 5: The employer must ensure that all

products and objects delivered by the contractor are correct. must meet specifications or the delivered product has been released by an authorized person.

Contractor

Clause 6: The contractor must have adequate buildings and equipment. Has knowledge and experience, has personnel who have Ability to work as ordered by the employer Production contracts must be made with the production licensee only.

Article 7: The contractor must ensure that every product or object delivered by the employer is appropriate. According to the objective of Section 8, the contractor

must not use the work assigned to him in accordance with the employment contract. to be entrusted to a third party without approval from the employer The agreement between the contractor and the third party must contain information about the production. and analysis as originally done by the employer and contractor. Clause 9: The contractor must not perform any

activities that may have a negative effect on the quality of the products produced or analyzed. to the employer

Employment

clause **contract** 10. An employment contract must be made between the employer and the contractor, which must specify the responsibilities of each party. Regarding the production and control of products, the technical criteria of the contract must be drawn up by a person with knowledge. Appropriate competence in pharmaceutical technology Analysis and principles and methods for drug production All agreements for production and analysis must be in accordance with the pharmaceutical registration and agreed upon by both parties. 11 Contracts must specify the method for

clause releasing each batch of product for distribution to the recipient.
Assigned that each model has to be produced and checked to be correct according to the requirements specified in the drug registration.

Article 12: The employment contract must clearly explain who is responsible for purchasing, testing, and releasing starting materials, packaging materials, and who is responsible for production and quality control. Including control during production Who is responsible for sampling and analyzing cases for the analysis contract? Whether the contractor will conduct sampling at the manufacturer's premises.

clause ÿÿ production record Record of analysis of sales records and reference samples Must be kept or arranged
To be available by the employer and the contractor must have records related to product quality assessment in the case of Complaints or suspected defects can be investigated and procedures for dealing with defects must be determined. or the employer's recovery. Clause 14 The employment contract must specify that the employer is

able to inspect the contractor's work location. Clause 15 The analysis contract must specify that the contractor consents to the

Food and Drug Administration. You can go in and check.

Section 8
Complaints and product recalls

Principle

All complaints and other information regarding possible product defects must be Careful review of the written instructions is required to be prepared for anything that may occur. Establish a system for quickly recalling defective or suspected defective products from the market. and effective

Complaints

clause 1 Must determine the person responsible for dealing with complaints. Finding corrective measures Including the team adequate support If the responsible person is not the person with decision-making authority Must notify the designated person. Be aware of complaints that have occurred. Including investigations or

collections. Item 2: Procedures must be written specifying actions related to complaints. Including the necessity that Chargebacks are required in the event of complaints related to defective products.

Item 3: Details of complaints regarding defective products must be recorded. and investigations conducted

All those responsible for quality control must be involved in studying the issue.

Article 4 If any product model is found to be defective or suspected of being defective You must consider checking other product models as well to check whether they are effective or not. In particular, an investigation must be made of the version of the product that carries the version of the product. Defects are reproduced and mixed together.

Article 5 All decisions and measures taken as a result of complaints must be recorded. with reference to the production record of the said model as well. Article 6:

The complaint record must be reviewed regularly. For specific or recurring problems Many times, special attention must be paid and the product may have to be recalled from the market. Item 7: Special attention

must be paid to complaints caused by counterfeit medicines. Item 8: Manufacturers

must notify the Food and Drug Administration. of the guidelines to be taken in the case Serious errors in the production of deteriorated pharmaceutical products have been discovered, counterfeit medicines have been detected, or other serious problems occurring with Product quality

product recall

Article 9: Persons responsible for carrying out and coordinating product recalls must be designated. Provide adequate work teams to recall products with an appropriate level of urgency. Those responsible must Independent from the sales or marketing department If the person responsible is not the person assigned Must notify the authority
Decide on product recall actions

clause 10 Activities related to product recall must have procedures and procedures in place.
Regularly reviewed and updated as necessary.

clause ÿÿ Product recall operations must be immediate and available at all times.

Article 12 If a product is recalled because it is defective or suspected of being defective, it must be notified.
Drug control authorities of all countries to which the product is shipped should be notified

clause immediately. 13 Those responsible for product recalls must obtain distribution records that contain adequate information.
of wholesalers and customers who receive products directly which includes address Fax phone number both at time and
Outside business hours Model and quantity delivered This includes exported products and medical samples.

Article 14 Recalled products must be identified and stored separately in a safe area while waiting for notification.
Decide on further management

Article 15: Progress in product recalls must be recorded and a summary report prepared, including
Check the consistency between the quantities sent for distribution and the quantities recovered.

Article 16: The effectiveness of recall management must be evaluated regularly.

Section 9

self-inspection

Principle

Must perform a self-inspection in order to monitor the practice to ensure that it is being carried out correctly and in accordance with According to the principles of rules and methods for producing drugs. Including to suggest necessary corrective measures.

1 There must be an inspection of personnel, buildings, premises, tools, document processing, and production procedures. Quality control Distribution of pharmaceutical products Handling of complaints and chargebacks and self-auditing at pre-determined intervals. To verify that there is Consistent with the principles of quality assurance, Section 2, self-inspection must be carried out independently and carried out according to

the details specified by a person with knowledge and ability assigned by the organization. or may be inspected by an independent auditor who is External experts

Section 3: Self-inspection must be recorded. The inspection report must include observations during inspection and recommendations for corrective measures (if any), including a record of the methods Corrective action that must be taken further.

MainCriteria and w Methods for producing medicine

The part ÿ

Attached to the Ministry of Public Health announcement

is the determination of details regarding the criteria and procedures. Method of production and

Current traditional medicine and amendmetts add criteria for methods of production

traditional medicine according to the law. Wow ya

2016

Category 1

Introduction

Objectives:

The criteria documents in this section are used as criteria and methods for production of biologically active substances. Pharmacy under an appropriate system for quality management and to help ensure that the substances are biologically active The pharmaceutical meets the required quality and purity

requirements. This section of the document does not cover the safety of personnel working in pharmaceutical production sites. Including not specifying methods for protecting the environment. by placing them under control under other relevant laws

In addition, this section of the regulatory documents does not include the requirements for registration of medicinal formulas. or modification Requirements of the drug book and does not affect the agencies responsible for creating regulations regarding registration,

drug formulas, or issuing production licenses for pharmaceutical active substances. Including all obligations in the registration documents. The recipe must meet the approved conditions.

scope

The regulatory documents in this section are for the production of active pharmaceutical substances used in medicinal products for humans and animals, using it for the production of sterile pharmaceutical active ingredients that are immediately sterile. After production, sterilization and sterile techniques For active pharmaceutical ingredients Sterile, follow the principles and requirements of the criteria and methods for drug production, including Appendix 1, Sterile Drug Production.

In the case of ectoparasitic agents used for animals, standards other than those announced may apply. The Ministry of Public Health can use this part if it can ensure that the objects are of appropriate quality. This section

of the guideline document does not include blood and plasma. Because there is an appendix ÿÿ Production of pharmaceutical products prepared from human blood or plasma, which has detailed sample collection requirements. and blood testing. However, this part of the criteria document applies to pharmaceutical active substances produced using blood or Plasma as raw material But it is not used for drug products that are in the form of products waiting to be packaged. Criteria document in this section Applies to other active substance starting materials which may undergo degradation as specified in other appendices. especially Specified in Appendix 2, production of bioactive substances and biopharmaceutical products for use in Humans until Appendix 6 Production of medicinal products from medicinal plants There may be additional regulations for substances. Has some pharmaceutical effects “Starting materials of pharmaceutical active

substances” are raw materials and products in process of production. or active ingredients Pharmaceutical ingredients used in the production of pharmaceutical active ingredients and are the building blocks of pharmaceutical active ingredients. Pharmaceutical active ingredient starting materials can be procured from one or more suppliers. Under a contract or commercial agreement or that is produced by yourself Normally, the structure and physical properties are specified. The chemistry of the starting materials of pharmaceutical active ingredients is included.

Manufacturers must design and document the rationale for starting production of the active pharmaceutical ingredient.
The synthesis process is where the precursors of active pharmaceutical ingredients are introduced into the process.
For other processes (e.g. fermentation, extraction, purification), reasons may be considered on a case-by-case basis. 1 represents the point
to Table. From at which the precursor of the active pharmaceutical ingredient is introduced into the process, according

that point The criteria according to the announcement of the Ministry of Public Health in this section must be used in the process of
Produce products during production and/or active pharmaceutical ingredients Including checking the accuracy of
Critical process steps that affect the quality of pharmaceutical active ingredients, however, must
Note that manufacturers that choose to validate process steps may not require those steps.
It can be a critical step.

The guidelines in this section generally apply to steps denoted by an asterisk (*) in a table, but the table is not an ÿ
exhaustive representation of all steps.
The criteria and methods for producing active pharmaceutical ingredients must be increased from the initial stage to the final stage.
The final step in the production process of active pharmaceutical ingredients Purification and packaging process
Physical aspects of the production of active pharmaceutical ingredients, such as granulation, coating or medical handling methods.
Particle size physicals (e.g. grinding, particle size reduction) must at least be documented.
Criteria in this section

This section of the criteria document does not apply to steps prior to implementation. “Starting materials for
pharmaceutical active ingredients (API Starting Material)” enter the process

In addition to following the rules and procedures for producing drugs, Part 2, follow:
Other appendices as relevant as well.

Table ÿ **This substances. Using multiple documents The requirements in this section are set for the production of pharmaceutical active** ÿ

Form of production	The principles in this section apply to the steps used in this type of production.				
chemical production	Production of starting materials of active ingredients pharmaceutical	***Bringing the starting object of active ingredients pharmaceuticals enter the process**	***Product production During production**	***Separation and purification**	***process physical and Packaging**
Active substances Pharmaceuticals derived from animals	collection or harvest organs liquid or tissue	cutting, mixing and/or Initial process	***Bringing the starting object of active ingredients pharmaceuticals enter the process**	***Separation and purification**	***process physical and Packaging**
Active substances Pharmaceuticals extracted from plants	collection or harvest plants	Cutting and Extraction start	***Bringing the starting object of active ingredients pharmaceuticals enter the process**	***Separation and** ÿ **Make it pure**	***process physical and Packaging**
herbal extracts used as an active ingredient pharmaceutical	collection or harvest plants	collection or harvest plants		***Initial cutting and extraction**	***Extraction in the next step**
process Physical and packaging package	collection of plants and/or cultivation and harvest	cutting/grinding			***process physical and Packaging**
Biotechnology: Fermentation/Culture cell	Establishment of Master Cell Bank and cell banks in use	***Maintenance cell bank used work**	***Culture cells and/or fermentation**	***Separation and purification**	***process physical and Packaging**
traditional fermentation to produce active ingredients pharmaceutical	Establishment of cell bank	Maintenance cell bank	***Introducing cells into fermentation**	***Separation and purification**	***process physical and Packaging**

Category 2

Quality management

Principle

Item 1: Quality is ␣ It is the responsibility of everyone involved in production.

Item 2: Producers must have a system for preparing documents and using an efficient system for dealing with
The quality of the product requires the full participation of management personnel and personnel.
production appropriately

Item 3 A system for quality management must include an organizational structure. Method of action
processes and resources, including necessary activities To ensure that the active pharmaceutical ingredients
Quality and purity requirements are met. All quality-related activities must be established.
and prepared as a document

Item 4: There must be a quality department that is separate and independent from the production department. which is responsible for both insurance
Quality and quality control It may take the form of a quality assurance agency. and control agencies
Separate quality Or is it a single unit or a work group? Depends on the size and structure of the organization.

Clause 5: Persons assigned to release products during production must be specified. and active ingredients
pharmacy

Article 6: All activities related to quality must be recorded while work is being performed.

Article 7: Any deviations from the prescribed procedures must be recorded with an explanation. There must be an investigation.
Find the cause of the critical deviation. and record the results of the investigation together with the conclusions as a document

Article 8: There must be no let-through. or use any object before the quality assessment has been completed by the quality department
unless there is an appropriate system in place (such as release under quarantine as specified in Section 10, delivery Topic Method
operations, Section 3, or use of raw materials or products in process of production that are waiting for evaluation to be completed) Item

9 There must be a procedure for reporting matters related to defect assessment in accordance with
Principles and methods for producing drugs Product quality problems and related actions (such as
Complaints about quality product recalls, legal proceedings) according to the time period specified
Required by law

10 to achieve quality objectives Must have design and use the quality system together with
Rules and methods for producing drugs Quality control and managing quality risks correctly

Risk management quality risks

clause 11 Quality risk management is a systematic process for evaluating, controlling, communicating and reviewing risks to the quality of pharmaceutical active substances. which can be applied
Both preparation in advance and retrospective review

Article 12: The quality risk management system must ensure that

12.1 Quality risk assessment must be based on scientific knowledge and experience.
about the process and must be linked to patient protection through communication with users of active pharmaceutical

substances. 12.2 The level of effort, protocol and documentation of the health risk management process
Quality must be related to the level of risk.

Examples of processes and applications of quality risk management may
Follow the recommendations on Quality risk management, Annex 20 of PIC/S GUIDE TO GOOD.
MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS ANNEXES: PE 009-12 (Annexes) 1
October 2015 and amendments

Responsibilities of the quality agency

clause 13 The quality agency must be involved in all matters related to quality.

Article 14 Quality agencies must review and approve all documents related to appropriate quality.

Article 15 The main responsibilities of an independent quality agency must not be assigned to other agencies.
act on behalf of All responsibilities must be specified in writing. and must at least consist of

15.1 Allow or not pass all pharmaceutical active substances. and products during production
For use outside of the manufacturer's control.

15.2 Arrange a system for allowing or not passing raw materials. Products in process Packing material including label

15.3 Review the steps of various critical processes in the production records and records.
Finished quality control in order to release pharmaceutical active ingredients before delivery

15.4 Investigate the cause of critical deviations and take corrective action.

15.5 Approve the requirements. and instructions for all production operations

15.6 Approve all practices that affect the quality of products during production or substances.
Active pharmaceutical

15.7 Arrange for self-examination.

15.8 Approve the production of products in process. and active pharmaceutical ingredients

15.9 Approve any changes that affect the quality of the product during production or pharmaceutical active substances

15.10 Review and approve the protocol. and report on checking accuracy.

15.11 Investigate the causes of complaints related to quality. Ready to take corrective

action. 15.12 Maintain and calibrate critical equipment using an efficient system.

15.13 Test objects using appropriate methods. and prepare a report on

test results. 15.14 Provide stability data to support retest dates. or expiration date and Storage conditions of active pharmaceutical ingredients and products during

production 15.15 Conduct product quality reviews. (As specified in the topic Quality review product)

Responsibility for production operations

Article 16 Responsibility for production activities must be specified in writing and at least Must consist of

16.1 Prepare, review, approve and distribute recommendations for the production of in-process products or pharmaceutical active ingredients. According to the procedures written in 16.2, proceed

with the production of active pharmaceutical substances. and products during production according to recommendations that has been approved

ÿÿ.ÿ Review records of all production operations. and ensure that records are entered with a complete and complete

signature. 16.4 Ensure that all deviations in production operations are assessed and reported, and critical deviations must be investigated to find the cause and a

summary of the results recorded. 16.5 Ensure that Facilitate clean and disinfected production operations. That's appropriate.

16.6 Calibrate necessary equipment. and keep

records. 16.7 Maintain premises and equipment. and

keep records. 16.8 Review and approve protocols and validation reports.

16.9 Evaluate the impact of changes in process products. or tools

16.10 Ensure that changes in products, processes Facilities tools and equipment that has been modified qualified

internal audit (self-check)

Clause 17 To be consistent with the principles of the criteria and methods of production for biologically active substances.
Pharmacists must have regular self-monitoring at specified intervals. which has been approved

Item 18: Defects detected and corrective actions must be documented and presented to the management.
that the organization's responsibilities know Corrective action that has been approved must be completed.
efficiently in the specified time period

Product Quality Review

Article 19 The quality of pharmaceutical active ingredients must be reviewed annually and written The objective is to review the consistency of the process. which must at least consist of

19.1 Review of the results of in-process controls that are critical points and the results of testing of active pharmaceutical substances in critical areas.

19.2 Review of all batches that are found to not meet

the requirements. 19.3 Review about every critical deviation. or non-compliance with requirements and investigation to find related causes

ÿÿ.ÿ Review of all changes related to the process. or analysis method

19.5 Review of the results of stability monitoring.

19.6 Review of product returns and complaints and recall of products at
All related to quality

19.7 Review of appropriateness and adequacy of corrective actions.

Article 20 The results of product quality reviews must be evaluated. and used to consider whether there must be Take corrective action. Or check the accuracy again or not? The reasons for corrective action must be documented. Make corrections that have been approved. The work must be completed efficiently in the specified time period.

Section 3

personnel

Qualifications of Personnel

1 There must be a sufficient number of personnel who are certified in education, training, and/or experience in operating and controlling the production of products during production. and active pharmaceutical ingredients

Article 2 Responsibilities of all personnel involved in the production of products during production. and active ingredients Pharmaceutical products must be clearly specified in writing.

Article 3 Training must be carried out regularly by personnel with appropriate qualifications. and at least must Covers responsible work Including criteria and methods for production, with training records required to be kept. and training must be evaluated periodically.

Hygiene of Personnel No.

4 Personnel must follow the principles of good hygiene and hygiene.

No. 5 Personnel must wear clean clothing appropriate for the production activities involved and must change clothing as appropriate if necessary. Additional protective equipment such as head, face, hands, and arms are worn to prevent product contamination during production. and active ingredients
pharmacy

Article 6 Personnel must avoid direct contact with products during production. or active pharmaceutical substances,

item 7, smoking, eating drinking drinks Chewing snacks and food storage must be limited to a designated area separated from the production area.

Article 8: Personnel who are sick from infectious diseases or have open wounds on the skin of the body must not participate In activities that may cause damage to the quality of pharmaceutical active ingredients Personnel with an apparent illness or open wound (whether diagnosed medically or through observation by a supervisor) must not perform activities that may have a negative effect on the quality of active pharmaceutical ingredients until they are cured or have been diagnosed by medical personnel. That Participation in personnel activities will not occur. Safety risks or the quality of pharmaceutical active ingredients

Consultant

No. 9 Consultants who provide advice regarding production. and control of products in process of production or active pharmaceutical substances Must have adequate education, training, and experience in the relevant field. To provide advice on matters that have been hired

10 Records must be kept by name. Address, qualifications and form of services of the consultant.

Chapter 4

Buildings and Facilities

design and construction

clause ÿ Buildings and facilities used in the production of products in process. and active pharmaceutical ingredients must specify a location. or design position and built in such a way that it is easy to clean. Maintenance and operations as appropriate to the type and process of production Including having to design Facilities to reduce potential contamination Where there are microbiological requirements for Products in process or active pharmaceutical ingredients, facilities must be designed to limit unacceptable microbial contamination as appropriate. Section 2: Buildings and facilities must have adequate space for placement. Keep tools and objects in order. To prevent mix-up and contamination

Point 3: If the equipment has an adequate protection system against various objects, such as a closed system or containment system, then the equipment can be placed outside.

Article 4: Direction of objects and personnel within the building. or facilities must be designed for Prevent mixing or contamination. Clause 5: Area must be specified. Or is there

any other control system for the following activities?

5.1 Receiving goods, verifying sampling identity and containment of incoming objects Waiting for release to pass or fail?

5.2 Quarantine before release or non-passage of products during production. and active ingredients pharmaceutical

5.3 Sampling of products during production and pharmaceutical active substances 5.4 Confining

objects that do not pass before destroying them, such as returning them or repeating the same process. or destruction, etc.

5.5 Storing objects that have been released.

5.6 Production operations

5.7 Operations for packaging and labeling 5.8 Laboratory operations

Article 6: Facilities for washing must be arranged. and clean restrooms and sufficient for soap, Decontamination facilities must be equipped with appropriate hot and cold water systems, personnel, or detergent. Have an air dryer or disposable paper towels available. and must separate facilities For washing and toilets removed from the production area but easily accessible. There must be facilities that Sufficient for cleansing the body or changing clothes as appropriate

Item 7: Quality control area and operations in the laboratory must be separated from the work area.

Proceed with production In the case of quality control during production Can be located in the production area if

Manufacturing operations do not affect the accuracy of laboratory measurements. and operations

The laboratory must not affect production operations. or products during production or active substances

pharmacy

Production support system

Item 8: All production support systems that may affect product quality [such as steam, gas

Compressed air and air systems [heating, ventilation and air conditioning] must be certified. and follow up appropriately and action must be taken when the limit is exceeded. Including the need to provide a diagram of the system.

Production support

Article 9: There must be an air circulation system. Air filtration system and ventilation system to the outside at

Sufficient as appropriate These systems must be designed and constructed to reduce the risk of contamination and cross-contamination. Including

tools for controlling air pressure. Microorganisms, dust, humidity, and temperature appropriate to the production process. Special attention must be

paid to the area where the active pharmaceutical ingredient must be.

Contact with the environment

clause 10 Air that circulates back into the production area must be properly measured. to control risk

in contamination and cross contamination

clause ÿÿ Permanently installed pipes must be properly identified. Using a computer control system

Documentation system, identification of each pipe or use other methods, the pipe must be installed in a location that avoids the risk of

Contamination of the product during production or active pharmaceutical ingredients

Item 12: The sewerage pipe must be of sufficient size and must be equipped with an air-trapping device. or other appropriate equipment

to prevent flow back

Water

13 Water used in the production of active pharmaceutical ingredients must be shown to be appropriate for

Terms of use

Article 14 Water used in the process At least it must meet the criteria for drinking water quality according to the guidelines of

World Health Organization Unless otherwise specified.

Item 15 If the use of drinking water is not sufficient to guarantee the quality of the pharmaceutical active ingredient and requires

Use more stringent chemical or microbiological water quality requirements. Appropriate requirements must be established for

Physical or chemical characteristics, microbial content, living organisms are not established. or endotoxin

Article 16 In the case that water used in the process is managed by the manufacturer in order to pass the defined quality criteria

Requires verification and continuously monitor the quality management process within operating limits

appropriate

Article 17 In the case of a manufacturer of non-sterile pharmaceutical active substances who intends or claim that it is suitable For use in the process of producing sterile pharmaceutical products. Water used in the final separation and purification steps The total number of microorganisms must be monitored and controlled. Unacceptable microorganisms and endotoxin

Containment

Article 18: There must be a separate production area. Including the facilities, air systems, and tools used. In the production of substances with a high potential for allergic reactions, such as penicillin,

cephalosporins, item 19, a separate area must be provided if contaminated materials are used. or has high pharmacological effects or is toxic (such as some steroids or cytotoxic anti-cancer substances) unless prepared and maintained according to Validated methods of destruction and cleaning.

Article 20: Appropriate measures must be prepared and implemented. To prevent cross-contamination caused by Move personnel and materials, etc., from one isolated area to another. Article 21 Production operations

(including weighing, grinding or packaging) of highly toxic non-drug substances such as herbicides and pest killers. Must not be carried out in the same building. or use the same tools as Used in the production of active pharmaceutical ingredients. Care and storage of highly toxic non-drug items must be separated. from active pharmaceutical ingredients

light

Article 22: There must be adequate lighting in every area. In order to facilitate the operation of cleaning, Maintenance and operations are carried out appropriately.

Sewage and Garbage

Article 23 Sewage, garbage, and other waste (such as solids, liquids, or gases generated from production) from within the building, the building, and surrounding areas must be disposed of in a safe manner. and is hygienic within the specified period The status of waste containers and pipes must be clearly displayed.

Hygiene and maintenance No. 24

Buildings used in the production of products during production and active pharmaceutical ingredients must be Proper maintenance Including repairs and maintaining it in a clean condition. Clause 25. Procedures

must be established for delegating sanitation responsibilities, determining cleaning schedules, methods, tools, and objects used in cleaning. Clean both the building and facilities. various conveniences in writing

Article 26 Must prepare written procedures for the use of rodenticides and insecticides. Fungicides, fumigants, and cleaning and disinfecting agents to prevent contamination of tools, raw materials, materials, and product labeling during production. and active pharmaceutical ingredients

Section 5

Tools used in the process

design and construction

clause ÿ Tools used in the production of products during production and active pharmaceutical ingredients must be designed appropriately and have sufficient size. Including must be arranged appropriately for use. Cleaning Disinfection and maintenance No.

2 The surface of tools that come in contact with the product during production and active pharmaceutical ingredients must not affect the quality of the product during production. and pharmaceutical active substances that have been exposed to more than Formally established regulations or other requirements

Clause 3: Tools must be used for production operations according to the working period of that tool.

Item 4: Main equipment (such as reactors, storage vessels) that are permanently installed must be specified in accordance with Production line of products in process or active pharmaceutical ingredients

Item 5: Substances related to the operation of the equipment, such as lubricants, hot liquids, or coolants, must not come into contact with the product during production. or active pharmaceutical ingredients Because it may cause the quality to be unsatisfactory. According to the official regulations or other requirements Including the need to evaluate any deviations that occur to ensure that there will be no negative effect on various objects. At least standard lubricants and oils must be used. Equivalent to those used in the food industry.

Item 6 must use equipment that is a closed system. or storage system as appropriate In the case of using open system tools or the tool is opened, appropriate precautions must be taken. To reduce the risk of contamination

Article 7: Up-to-date diagrams for the equipment must be maintained. and installation of critical systems (such as equipment operating systems and production support systems)

Maintenance and cleaning of tools

Clause 8: The timetable and procedures for implementation must be specified. (including delegation of responsibility) for preventive maintenance of

equipment. Item 9: Written procedures must be established for cleaning equipment and releasing such clean equipment. in the production of products in process and active ingredients Pharmacies must have detailed cleaning procedures sufficient to assist workers. Clean each type of tool in a repeatable and efficient manner. How to do these at least

Must consist of

9.1 Assigning responsibility for cleaning tools

9.2 Schedule cleaning time and disinfection as appropriate

9.3 A clear explanation of the methods and materials used, including how to dilute the cleaning agent used.
Used to clean tools

ÿ.ÿ Instructions for disassembly and assembly of each tool. To ensure that
can be cleaned properly

9.5 Recommendations for removing any indications of previous production models from equipment before cleaning.

ÿ.ÿ Recommendations for protecting cleaning tools from contamination before use

9.7 Checking the cleanliness of tools immediately before use. (If possible) 9.8 Determination of the

longest period of time acceptable after completion of the production process until
Cleaning tools

clause ÿÿ must be cleaned Store tools and utensils and disinfect them. or make it sterile according to

Suitability: To prevent contamination or residue of any objects that may affect the quality of
Products in process or active pharmaceutical ingredients exceeding official requirements or other requirements
prepared

clause ÿÿ In the case of using The tool is used to carry out continuous or split-time production.

Produced in consecutive production batches for products in process. or the same type of active pharmaceutical ingredient must be made
Cleaning tools at appropriate intervals To prevent contamination and residues of substances

Contaminants (such as decomposing substances or microbial contamination at an unacceptable

level) Item 12. Equipment that is not used separately. Cleaning is required during production operations.

Different raw materials to prevent cross-contamination

The ÿÿ Acceptance criteria for residues must be established. and selection of cleaning methods and types
terms of cleaning agents must be clearly stated.

Item 14 must specify components. and the cleanliness status of tools with appropriate methods

Calibration

Article 15: Instruments used for control, weighing, measuring, measuring, monitoring, and critical testing.
To insure the quality of products during production or active pharmaceutical ingredients Must be calibrated according to procedures.
that is written in writing and according to the specified period

Article 16: Calibration of instruments must be carried out using standards that can be traced back to the received standards.
Certification (if any)

Article 17: Calibration records must be kept.

Item 18 must show the current calibration status of the critical equipment.

Article 19: Do not use equipment that has not passed the calibration criteria.

Article 20: There must be a retrospective investigation to find the cause. To consider the impact on product quality During production or active pharmaceutical substances when deviations from the calibration standards of the equipment are found. critical since the last calibration results passed the criteria

computer based system

Article 21 The accuracy of computer-based systems related to the criteria and methods for drug production must be verified. The depth and extent of verification depends on the variety, complexity, and complexity of the system. and the criticality of computer applications

Article 22 Installation verification and verification of proper functioning Must demonstrate Suitability of computer hardware and software to perform assigned tasks.

Article 23 Commercially distributed software that has been certified for quality. There is no need to check. at the same level If the existing system is not authenticated at the time of installation Can do inspection Accuracy can be traced back if proper documentation is done.

Article 24 Computer-based systems must have adequate controls to prevent unauthorized access. or change Information by those not assigned Controls must be in place to prevent data loss (e.g. the system is shut down and Unrecorded information) Change information must be recorded, which is a change to a previous transaction. Maker change And times have changed

Article 25: There must be written procedures for working. and maintenance of the systems used computer

Article 26 In the case of making a critical information transaction yourself, there must be additional verification of the correctness of the transaction, which can be done by a second operator. or by electronic means that have been Verified

Article 27: This Record and investigate the cause of incidents involving computer systems that Affects the quality of the product during production. or active pharmaceutical ingredients or the reliability of the information or test results

Article 28 Changes to computer-based systems must follow the procedures for changes. and must be officially assigned It is recorded as a document. and has been tested Must keep records All changes Including modification or additions made to hardware, software and Other critical components of the system These records must demonstrate that the system remains in a passed state. validate

Article 29 If the system is damaged or failure may cause permanent data loss. A system must be in place. Backups ensure data protection for all computer-based systems.

Article 30 Data recording can use other ÿ methods than from a computer-enabled system

Section 6
Documentation and recording operations

Document processing system and requirements

clause ÿ All documentation related to the production of in-process products must be created, reviewed, approved, and distributed. or active pharmaceutical ingredients according to the procedures specified in writing Such documents can be in paper form or electronic form. Clause 2. New creation,

amendment, substitution, and cancellation of all documents. must be controlled and maintain the improvement history as evidence

Item 3: Procedures must be established to maintain all appropriate documents (such as document history reports Production scale expansion report Technology transfer reports, process validation reports, training records Record of production operations Control record and shipping records) There must be a specified period for the retention of these documents. and all deliveries Must be kept for at least a period of time. Section 4:

expiration date of the production batch. For active Record of production operations and control for 1 year from the pharmaceutical substances that have a specified retest date, they must be stored. Saved for at least 3 years after sold out.

Section 5 must be permanently recorded when each step of work is completed. The person who made the recording must be specified and corrections made to the record must be signed and dated. Must be able to read the original data if It is also necessary to record the reasons for the correction.

Article 6 During the original record retention period or a copy of the record must be available.

Where relevant activities are taking place, records must be readily available for viewing from any location, for example by physical means. electronics

Item 7. Requirements, recommendations, procedures and records can be kept as originals or accurate copies, such as photocopies, microfilm or original copies. If reduction techniques such as photocopying are used, microfilm or electronic records must have appropriate discovery tools. And there is a way to produce permanent copies.

Clause 8: Requirements must be prepared and recorded as documents for raw materials. Products in process, active pharmaceutical substances, labels and packaging materials including auxiliary equipment, gaskets, and other objects used in the production process. Products in process or active pharmaceutical ingredients that have a critical impact on quality, criteria must be developed. Accepted as a document for control during the production process.

Article 9: If electronic signatures are used in documents, they must be able to confirm the identity and have a security system. safety

Tools for cleaning and recording usage

clause 10 Records of use of main tools must indicate cleaning. Elimination of germs sterilization

and maintenance It also shows the date and time. Additionally, the record must show the product name and model number.

Each model uses the main tools Including those who clean and maintain it.

clause ÿÿ In the case where separate equipment is used for the production of products in process or active substances

Each type of pharmaceutical There is no need to maintain separate logs for each tool. If each production record

Production models have a traceable inspection sequence and can record cleaning, maintenance and use.

It is part of the production record. or recorded and stored separately

Record of raw materials Products in process, labels and packaging materials of biologically active ingredients pharmacy

Article 12: Records must be kept with the following details:

12.1 Name of producer, identity and quantity received each time of each batch of raw materials.

Products in process of production or labels and packaging materials of active pharmaceutical ingredients Including the name of the deliverer

Control number of the deliverer 12.2 Test (if known) Other identifying numbers Number of containers received and date received

or inspection results and summary of results

12.3 Record of traceability of object use.

12.4 Inspection documents and review the accuracy and consistency of labels and materials.

Packing of active pharmaceutical ingredients

12.5 Conclusions regarding the imperviousness of raw materials Products in process or labels and materials

Packaging of active pharmaceutical ingredients

clause ÿÿ The original certified label must be preserved for comparison with the label in use.

Recommendations for master production (Record of production operations and master control)

Article 14: Documents must be prepared for production instructions for products in process or substances.

Each pharmaceutical action is dated and signed by one person. and is independently verified.

by personnel in the quality department To ensure that every model is produced consistently.

Item 15: Recommendations for the production of prototypes. Must at least consist of

15.1 Name of product in process or active pharmaceutical ingredients produced and documents

Specify the product reference code (if any). 15.2

List of raw materials and all types of products in process of production must be written using the specified name.

and the specific reference code of the raw material

15.3 Quantity or ratio of raw materials or each type of product in process, including the unit of measurement used must be clearly specified. If the quantity used is uncertain, the calculation of the size of each production batch or the production rate must be shown. and quantity adjustments must be accurate. 15.4

Location for production operations. and important tools used in production

15.5 Detailed instructions for production operations Must at least consist of

(1) sequence of work steps (2) range of

process parameters used

(3) Recommendations for collecting samples. and control during the production process along with Appropriate acceptance criteria

(4) Time taken to complete each step. or until the entire process is completed. (5) the range of

output expected in each step of the process. or appropriate time

15.6 Special practices and precautions or other relevant references.

15.7 Recommendations for storing products during production. or active pharmaceutical ingredients This includes labels and packaging materials and specific storage conditions (if applicable) to ensure suitability for use.

Production operations records (production operations records and controls) Article 16

Production operations records must be prepared for products in process of production. and active ingredients Each type of pharmaceutical It contains complete information on the production operations and controls of each model. and production records must be inspected before approval for use to ensure that they are original and accurate copies. Distribute correctly according to the documentation system. If production records are prepared separately from the master document, they must Reference is made to the current production instructions.

Article 17: The production batch number must be specified only in the production process record, dated and signed before distribution. In the process of continuous production, the product code which also indicates the date and time can be used. Until the final number is determined,

Item 18: Documentation procedures upon completion of each important step in the production record. (Record of production and control operations) must include: 18.1 Date and time

as appropriate.

18.2 Main equipment used (e.g. reaction equipment, drying equipment Granulator) 18.3 Unique

characteristics of each production model including weight, measurement and production model number. of raw materials and products in process or substances that are repeated using the same process during

production. 18.4 Critical process parameters based on actual results.

18.5 Sampling operations. 18.6

Signatures of workers at each critical step. and must have the signature of the inspector in each step

18.7 Control results during the production process and laboratory results Quantity

ÿÿ.ÿ actually produced in each step or appropriate time

18.9 Details of packaging and labels for products during production. or active ingredients pharmaceutical

18.10 Examples of printed labels or packaging materials for active pharmaceutical ingredients. or products in process if produced for sale

18.11 Record deviations. along with details of the evaluation results, investigation results, including references to the investigation to find the said

cause. 18.12 Results of testing for product release.

Article 19 Procedures for investigating the causes of critical deviations must be established and followed. or failure of the production version of the product during production. or active pharmaceutical ingredients, the investigation must be extended to other batches that may be involved in the failure. or there is such deviation

Laboratory control records Item 20 Laboratory

control records must contain information obtained from all tests. To ensure that the results including inspection and analysis comply with the requirements and The standards established are as follows: 20.1 Details of the samples. Objects to be tested Must contain at least the

name or

Origin, batch number or other code, sampling date, quantity, and date the sample was received for testing.

20.2 Reference documents for each method used in testing.

20.3 Documentation of data on weighing, measuring, or measuring samples used for each test according to Methods listed with information or references to preparation and testing for reference standards, reaction materials, and standard solutions. 20.4 Record all raw

data generated during each test. In addition, if the results The test is in graph form. Charts and spectra obtained using laboratory equipment must display the name of the substance. specific and sample models that were tested

20.5 Record all calculations related to the test. Including the unit of measurement Factors that have changed and equivalent factors

20.6 Test results report and comparison with established acceptance criteria.

20.7 Signature of the person doing the test. and the date of each test.

20.8 Date and signature of the reviewer. or recheck to show that there has been a review, accuracy, completeness, and compliance with the standards that have been established.

Article 21. A complete record must include: of the

created. 21.1 Any modifications. analytical method that has been

21.2 Calibration of instruments. Measuring equipment and recorders used in laboratories periodically

21.3 Results of stability testing of pharmaceutical active ingredients. 21.4

Investigation to find reasons in cases where test results do not meet the requirements.

Review of production process records

Article 22 Must prepare and follow procedures for reviewing and certifying production process records. and laboratory control Including packaging materials and labels to check compliance with Established specifications of the product during production. or active pharmaceutical substances before release or Delivery of production models, item 23, must review and certify production process

records. and laboratory control of various steps of the critical process by the quality department before release. or deliver the manufactured version of the substance Active pharmaceutical For non-critical processes, records of production operations and laboratory controls can be reviewed by production personnel. or other agencies assigned according to the procedures passed Certification from a quality agency, Article 24: Reports of deviations must be reviewed. Report on investigations to find out the cause and report things that are not in order.

according to all requirements It is part of a review of production model records before release.

Article 25 Quality agencies can assign responsibilities. and authority to release products during production to the production operations unit Except in the case of exports outside of the manufacturer's control.

Section 7

Object manipulation

General controls

clause 1 There must be a written procedure explaining the receipt of goods. Identification, quarantine, storage, handling, sampling, testing, and approval or non-approval of objects.

Article 2: Manufacturers of products in process of production and/or active pharmaceutical ingredients must have an evaluation system. The deliverer of critical parts,

item 3, must purchase the object according to the specifications agreed upon by the deliverer. or a certified delivery person from the agency quality

No. 4 If the deliverer of the critical item is not the producer himself The name and address of the manufacturer of products in process of production and active pharmaceutical

ingredients must be known. Section 5 Changing the source of delivery of critical raw materials must be done in accordance with Section 13 Control of Change.

Reception and quarantine

Item 6: Before receiving an object, you must check the correctness of the label on each container. or group of containers (including the relationship between the name used by the supplier and the name used internally) if different) breakage, sealing damage, sealing damage and evidence of mix-up and contamination. Objects must be quarantined until they are cleared. sampling inspection or test as appropriate It is then released for use. Item 7: Before storing the object with the original item (such

as a solvent or an object that must be stored in a large container), the identification must be checked to be correct. Tested as appropriate and has been released There must be a method. Practice to prevent mistakes in receiving objects and storing them together with the existing ones. Item 8: If objects are delivered in large quantities using containers shared

by many products, be sure to

Cross-contamination from the tank must not occur and must at least be checked by one of the following methods:

8.1 Cleaning certificate

8.2 Testing for impurity of substances 8.3 Inspection

of suppliers

Item 9 must indicate the status of large storage containers. and the attached dispenser set The path of taking in and Proper release path

clause 10 There must be an indication of the status of each container. or group of containers of objects clearly by specifying the reference code Received model number or different production model numbers The said number must be correct. Used to record the management of each production batch.

clause must be tested to verify the identity of each batch of objects. At least one test Except for the objects specified in Article 13, the supplier's certificate of analysis can be used in place of such verification, provided that the manufacturer has a system for evaluating the supplier.

Article 12 Certification of the supplier must include sufficient evidence such as Past quality history so that the deliverer can Procure objects that meet specifications. A full analysis must be performed for at least three production batches before opting for customized testing. However, a full analysis must be performed periodically. at the appropriate time and then compare with the certificate of analysis, and the reliability of the certificate of analysis results must be checked regularly.

13 objects that help in the production process Dangerous or highly toxic raw materials Other special objects or objects that are transferred to another organization under the control of the manufacturer. Identity testing is not required if applicable. Manufacturer's certificate of analysis, which demonstrates that these raw materials meet established requirements. Must bring information Visual inspection of label containers and record the production model number for inspection. This identity must be explained and recorded in writing in cases where the above tests are not

performed. Article 14: Random samples of objects must be representative of the entire production batch. By sampling method, the number of the container being sampled must be specified. Sampling location and the quantity of objects sampled in each container. The number of containers and quantity of samples drawn shall be based on a sampling plan that takes into account the importance and variability of the material. Supplier's past quality history and the quantity required Analysis

Article 15: Sampling of objects must be carried out in the specified location. and follow the methods that have been designed to prevent contamination and cross-contamination from

other objects. Item 16. Containers being sampled must be opened carefully. and close it back immediately and must do A mark to show that the sample has been taken.

Storage

Article 17 Objects must be handled and stored in a manner that prevents deterioration, contamination, and cross-contamination.

Item 18: Objects packed in fiber bags Or boxes must be stored at an appropriate height from the floor, with an appropriate distance to allow cleaning and inspection.

Article 19 Objects must be stored under specified conditions. Including the storage period must not affect The quality of objects and objects must be controlled by putting the received objects into use first. Article 20

Objects stored in appropriate containers can be stored outside the building with
The label clearly indicates and containers must be properly cleaned before opening.

Article 21 Objects that do not pass the requirements must indicate their status. and controlled under a quarantine system that was designed To prevent unauthorized use

Re-evaluation No.

22: Objects must be re-evaluated as appropriate. In order to decide whether it is appropriate to use such as In the case of long-term storage or exposed to heat or humidity

Section 8

Production operations and control during the production process

Production operations

1 Raw materials used in the production of products during production and active pharmaceutical ingredients must be weighed, measured, or measured under appropriate conditions that do not affect their use. Weighing, measuring or measuring equipment must be Suitably accurate for the intended use.

Article 2 If objects are shared for use in production operations The container used must be suitable and must include at least the following information:

2.1 Name of the object and/or

reference code. 2.2 Receiving number. or control

number 2.3 Weight or volume in the new container

2.4 Date of re-evaluation or date of retest As appropriate, Section 3.

Weighing, measuring, or dividing objects in critical stages must have witnesses. or equivalent controls, prior to use, it must be verified that it is the material specified in the production record of the product in process. or active ingredients pharmaceutical products to be produced

Item 4: Other critical activities must have witnesses or equivalent controls.

Item 5: The actual output must be compared with the expected output at each step of the production operation. The expected yield range must be determined appropriately based on laboratory data, pilot scale data, or previous production data. An investigation is required to determine the cause of the deviation. The output is related to the critical steps of the process to determine the impact. or the severity of the impact It affects the quality of the production model. Item 6: Data must be recorded and explained any

deviations that occur and an investigation must be carried out to find the cause. In the event of a critical deviation, Item 7 must indicate the status of

each main equipment used in the process. or by preparing documents Computer control system or other appropriate alternatives. Item 8. Objects that can be duplicated using the same

process. or repeating with a new process must be controlled. appropriately to prevent unauthorized use.

Determination of time period

Article 9 If there is a time limit for each step of the instructions for master production (see Section 6, Section 15), it must be ensured that the product during production or the quality of the active pharmaceutical ingredients is

As specified, the deviations that occur must be recorded and evaluated. The specified period may not be suitable for will get the target value, such as adjusting the pH value Hydrogenation reaction, drying as specified.

- ÿÿ Process products stored for use in the process must be stored under appropriate conditions.

Items to ensure that they are appropriate for use

Sampling and control during the production process

clause 11 Must prepare written procedures to monitor progress and control the efficiency of the process at each step that may cause deviations in product quality during production. and active pharmaceutical ingredients Acceptance criteria must be established for controls during the production process. It is based on data generated during the development process or legacy data.

Clause 12 Acceptance criteria, format and scope of testing must be determined according to the technical characteristics. Nature of products during production or active pharmaceutical ingredients produced The reaction process or process steps must be especially stringent in the final process steps, such as the separation step. and purification

clause 13 Critical controls during the production process (and monitoring in critical processes) including control points and control methods must be specified in writing. and has been certified by the quality agency. Item 14. Control during the production process must be

carried out by production personnel with appropriate qualifications. Modifications to the production process that are not approved by the quality agency can be made. within the limits set by the quality agency by testing and all test results must be recorded in

production record

Item 15: There must be a written procedure for explaining the sampling methods of objects during the production of products in process. and active pharmaceutical ingredients during the production process Plans and methods Sampling must be based on science. Item 16. Sampling during the production process must be carried

out using practices that can prevent contamination of the objects being sampled. Products in process or active pharmaceutical ingredients must be prepared in a method Practice to ensure the stability of the sample after storage. Item 17 in the case of test results during the production process to follow up. and/or process adjustments Non-

compliance may not require investigation to determine the cause.

Mixed production version of products in process or active pharmaceutical ingredients Mixing

Article 18 according to this topic means The process of combining products during production or active ingredients. pharmaceuticals with the same requirements to get products during production or active pharmaceutical ingredients that are Homogeneous Combining production processes of different parts from a single batch (e.g. storage of substances derived from multiple centrifuges from the same crystallization batch) or combining sections from multiple batches produced to pass The next process is considered part of the production process. and is not considered a mixture.

Article 19 Non-conforming lots must not be mixed with other lots for the purpose of meeting the requirements. Each mixed lot must be produced using a specified process. d and must test each model which must meet the specified standards in order to be mixed together. Section 20. Acceptable mixing operations such as

20.1 Mixing of small batches to increase the size of the batch. 20.2 Mixing

scraps left over from other batches of products in process. or active substances
same type of pharmaceutical

Article 21 The mixing process must be controlled. and adequately document and test the combined model. To be consistent with the regulations that have been established.

Item 22. Batch records of the mixing process must be traceable to each batch that is mixed. In the form of a solid oral

medication. or suspension form), the correctness of the mixing operation must be checked to ensure the homogeneity of the mixed lot. Validation This includes testing of critical characteristics (e.g. particle size distribution, density) that may be obtained.

Effects from the mixing process

Article 24 If mixing affects stability The final stability test of the mixed batch must be carried out. Item 25 The expiration date or date of

retesting of the mixed batch depends on the production date of the remaining batches or the oldest batch that was mixed.

Control of Contamination No. 26

Substances that are residues in production can be mixed with products during production or the same active pharmaceutical ingredients if they are adequately controlled, such as remaining substances that stick to the walls of fine granulator A residual layer of moist crystals remains in the container of the centrifuge, and the liquid or crystals from the device or container are transferred to the next step of the process. which must not have Contamination of decomposition substances or microorganisms which adversely affect the specified impurity value of the biologically active substance.

pharmacy

Article 27 Production must be carried out in a manner that prevents product contamination during production. or active ingredients pharmaceutical products

from other materials, No. 28, precautions must be taken to avoid contamination. When biologically active substances are administered Pharmaceuticals after purification

Section 9

Packaging and labeling of active pharmaceutical ingredients and products in process

General principles

clause 1 There must be a written work procedure explaining the receipt of goods. Quarantine indication, randomization Inspection example and/or testing, release and handling of packaging materials and labels.

Article 2: Packaging materials and various labels Must comply with established regulations. If it doesn't follow must not be allowed to pass through. To prevent inappropriate use in the process.

Item 3: Records of label delivery must be kept. and packing materials every time By showing the product receipt Inspection or testing both accepted And that doesn't let it pass.

Packing material

Clause 4: Containers must have appropriate protection to prevent deterioration. or contamination of Products in process or active pharmaceutical ingredients that may occur during transportation. and storage accordingly Recommendations

Item 5: Containers must be clean. and according to the properties of the product during production or active ingredients pharmaceutical products and sterilize them to ensure that they are suitable for their intended use. The containers must Does not react to cause changes in product quality during production. or active pharmaceutical ingredients to not pass the requirements

Item 6: If the container is reused, it must be cleaned according to the instruction document and the original label must be removed. all go out

Label printing and control u

Clause 7 Access to the label storage location must be restricted. You can enter only those assigned to you.

Article 8: There must be procedures for labels regarding consistency of quantity, disbursement, use and Returning labels requires an investigation to determine the cause in cases where the amounts affixed to the container and those dispensed are found to be inconsistent. which must be investigated and approved by quality agencies

Item 9: Packaging materials remaining from use that have the production model number printed on them. All must be destroyed. Returned labels must be stored separately. To prevent confusion or mix-up and must have accurate status indication

clause 10 labels that are old models are no longer in use. or those that are outdated must be destroyed

clause 11 Tools used for printing labels must be controlled to ensure that what is printed is in accordance with Characteristics specified in production records

Clause 12 Packaging materials with printed messages The correctness of the message must be verified.
As specified in the master production record. and the inspection results must be recorded as evidence. A sample of the

clause ÿÿ printed label must be included in the production record.

Packaging and shipping label

Item 14: Documents of work procedures must be prepared to ensure that the correct packing materials and labels are used.
to use

Article 15 Labeling operations must be designed to prevent mixing. There must be physical separation.
or keeping a distance from operations related to products during production or other pharmaceutical active substances. Clause 16.

Labels affixed to product containers during production. or active pharmaceutical ingredients must specify the name, code, batch number of the product and storage conditions. When this information is critical information that causes Ensure the quality of products during production or active pharmaceutical ingredients.

Article 17 If there is movement of products during production or active pharmaceutical ingredients removed from Control of the manufacturer's management system The name and address of the manufacturer must be specified. Quantity or quantity and special transportation conditions Include special legal requirements on the label. For products in process of production or active pharmaceutical substances that have an expiration date, the expiration date must be specified on the label and the certificate of analysis if Products in process or active pharmaceutical ingredients that have a retest date must indicate the retest date on the label. and/or in the analysis results certificate

Article 18 Facilities used for packaging and labeling must be inspected immediately before use to ensure Ensure that no unrelated packing material remains and the results of the inspection are recorded in the records. Production operations Record of facility use or other document systems. Article 19. Packaging materials and product labels must

be inspected during production. or active substances pharmaceuticals to ensure that containers and packing materials in production batches are properly labeled. This inspection is part of of the packing operation, the results of the inspection must be recorded in the production record. or control record

Clause 20. Containers of products during production. or active pharmaceutical substances being transported out of the control of the manufacturer It must be sealed in such a way that if the seal is broken or missing, the recipient will be aware of the possibility that the contents may have been altered.

Section 10

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Storage and shipping

Methods for performing work in the storage

location: 1 There must be facilities for storing various objects. Under appropriate conditions, such as controlling temperature and relative humidity as necessary. Records of storage conditions must be maintained in case of Storage is critical for maintaining stability.

Item 2 If there is no other control system that can prevent unauthorized use, there must be a separate area for storing objects in quarantine status. Not passing the requirements was returned and was charged back Make it a clear proportion. Until a decision is made on the next steps.

Methods of operation for delivery,

item 3, must allow the release of pharmaceutical active substances and products during production. to deliver to another location by quality agency Active pharmaceutical substances and products in process transported under Quarantine to another unit of the manufacturer must be approved by the quality authority. There is a document system and Proper

control No. 4 Pharmaceutical active substances must be moved. and products during production in a manner that is not sent Quality impact

Item 5 must specify special conditions in transportation. or stored on the label of the active pharmaceutical ingredient; and Products in process

Article 6: Manufacturers must ensure that contractors transporting pharmaceutical active substances or products during production know and comply with the transportation conditions. and

appropriate storage. Clause 7: The production site must have a system for distributing pharmaceutical active substances. and/or products During production, each production batch is available for recall.

Section 11
Laboratory controls

General controls

1 The quality agency must have adequate facilities for the disposal of waste from the laboratory. 2 There must be

documented procedures regarding sampling, testing, release or inclusion methods. Recording and various objects. Laboratory preservation of laboratory data which must be preserved Do not allow the passage of records according to Section 6, Topic: Laboratory Control Records, Section 3,

Requirements, Sampling Plan. and testing methods must be appropriate and according to academic principles. To ensure that the raw materials Products in process pharmaceutical active substances and the packing materials are in accordance with Standards set for quality and/or purity requirements and testing methods must be consistent with Requirements according to the drug textbook and may have additional requirements. Requirements Sampling plans and testing methods, including all variations, must be drafted by the appropriate agency, reviewed and approved by the

Item 4: Appropriate requirements for pharmaceutical active ingredients must be established to meet accepted standards and be consistent with the production process. The requirements must include impure substances (e.g. impure substances organic, inorganic impurities and residual solvents) also if the pharmaceutical active ingredients have the requirements Microbiology and endotoxin Appropriate operating limits for the amount of endotoxin-contaminating microorganisms must be established. and other microorganisms. Laboratory control must be carried out Item 5:

and recorded at the time of work. If there is a way to practice

that are different from those specified must be recorded. and explain the reasons

Clause 6: In the case of non-compliance with the requirements The cause must be investigated and recorded according to specified methods, which requires data analysis. Assess the level of the problem Determine corrective methods and summarize results. If sampling and/or testing is repeated, the specified

procedures must be followed. Section 7: Standard solutions and chemicals used in analysis and testing must be prepared and labeled according to the methods. specified, with an expiration date

specified as appropriate. Clause 8. Appropriate primary reference standard substances must be procured for the production of pharmaceutical active substances. Ready to record the source and must keep records regarding the use and storage of primary reference standard substances in accordance with Sender's advice Primary reference standards obtained from reliable sources do not need to be tested before use. If stored in conditions

according to the supplier's instructions, Section 9, if the primary reference standard substance does not come from a reliable source, standard specifications must be established. Introduction of the manufacturer and complete testing in the topic of identification and purity, ready for st Saved

10 Secondary reference standard substances must be prepared for identification testing. Approve and store

Item: Appropriate: The suitability of each batch of secondary reference standard substances produced must be assessed before the first use by Calibrated with a primary reference standard and subject to repeat testing as specified in the protocol.

Product testing during production and active pharmaceutical ingredients

clause 11 each production batch of products in process of production and active pharmaceutical ingredients There must be a test at Appropriate according to the specified standards.

Item 12 Must prepare information on impure, contaminated substances. Both can and cannot prove identity. that occur during production by specially controlled production processes for biologically active substances. Each type of pharmaceutical Information on impurity impurities must include identity or qualitative analysis. Range of each type of impure substance found and classification of impure substances whose identity can be verified (e.g. Inorganic substances, organic substances or solvent) information on impurities that depend on the production process and Origin of active pharmaceutical ingredients Impurity information is not required for active ingredients. Pharmaceuticals obtained from plant origin or animal tissue in the case of biotechnology shall comply with ICH.

Guideline Q6B

clause 13 There must be a comparison of information on impure substances mixed with the information required by law in suitable time or compare with the original data to check for changes that have occurred with the active ingredient. pharmaceuticals due to changes in raw materials Operating parameters of the instrument or process of production operations

Item 14: If microbiological quality is determined, appropriate microbiological testing of the product must be carried out. Each model is produced for products in process. and active pharmaceutical ingredients

the correctness of the methods This **Analysis methods (see section 12, checking the correctness) Checking**

Certificate of analysis esults

Clause 15 Issuance of certificates of analytical results of products in process of production or active pharmaceutical substances. Each production model must be the original. or an edition that has reliable certification

Article 16 Certificate of analysis of products during production. or active pharmaceutical ingredients must have Information on name, grade, production model number and release date For products with an expiration date, the expiration date must be specified. on the label and the certificate of analysis in which the date of retesting must be specified on the label. and/or certificate

Analysis results

Item 17 The certificate of analysis must indicate each test according to the drug book. or according to the requirements of customers, along with acceptance limits and the results are numerical values (If the test results are numerical)

Section 18: The analysis results certificate must indicate the date. and signed by the person assigned by Quality agency and must show name Address and telephone number of the original manufacturer If the analysis results certificate

Issued by the packer or a repeater using the same process must display the name, address, and telephone number of the packer or repeater using the original process. and references to the name of the original manufacturer

Item 19 If a new certificate of analysis is issued by the repeat packer using the same process, the representative or broker must show the name, address and telephone number of the laboratory that performs the analysis and must have Reference to name Address of original manufacturer and the original manufacturer's model certificate Along with attaching a copy of the model certificate. Analysis of the original manufacturer

Monitoring the stability of active pharmaceutical ingredients

Article 20: A document must be prepared for the continuous monitoring of the stability. To follow the characteristics Maintains the condition of active pharmaceutical ingredients and the results must be used to confirm appropriate storage conditions, including Date of retest or expiration date

Item 21: The accuracy of the testing methods used in the stability test and the testing methods must be checked. Must be able to indicate stability.

Article 22 Samples used for stability testing must be stored in similar or simulated containers. Containers sold in the market such as If the active pharmaceutical ingredient is packaged in a bag in a fiber sample tank The test equipment can be packed in bags of the same material. and in tanks using similar or the same materials as Sold in the market in smaller sizes.

Item 23: A stability study must be conducted on the first three production models for sale in order to confirm the date of retesting. or expiration date, however If there is data from previous studies showing that the active pharmaceutical ingredient has Stable for at least 2 years. Data for less than 3 generations can be used.

Item 24: Stability studies must be conducted continuously at least once a year, unless there is no production during the year. Item 25:

For pharmaceutical active substances with a short shelf life, testing must be done more frequently, such as biotechnology substances. or other biological substances and pharmaceutical active substances that have a shelf life of 1 year or less. Must be tested every month during The first 3 months after that, testing should be done every 3 months if the data confirms the stability of the active ingredients. The pharmaceutical company is not damaged and can consider canceling the test during the period before the expiration date.

Article 26 Storage conditions for stability testing must be in accordance with the guidelines of

Stability study according to ICH guidelines (ICH guidelines on stability)

Determining the expiration date and Date of retest

Article 27 If there is movement of products during production outside the control of the management system Producer's object and there is a specified expiration date or retest date, there must be information supporting its stability (e.g. Published information on test results)

Article 28: The expiration date or date of retesting of pharmaceutical active substances must be obtained from the evaluation. Information obtained from stability studies This is generally defined as the test date rather than as the expiration date.

Article 29: Initially, determining the expiration date or retest date of pharmaceutical active substances.

Can use data from prototype production models In the following cases:

29.1 The prototype production model uses the production method and procedures that simulate the production process used for commercial production

29.2 The quality of pharmaceutical active substances is representative of commercially produced substances.

Section 30. Samples that can be representative must be collected for repeat testing.

Backup sample/collection sample

31 The purpose of packing and storing reserve samples is to assess the quality of future production batches of pharmaceutical active substances. Not for stability studies. Item 32. Reserve samples

of each batch of active pharmaceutical ingredients that have received appropriate identification, 1 year after the least distribution, choosing a expiration date specified by the manufacturer. or keep for at least 3 years after must be kept for at longer time For active pharmaceutical ingredients with a repeat test date specified, they must be stored. Maintain backup samples for at least 3 years after the production lot has been sold. Item 33. Reserve samples must

be stored in the same container system where the active pharmaceutical substance is stored. or in a protection system that is not inferior to those currently on the market and must be kept sufficient for analysis Complete at least 2 times according to the analysis method specified in the drug textbook. or according to the analytical method according to the manufacturer's specifications. If it is not specified in the medicine textbook

Section 12
Validation

Validation Policy

Item 1: Overall policy of the producer Intent and guidelines for checking accuracy, including checking the correctness of the production process. Methods for cleaning Analysis method Methods for testing during the manufacturing process Computer-based systems and personnel responsible for the design, review, approval and documentation of each phase of validation must be in writing. Section 2: There must be an

indication of critical parameters or characteristics during Development operations or from the original data and the acceptance interval required for reproducibility must be defined and must include:

2.1 Determination of critical characteristics of pharmaceutical active ingredients.

2.2 Identification of process parameters that affect the critical quality characteristics of pharmaceutical ingredients. pharmaceutical active substances

2.3 Determination of the tolerance range for each critical process parameter that is expected to be used during production and control of processes that operate normally. Item 3: Verification of

accuracy. Must cover critical processes that affect the quality and purity of pharmaceutical active ingredients.

Verification Documents Item 4: A

written verification protocol must be prepared. which specifies the method for Verify the correctness of special procedures The protocol must be reviewed and approved by the quality department and other designated agencies.

Article 5. Protocol of verification. Critical process steps and acceptance criteria must be specified, including the type of validation performed (e.g. retrospective validation). Verification of correctness before production for sale Verification of accuracy with production for sale) and the number of times of the process

Article 6: A verification report must be prepared based on the protocol, which includes: Report the results received Comments on deviations found and appropriate conclusions Including advice on Change processes to correct deficiencies.

Section 7. Any changes from the authentication protocol. Must be documented Ready to show appropriate reasons

Verification

Item 8: Before starting the activity to check the correctness of the process. Must be verified. Appropriateness of crisis tools and a complete support system. This verification consists of carrying out activities (either separately or in combination with activities) as follows: 8.1 Design verification

is verification and documentation to confirm that
Design a site where facilities, equipment, or systems are appropriate for the intended purpose.

8.2 Installation certification is verification and documentation to confirm that the equipment or installed or modified systems Conforms to the approved design according to the manufacturer's recommendations and/or the user's requirements.

8.3 Verification of work is verification and documentation to confirm that the equipment
or installed system or modified, able to work as intended throughout the specified working period

8.4 Competency verification is verification and documentation to confirm that the equipment and connected systems can work effectively and can be repeated according to approved methods, processes and specifications.

Guidelines for verifying the correctness of the process, Section

9. Verifying the correctness of the process is a document of evidence to prove that the process Able to work efficiently according to the specified parameters. and can be repeated to produce products during production or pharmaceutical active substances according to the product specifications and quality characteristics previously

clause specified. 10 There are 3 approaches to checking accuracy, by checking accuracy before production to Distribution that should be carried out more However, there are exceptions if other methods can be used instead.

clause 11 Verification of correctness before production for sale. Normally used for all processes of active substances. pharmaceutical products as defined in Section 3, which must be completed before selling finished drugs produced using Active pharmaceutical

substances in commercial use, Section 12, Verification of correctness in preparation for production for sale. Take action in the event of being unable to procure Data from limited batch remanufacturing of infrequently produced pharmaceutical active ingredients. or the production version of the active pharmaceutical ingredient is produced through a modified verification process. Therefore, before the verification process is complete and ready for sale, the substance can be released through Active pharmaceutical production version and used in the production of ready-to-use drugs for commercial purposes, which must be followed up and

thoroughly test production batches of pharmaceutical active ingredients. 13 Retrospective verification can be performed when the production process has not changed significantly to the quality of pharmaceutical active ingredients. due to changes in raw materials, tools, systems, and facilities or production process Retrospective verification can be used. In the following cases

13.1 Critical quality characteristics are indicated. and critical process parameters. 13.2

Acceptance criteria are established. and appropriate control during the production process. 13.3

There are no significant failures of processes and products due to causes other than personnel or equipment errors. This does not include the suitability of the tools. 13.4 History of impure contaminants is recorded. or

contained in pharmaceutical active substances. Item 14. The production batches selected for

retrospective verification must be representative of all production batches. During the period of reviewing information Including production models that do not meet specifications. and there must be a sufficient number of models Show the results of process consistency. Collected samples can be used for testing as data for Retrospective verification

Process Validation Program No. 15 The number of processes for

verification depends on the complexity or level of variation of the process. For checking accuracy before production for sale and ready for production for sale. Must use at least 3 consecutive production models or possibly more. In a situation that must be proven The consistency of the process (e.g., a complex or time-consuming process for producing active pharmaceutical ingredients) for retrospective validation uses data from 10-30 consecutive production batches to assess consistency. always of the process However, a smaller number of production models may be used if there is sufficient justification.

Article 16 Critical process parameters must be controlled and monitored during the study. Validate the process For process parameters not related to quality, such as adjustments to reduce energy consumption. This does not need to be specified in process validation.

Article 17: Verifying the accuracy of the process must confirm that the substance information is not pure and contaminated in Active pharmaceutical ingredients are within specified limits. The impurity impurity data must not be greater than the original historical data and the impurity impurity history generated from data collected during process development. or for production models used in key clinical and toxicological studies.

Periodic review of the verification system. Article 18. Systems

and processes must be evaluated periodically. To prove that the operation is still is going correctly Where no significant changes have occurred to a system or process and a quality review confirming that the system or process continues to produce compliant substances is not necessary. The accuracy must be re-verified.

checking the correctness of the work, Cleanliness,

No. 19, the correctness of the cleaning method must be checked. In general, checking The accuracy of the cleaning method depends on the situation or procedure with which the tool or equipment is exposed. Many substances pose the greatest risk to the quality of active pharmaceutical ingredients, such as in the early stages of

During production, it may not be necessary to validate the method of cleaning tools where residues are present. is removed in the next purification step.

Article 20: Verifying the accuracy of cleaning methods must reflect the usage pattern of the cleaning method. Real tools If different types of active pharmaceutical ingredients or products in process are produced by the same equipment and cleaned using the same methods, Can select representatives of products in process or substances Active pharmaceutical substances can be used to check the accuracy of cleaning. In selecting Based on the solubility factor and the difficulty of cleaning and calculating the residue limit value, which depends on Potency, toxicity, and stability

Article 21 The cleaning method validation protocol must describe the equipment to be cleaned, the methods of treating the objects used, the acceptable level of cleanliness. Parameters to be monitored and controlled and the method of analysis protocol must specify the type of sample collected. How to store and labeling

Item 22 Sampling must include swabs or other methods (such as direct extraction), as appropriate, to check for insoluble and water-soluble residues. The sampling method used must be measurable. The amount of residue remaining on the tool surface after cleaning. Sampling from Rinsing may not be practical if product contact surfaces are not easily accessible. Due to design Equipment or process constraints, such as the inner surface of hoses, transfer pipes, reaction vessels with small chambers, or working with toxic materials. and small complex equipment (such as a small particle crusher). Item 23 must use analytical methods that have been validated. that

is sensitive to detecting substances Residues or contaminants The limit of detection for each analytical method must be sensitive. sufficient to detect the established acceptance level of the residue or contaminant. Residue limit It must be practical, verifiable and verifiable and based on the most hazardous residues. Restrictions must be established based on the pharmacological activity, toxicology or physical characteristics of the active substance. Pharmaceutical as far as I know or the most dangerous components. Item 24. Study of cleaning and disinfection of tools. Microorganisms and Endotoxin contamination in

various processes which require reducing the number of microorganisms or endotoxins in the substance. Active pharmaceutical or other processes that consider contamination (such as the use of active pharmaceutical ingredients that are not sterile to produce sterile products)

Item 25: Cleaning methods must be checked for a reasonable period of time after verification to ensure that the methods are effective when used in normal production operations. The cleanliness of the The instrument can be checked by analysis and visual inspection. In the case of checking contaminated with a large amount of contamination in a small area that cannot be verified by random sampling; and/or Analysis is by visual inspection.

checking the correctness of the method. Article 26. The **Analytical method,**

correctness of the analytical method must be checked, unless it is the method specified in the drug textbook or Other standard reference books announced by the Food and Drug Administration specifying the suitability of methods. Test every topic It must be verified under actual conditions of use. and is recorded as a document

Article 27 Analysis methods must be checked for accuracy by considering them together with the guidelines of the organization. International Conference on Harmonization (ICH) guidelines by level of verification The correctness of the analytical method must reflect the purpose of the analysis and the steps of the process performed. Manufacture of pharmaceutical active substances. Item 28. Analytical equipment must be verified before

beginning the verification of analytical methods. Item 29. Analytical methods that have been completely verified must be

kept. And if you change The analysis method must specify the reason for the change. There is information to support and verify the results of the adjustments to see if they are correct. Accurate and reliable

Section 13
change control

clause 1 Must establish a change control system. To evaluate all changes that may affect to the production operations and control of products in process or active pharmaceutical ingredients

Article 2: There must be a procedure for indicating document processing. Appropriate review and approval of changes to raw materials, requirements, facility analysis methods, support systems, tools (including computer hardware), process steps. Packaging and labeling materials and computer software

Article 3 Proposals for changes related to the rules and procedures for drug production must be drafted, reviewed and approved by the agency according to the appropriate organizational structure. and has been reviewed and

Approved by the quality department. Item 4: The potential impact of changes on the quality of the product during production must be assessed. or active pharmaceutical ingredients Classification of procedures helps determine the level of testing. Validation and document operations required to decide on changes to The process has been verified for accuracy. Classification of change depends on the nature and extent of the change. and may affect the decision-making process. By relying on academic principles Further testing must be considered. and study of appropriate verification methods. to decide In making changes to processes that have already been verified,

Section 5, when starting to implement the approved changes, must check to ensure that the documents All systems affected by the change have been

updated. Item 6: After the implementation of the change, an evaluation must be made of the first production version produced or

tested under the change. Item 7: Critical changes must be evaluated. This is likely to affect the retest date or, if necessary, the scheduled expiration date. Able to take samples of products during production or active pharmaceutical ingredients Produced by a process that has been modified to study stability in accelerated conditions. and/or added to Stability monitoring program

Article 8: Manufacturers must notify changes from process control methods. and the resulting production operations Prepare information that can affect the quality of pharmaceutical active ingredients to be informed to those involved at all times.

Section 14
Prohibition and reuse of objects

not letting go

clause ÿ Product identification and quarantine must be performed during production. and pharmaceutical active ingredients that are not According to the regulations, products in process of production or active pharmaceutical ingredients can also be reused. original process or repeat with a new process and must record methods for handling products during production or pharmaceutical active substances that do not pass through

Repeating the same process, item

2, can bring products during production or active pharmaceutical ingredients that do not meet standards or requirements Going to repeat the same process. by crystallization method or appropriate chemical or physical handling steps (e.g. distillation, filtration, chromatography, grinding) that are part of the production process. was determined, however If a repeat of the same process is used regularly, it must be written Additional procedures are part of the production process standard, Section 3, during the

production process. If production is stopped at a stage that has not yet been completed, such as testing to control the process. and production has continued. It is considered a normal process and is not considered a repetition. with the original process

Item 4 Bringing unreacted substances back into the process to repeat the chemical reaction. It is considered a repetition. with the original process Unless it is part of the normal production process that has been established, it must be evaluated. The replication of the same process should be approached with care. To ensure product quality during production or pharmaceutical active substances It will not be affected due to the formation of undesired substances and over-reaction substances.

Repeating with a new process

Item 5: An investigation must be conducted to find the cause before proceeding with the production of models that do not meet the standards or The requirements must be

repeated with the new process. Article 6: Production models that are repeated with the new process must be evaluated, tested, and tested for stability as necessary and must have supporting documents. To show that the products that are duplicated with the new process have The quality is the same as the products produced by the old process with verification and accuracy along with production for distribution along with repeating with the new process. The protocol must also specify procedures for replication. How will the new process be implemented? with expected results If it is repeated with a new process only One production batch must be reported. And the release of such production models will be possible only if the quality is acceptable.

Item 7: The practice method must compare impurity data in each production batch that is repeated with the new process.
Compared with the production model operated according to the specified process. If normal analytical methods are not sufficient to explain
Characteristics in the production batch reproduced with the new process will require additional analytical methods.

Reusing substances or solvents

Item 8: Reuse (such as solution after crystallization or filtered solution) of
Substances used for the reaction Products in process or active pharmaceutical ingredients Can be done if followed
Approved practices and recycled materials meet the appropriate requirements for their intended use.
put to use

Item Solvents can be recycled and reused in the same process. or in the process
9 can be different if there is control and monitoring. To ensure that the solvent meets the specified standards.
before being used or mixed with other approved substances. 10 New

clause solvents, recycled solvents and reaction materials can be mixed.
can be combined in each production process If there are sufficient test results

clause ÿÿ Using solvents Solution after crystallization and other substances that are recycled must be
Save as a document

Shipping products

Article 12 Must quarantine and identify the identity of the product during production. or active pharmaceutical ingredients that
get it back

clause ÿÿ Must repeat the same process. Repeat with new process or destroy as appropriate
For products during production or pharmaceutical active ingredients that are returned If the storage conditions
Conditions during transportation or the container used for transport has questions about its quality

Article 14: Records of products during production must be kept. or active pharmaceutical ingredients that are returned every time
and the record must include

14.1 Name and address of the returnee.

14.2 Name, production model number and returned quantities of products in process or active ingredients
pharmaceutical

14.3 Reason for return

14.4 Use or disposal of products during production or pharmaceutical active substances returned

Section 15
Complaints and recalls

clause 1 All complaints related to quality, both verbal and or in writing, must be recorded and investigate according to the established procedures.

Section 2. The complaint record must include:

2.1 Name and address of the complainant

2.2 Name (and position, as appropriate) and telephone number of the complainant.

2.3 Nature of the complaint (Specify the name and production model of the pharmaceutical active ingredient) 2.4 Date the complaint was received.

2.5 Commencement of operations (including the date and name of the person who performed the action)

2.6 Following up on the results of operations

2.7 Notification of results to the complainant (including the date of notification) 2.8 Summary of final actions on production batches of products in process or active substances pharmacy

Item 3: Complaint records must be kept in order to assess trends in frequency. and the severity of the complaint along with comments on further amendments. And in some cases, corrective action must be taken to prevent it from occurring. Repeat the problem immediately as appropriate.

Clause 4: Written procedures must be prepared. It specifies the circumstances in which a product must be recalled. during production or pharmaceutical active substances

Article 5: There must be a procedure for recalling products, which includes:

5.1 Person responsible for evaluating data 5.2 Initial methods for retrieval

5.3 Who must receive recall information?

5.4 Methods for dealing with recalled items

Article 6 In the case of a serious incident or is life-threatening, must notify the Office of the Commission. The Food and Drug Administration and/or the drug control authority of every country to which the product is being sent should be informed immediately.

Section 16

Outsourcing production and outsourcing analysis

clause 1 contract manufacturer and analysis must follow the principles of the criteria and methods of production. Specified in this announcement of the Ministry of Public Health and special attention must be given to preventing cross-contamination.
and traceability

Article 2: The employer must evaluate the contractor. To ensure that the contractor complies with the principles and methods of production. Especially in relation to the contractor's premises.

Article 3: An employment contract must be made between the employer and the contractor. which must determine responsibility regarding Criteria and methods for production Including quality measures of each party. Clause 4: The employment

contract must specify that the employer can inspect and evaluate the contractor's work location. To ensure compliance with the principles and methods of production. Including specifying that the contractor agrees to
Food and Drug Administration You can also go in and check.

Clause 5: The contractor is prohibited from hiring third parties for the work he hires as specified in the contract unless there is Evaluation and approval of the agreement by the employer first.

Item 6: Production and analysis records must be kept at the activity location. and is ready for inspection. Clause 7. Must not make

changes to processes, equipment, testing methods, specifications, or other agreements as specified in the contract. unless notified to the employer and received approval of such change.

Section 17
Agents, brokers, traders distributor Repackers and relabelers

Enforcement

clause 1 This section applies to sectors that are not direct producers. which may conduct commercial business and/or enter into Ownership of repackaging, labeling, handling, shipping, or storing active pharmaceutical ingredients. or products During production

Article 2: Agents, brokers, traders All distributors, packers, or re-labelers must Follow the rules and procedures for producing medicines as specified in this announcement of the Ministry of Public Health.

Traceability of shipments of active pharmaceutical ingredients and products in process

Article 3: Agents, brokers, traders Distributors, repackers, or relabelers must keep Information that can be and complete acceptance of the delivery of active pharmaceutical substances. and products during production examined by preparing and keeping documents for inspection. The information includes:

3.1 Name of manufacturer

3.2 Address of the manufacturer

3.3 Purchase order

3.4 Shipping documents

3.5 Product receipt documents

3.6 Original name or name? Newly established names of psychoactive Is it the result? Products in process substances 3.7 Manufacturer's batch number

3.8 Transportation and delivery records

ÿ.ÿ Certificate of all analysis results (including from the manufacturer) that is the original. 3.10 The date the retest is due or the expiration date.

Quality management

Article 4: Agents, brokers, traders Distributors, repackers, or relabelers must prepare document system and implement effective quality system management As specified in Chapter 2 Administration Manage quality

Repackaging and labeling and storage of active pharmaceutical ingredients and products

During production

Item 5: Repackaging and labeling And the storage of pharmaceutical active ingredients and products during production must be in accordance with the criteria and methods of production specified to avoid mixing and having a negative effect on the identification or purity of the pharmaceutical active ingredients or Products in process

Clause 6: Packaging must be carried out under appropriate environmental conditions. To avoid contamination and cross contamination

Stability

Article 7: A stability study must be carried out to determine the expiration date. or the date the retest is due. If active pharmaceutical ingredients or products in process are packaged in different types of containers than those of the manufacturer

Forwarding

information, Section 8: Agents, brokers, distributors, repackers, or relabelers must report quality information. or legally required information received from the manufacturer of the active pharmaceutical ingredient. or products in process of production to customers, including from

customers to manufacturers. Article 9: Agents, brokers, traders Distributors, repackagers or relabelers must provide the customer with the name of the manufacturer and the delivered lot number of the active pharmaceutical

clause ingredient or product in process. 10 Agents must provide the name of the manufacturer of the active pharmaceutical ingredient or product. During production Food and Drug Administration Upon request, manufacturers can notify the Food and Drug Administration directly or through an authorized person. It depends on the legal relationship between the producer and delegation of authority

11, Topic Certificate of Analysis Results contained in Section

Management of information Complaints and Chargebacks

Article 12 Agents, brokers, traders Distributors, repackers, or relabelers must store Record details of complaints and recall of all matters according to Chapter 15, Complaints and Recall.

Article 13 If there is reasonable cause, agents, brokers, traders Distributors, repackers, or relabelers must work with manufacturers of active pharmaceutical ingredients. or products during production, review complaints that occurred to determine additional measures together with customers and/or the Food and Drug Administration investigation Finding the cause of complaints or recalls must be done. and recorded by the appropriate person.

Article 14 In the case where the complaint concerns the manufacturer of a pharmaceutical active ingredient. or products during production, various records kept by agents, brokers, traders Distributors, repackers, or relabelers must have information provided by the manufacturer. (including date and information carried out)

Product management Products that

are returned, Item 15. Products that are returned must be processed as specified in Section 14, Topic: Returned Products, Item 14, Agents, Brokers, Traders. Distributors, repackers, or relabelers must keep Documentation of active pharmaceutical ingredients and products in process that were returned

Section 18

Specific requirements for active pharmaceutical substances produced by cell culture methods or fermentation

General

Principles 1 The purpose of this Article is to establish specific control methods for pharmaceutical active substances. or in-process products produced by cell culture or fermentation using natural or recombinant organisms. Traditional fermentation principles for the production of small molecules. and for the process used Natural or hybrid organisms that produce protein. and/or polypeptides use the same principles, although the level of control is different. In general, the biotechnological processes used to produce proteins and Polypeptides have a greater degree of control than traditional fermentation processes. Section 2:

Biotechnology processes (biotech) refer to the use of cells or living organisms that have been produced or modified by DNA technology. mixed line Hybridization or other technology to produce active pharmaceutical substances. Active pharmaceutical substances produced by biotechnology processes contain substances that There are large molecules such as proteins and polypeptides while small molecule active pharmaceuticals such as antibiotics, amino acids, vitamins and carbohydrates. They can be produced using recombinant DNA technology. The level of control of the production of active pharmaceutical ingredients is similar to that used in the fermentation process. traditional method

Item 3: Fermentation using traditional methods means a process that uses naturally occurring microorganisms and/or Modified by traditional methods (e.g. irradiation or chemical mutagen) to produce active pharmaceutical substances. Active pharmaceutical substances produced by fermentation by traditional methods are generally Products with small molecules such as antibiotics, amino acids, vitamins, and carbohydrates

Clause 4 Production of pharmaceutical active substances or products in process of production from cell culture or Fermentation involves biological processes such as cell culture or extraction. and making the obtained objects From living things there is purity. This method may involve additional processes such as physicochemical modification, which Part of the production process Raw materials used (e.g. cultured food Buffer components) may cause the growth of contaminating microorganisms depending on the raw material source. Method of preparation and the purpose of use of Active pharmaceutical substances or products in process Controlling existing infections Virus contamination and/or endotoxins during production and appropriate process monitoring at each step may be necessary.

Article 5: Appropriate control must be provided at every step of production. in order to ensure the quality of Products in process and/or active pharmaceutical ingredients The criteria documents in this section cover raising Cells and fermentation It started with using cell bank bottles in production. However, the preparation first Actual work (such as cell banking) must be performed under appropriate control procedures.

Article 6: Production equipment must be used. and have appropriate environmental controls in place to reduce the risk of Minimize contamination. Environmental quality acceptance criteria and the frequency of monitoring must Depends on the steps in the production process. and production operating conditions (such as open systems, closed systems, or containment system)

Section 7: Process control must be controlled as follows:

7.1 Proper maintenance of a working cell bank.

7.2 Cultivating and expanding the number of germs appropriately

7.3 Control of critical parameters during fermentation or cell culture.

7.4 Monitoring the growth and survival processes of cells (for the cultivation process cells) and produce as appropriate

7.5 Procedures for harvesting and purifying in the process of separating cells, dead cells and The components of cell culture media must at the same time protect the product during production. or active substances pharmaceuticals from contamination (especially microbial contamination) and loss of quality

7.6 Monitoring of existing infections and endotoxin levels (if necessary) to keep them at appropriate levels. In the process of production

7.7 Safety considerations from virus contamination As specified in ICH Guideline Q5A Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

Item 8 must demonstrate the appropriateness of eliminating the components of the culture medium, the protein of host cell Impurities involved in the process Impurities related to Products and contaminants

Cell Bank Maintenance and Record Keeping

Article 9: Access to the cell bank must be limited to designated persons only.

clause ÿÿ Cell banks must be stored under specified conditions. To maintain cell survival and prevention of contamination

clause ÿÿ Records of vial (vial) use must be maintained from the cell bank and storage conditions maintained.

Article 12 Cell banks must be monitored periodically as appropriate. to check whether there is still suitable for use

clause 13 Follow what is specified in the ICH Guideline Q5D Quality of Biotechnological. Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products for a more complete discussion of cell banking

Cell culture/fermentation

Item 14: If necessary, use of sterile techniques of cell substrates, food

Raising buffer cells and gases must use a closed system or storage system. If cultures are grown in the starting container, cell transfection

Or the addition of additional substances (such as cell culture media and buffer) in open containers must be controlled and there must be a method.

Take steps to reduce the risk of contamination.

Item 15 If microbial contamination affects the quality of the pharmaceutical active ingredient. Operation

in open containers must be carried out in a biosafety cabinet. or operated under the same level of controlled environment.

Article 16 Personnel must dress appropriately. And take special care in cultivating living things.

Item 17: Critical parameters (such as temperature, pH, and alkalinity) must be monitored. Stirring speed, gas addition,

pressure) to ensure consistency according to the specified process. Cell growth, survival, and productivity must be monitored. (For

cell culture processes) the critical parameters vary from

one process to another process and for the traditional fermentation process, some parameters (such as

cell survival) may not need to be monitored.

Article 18 Cell culture tools must be clean. and sterilize after use

As for fermentation tools, they must be cleaned, disinfected or sterilized as appropriate.

Clause 19 Active pharmaceutical Before using the culture medium, it must be sterilized as appropriate. to maintain the quality of

substances Clause 20 Appropriate procedures for checking contamination must be established. and determine the method

Take action to address detected issues. Including the need to have procedures in place to consider the effects of contamination.

on the product and in decontamination of equipment before use in the production of the next batch. If living things are found

Foreign substances in the fermentation process must be specified. and must evaluate the impact on the quality of

product if necessary The results of such assessment must be taken into account in considering methods for dealing with the problems that arise.

Article 21 Must maintain records of contamination that has occurred.

Article 22 If tools are used together to produce many types of products. Further testing is required accordingly.

Suitability after cleaning To reduce the risk of cross-contamination during product production.

Continuously separated by production time (campaigns)

Harvesting, Sorting and Purifying

Article 23: Steps in harvesting cell removal or cell components or storage

Cell components after cell rupture Work must be performed in tools and areas designed to minimize risk.

of contamination

Article 24: There must be procedures for harvesting. and purification by eliminating or destroying the effect

of microorganisms used in production Cell debris and components of the culture medium (while trying to reduce

decomposition, contamination, and loss of quality) adequately to ensure that products during production or pharmaceutical active substances that are recycled have consistent

quality. Item 25. Tools and equipment must be clean. correctly as appropriate There is disinfection. After using continuous production for several generations, production without cleaning can be done if there is no damage or impact on the quality of the product during production. or active pharmaceutical ingredients

Article 26 If an open system is used Purification must be carried out under appropriate environmental conditions in order to maintain

product quality. Section 27. Other additional controls such as the use of resin chromatography. or additional specific testing This may be appropriate if a combination of tools is required for multiple products.

Virus elimination/destruction steps, item 28,

shall be performed as specified in ICH Guideline Q5A Quality of Biotechnological.

Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin for more specific information

Article 29: Disposal procedures and inactivation of the virus is a critical process step for some processes and must follow validated parameters. Section 30: Appropriate precautions must be followed. To

prevent the possibility of virus contamination from the moment Before and after the process of eliminating or destroying the virus. Therefore, the process of an open system must be carried out in an area that is The proportions are separated from other activities and there is also a separate air

clause system. 31 The same equipment is not normally used for different purification steps. However, if it is necessary to use the same equipment Tools must be properly cleaned and disinfected before reuse, and appropriate precautions must be taken to prevent the possibility of the virus being carried to other areas (e.g. via equipment, etc.). or environment) from previous steps

Section 19
Active pharmaceutical ingredients used in clinical trials

General principles

development. 1. Other Some of the preceding items may not be appropriate to use during

controls. 1. In the production of new pharmaceutical active substances used for

clinical trials. 2. Controls used in Production of active pharmaceutical ingredients used for clinical trials. Must be consistent with the development process for products containing active pharmaceutical ingredients. Manufacturing processes and testing methods must be flexible to allow for change as knowledge of the process increases and experimental testing occurs. The clinical phase of a medicinal product progresses from the pre-clinical stage to the clinical trial stage, when drug development progresses to the stage where the active pharmaceutical ingredient is taken to produce a usable medicinal product. for clinical trials Manufacturers must ensure that active pharmaceutical ingredients are produced under cover. Facilities location Production operations and appropriate co

quality

Item 3: The principles of production criteria and methods must be applied to suit the production.

Active pharmaceutical ingredients used for clinical trials Using an appropriate mechanism for releasing it through production batches.

Item 4: There must be a quality unit that is independent from the production department. to perform the function of releasing or not passing through the active ingredients Pharmaceutical products used for clinical

trials in each production batch. Item 5. Duty to perform certain testing steps normally performed by quality agencies. Can be practiced by Other departments of the organization

Item 6: Qualitative measures must include testing systems, raw materials, and product packaging materials during production. and active pharmaceutical ingredients. Item

7: Process and quality problems must be evaluated. Item 8. Labeling of active

pharmaceutical ingredients used for clinical trials must be properly controlled and must indicate the substance used. for clinical trials

Tools and facilities

During the clinical development phase Including the use of facilities or item 9, small laboratories for the production of active pharmaceutical substances used for clinical trials. There must be a method. Practice ensuring that equipment is calibrated, clean, and fit for its intended use.

clause 10 Facility use procedures must ensure that objects are handled in Characteristics that can reduce the risk of contamination and cross-contamination

Control of raw materials

clause 11 Raw materials for the production of active pharmaceutical ingredients used for clinical trials must be evaluated by testing or receiving analytical results from the supplier. And there is additional identity testing. If the raw material is a hazardous substance, there must be sufficient analysis data from the supplier.

Item 12. In some cases, small-scale production requires an evaluation of the suitability of the raw materials before using them together. with testing and analysis

production

13 The production of active pharmaceutical substances used for clinical trials must be recorded in the laboratory records and production records. or other appropriate methods They must record information on the use of objects used in production, tools, processes, and observations.

Article 14 The expected output from production may be more or less different than the expected output. in the production process for commercial use This may not require an investigation to find the cause.

Verification of accuracy No.

15 Normally, the process of verifying the correctness of the production of pharmaceutical active substances used For clinical trials it would not be appropriate. If only one model is produced or has changed Processes during the development of active pharmaceutical ingredients which makes the production process repetitive Traditionally difficult to achieve, appropriate control, calibration, and certification of equipment will ensure quality. of active pharmaceutical ingredients during

the development process. Item 16. Validation of the process. Must proceed in accordance with the requirements in Chapt Validation In the commercial production version Model produced in prototype production size. and small production models

change

Article 17 Changes are expected during development. Due to learning and expansion of production scale, every change that occurs in the production process, specifications, or testing methods must properly recorded

Control in the laboratory No. 18 If

the analytical method used to evaluate the production version of the active pharmaceutical ingredient used for Clinical trials have not been validated. There must be a valid academic reason to support it.

Article 19: There must be a system for collecting backup samples of every production batch to ensure that there is a certain amount of each batch. Sufficient backup samples are stored for a reasonable period of time after approval of termination or discontinuation of the trial. Clinical

Item 20: Determination of expiration date and retest date as specified in Chapter 11, topic: Determination of expiration date. and retest date It applies to active pharmaceutical substances used in clinical trials, but does not apply to new active pharmaceutical substances in the initial stages of clinical trials.

Document operations

Article 21: There must be a system to ensure that information generated during development and production of biologically active substances Pharmaceuticals used for clinical trials are documented.

Article 22 Development and analytical methods used to support release of production batches of biologically active substances. Pharmaceuticals used for clinical trials must be properly recorded.

Article 23 A production record keeping and control system must be established to ensure that information and documents are stored for an appropriate period of time after release.

Section 20

Definition of words

Acceptance Criteria means a numerical limit, range, or other measurement value that is appropriate to use as a criterion for accepting test results. **pharmaceutical active**

substances (or drug substance) [Active Pharmaceutical Ingredient (API) (or Drug Substance)] means a single substance or mixture intended to produce a drug product, which such substance is an important substance that has pharmacological action. or has the effect of curing, mitigating, curing, preventing disease, or causing an effect on the health, structure, or functioning of any function of the human or animal body, or causing Implications for diagnosis

Starting material of pharmaceutical active ingredients (API Starting Material) means raw materials, products in process of production. or pharmaceutical active substances used in the production of pharmaceutical active substances and which are part of the main structure of the pharmaceutical active substance. The starting material of the pharmaceutical active substance may be a commercially available substance. or can be purchased from one or more suppliers under contract. or a trade agreement or an object that is produced by oneself Normally, the starting materials of pharmaceutical active ingredients are specified. Chemical properties and structure

clearly specified, **production batch or time of receipt/production [Batch (or Lot)]** means a specified quantity of an object which is produced in one process or continuous processes. Therefore, it is expected to be homogeneous within the

specified limits. In the case of continuous production, it may be necessary to divide the production batch into smaller batches. The size of the batch can be determined by exact quantity or production volume over a fixed period of time

Production model number [Batch Number (or Lot Number)] means a number, letters and/or symbols that indicate the batch or the time received or produced which can be used for tracking. Production and transportation history information is available. **Bioburden** means the level and

type of microorganisms (i.e., microorganisms that are accepted or unacceptable) which may be found in raw materials Precursors of pharmaceutical active ingredients Products in process of production or active pharmaceutical ingredients The presence of germs is not considered contamination. Except the amount exceeds the specified limit. Or is it a microorganism that Don't accept

Calibration means showing that a specific instrument or device provides results. Performance is within the limits established by comparison with a reference standard. or standards that can be traced back within the appropriate range for measurement

Computer system means a group of hardware components and

Related software which are designed and assembled for use in work or group of work

computer based system (Computerized System) means a process or operation. that is integrated with the computer system

Contamination means the mixing of impurities of chemicals. Natural microorganisms or foreign substances introduced into raw materials Products in process and active ingredients pharmaceuticals during production, sampling, packing, repackaging, storage, or transportation. **Contract Manufacturer** means a manufacturer that performs the

production methods. Some parts are on behalf of the original manufacturer. **Critical** means a description of the steps. and production

process conditions, testing requirements, or other related parameters. or other topics that must be controlled according to the criteria that have been established in order to Ensure that the quality of active pharmaceutical ingredients meets specifications. **cross contamination (Cross-**

Contamination) means contamination of raw materials or products. by raw materials or other types of products **Deviation** means a

difference from the approved or approved recommendations. Defined standards . **Drug (Medicinal) Product]** means the form of the

product contained in materials. Final packaging for sale in the market, **drug substance (Drug Substance),** see the word pharmaceutical active substance,

expiration date [Expiry Date (or Expiration Date)] means the date

specified on the container or label of the substance. The pharmaceutical active ingredient defines the period during which the pharmaceutical active ingredient is expected to remain active. Standard quality according to the requirements for the specified shelf life if stored under specified conditions and must not used after the specified date. **Impurity** means any

component that appears in a product during production.

or active pharmaceutical ingredients which are not intended to be present

Impurity Profile means the characteristics of impurity substances that are mixed in pharmaceutical active substances which can prove identity and which cannot prove identity

Control during the production process (or process control) [In-Process Control (or Process Control] means inspection during production operations to monitor and, if appropriate, to adjust the process. and/or to ensure that the product is received during production or active substances Pharmacy according to regulations **Products in process (Intermediate)**

means a substance produced during the process of The process of producing active pharmaceutical ingredients in which the molecular level has been changed. or purification Before becoming a pharmaceutical active ingredient which products during production may be separated or not separated (Note: The announcements in this section apply only to in-process products that are produced after the manufacturer Defined as the starting point for the production of pharmaceutical active substances) **Production model or the time**

received/produced (Lot) See the production

model. **Production lot number (Lot Number)** See the production model number.

Production (Manufacture) means every operation related to receiving objects. Performs the manufacturing, filling, repackaging, labeling, relabelling, quality control, release, storage, and delivery of pharmaceutical active ingredients. and other related controls

Material means a general term used to denote raw materials. (original object substances used for reactions, solvents), substances that help in the process Products in process Active pharmaceutical ingredients Packing material and label materials

crystallization (Mother, crystallization **Liquor)** means the remaining liquid after **Solution after** process or separation process The post-crystallization solution may contain unreacted substances, products of the production of the active pharmaceutical substance. and/or impure substances. The solution after crystallization may be used in other processes.

Packaging Material means any material used to protect products during production. or active pharmaceutical substances during storage and transportation. **Procedure (Procedure)**

means a document describing operations, precautions, and measures taken both directly and indirectly related to Produce in-process products or active ingredients
pharmaceutical

Process Aids means substances (except solvents) used to assist in production. Processed products or active pharmaceutical ingredients that are not involved in chemical or biological reactions (e.g. filtration aids, charcoal powder)

Process Control (Process Control) See control during the production process. **Production**

means all operations involved in preparing pharmaceutical active substances Starting from receiving the object through to the production process. and packaging of biologically active substances
pharmacy

Verification (Qualification) is installed It means to prove and prepare documents to confirm that tools or systems. Verification is properly. Is working correctly and get the results as expected. Various additional part of the verification. But verification of each step alone does not validate the process. **Quality Assurance [Quality Assurance (QA)]** means the sum of the

management that has The objective is to ensure that active pharmaceutical ingredients are of the quality for their intended use. and still remains
Quality system

Quality control [Quality Control (QC)] means inspection or testing according to requirements.

Quality unit [Quality Unit(s)] means a unit that is independent of production operations. Have responsibilities Covers both quality assurance and quality control. This may be separate quality assurance and quality control units or combined. It depends on the size and structure of the organization.

Quarantine means the state of objects being separated by physical means.
physical or other effective means while waiting for the decision to pass or fail

Raw Material means a general term that represents the starting material. Reactive substances and solvents used for the production of processed products or active pharmaceutical

ingredients. **Primary reference standard (Reference Standard, Primary)** means a substance that shows the results of analysis and testing to be an authentic substance with high purity. which may be obtained by any of the following methods: (1) obtained from

officially recognized sources (2)

prepared by synthesis (3) obtained from the production

of substances that have Highly pure substances that already exist.

(4) Prepared by purifying substances that are already in production. **Secondary reference standard substance (Reference Standard, Secondary)** means a substance having the quality and purity as specified. This is shown by comparing with primary reference standards and using It is a reference

standard substance for routine laboratory analysis. **Repeating the same process (Reprocessing)** means taking products during production or Active pharmaceutical ingredients whose quality does not meet standards or specifications are returned to the process and the crystallization step is repeated. or other appropriate chemical and physical steps [such as distillation, filtration, chromatography [Chromatography, Grinding] which is part of the production process specified only for Steps of a continuous process After testing and controlling during production It was found that the production process Incompleteness

is considered a normal process and is not a repeat of the same process. **Retest Date** means the date on which the object m
It is appropriate to use

Reworking means using products during production or active pharmaceutical ingredients that do not meet the standards. or specifications through a production process that is different from The same process in any step or one or more steps (such as recrystallization with a different solvent) to obtain a product in process or active pharmaceutical substance of acceptable quality. Signature (signed) **[Signature (signed)]** See

definition Signature **Signature (signature) [Signed (signature)]** means a

record of each person who performs Practice or review of a particular matter. This note may be an abbreviation. Full signature, seal, or signature Correct and safe electronic **equipment. Solvent** means an inorganic or organic liquid used as a solvent for

Prepare the solution or liquid suspension in the production of products in process or active pharmaceutical substances. **Specification** means a list of tests that refer to methods of analysis and Appropriate acceptance

criteria that include numerical limits, ranges, or other criteria for specified tests. A specification defines a set of criteria that an object must satisfy in order to be considered acceptable for its purpose.

In use, the term “conformity” means that an object satisfies acceptance criteria when tested. according to the topic in the specified analysis method

Verification (Validation) means that the documented program shows that There is quality assurance at a high level of confidence. which process, method, or system will produce results according to Criteria that are regularly set

Validation Protocol means an action plan. written document specifying verification methods and acceptance criteria, such as a protocol for A manufacturing process that specifies the tools used in the process. Critical process parameters/operating range Product characteristics Sampling Storage of test data Number of inspections, accuracy, and acceptable test results. **Expected yield (Yield, Expected)** means the amount of substance or percentage of

the yield. This is theoretically expected at any reasonable stage of production. Based on laboratory data Prototype production model information or past production information

Theoretical yield (Yield, Theoretical) means the quantity that can be produced at any appropriate stage of production. which depends on the amount of substance to be used without any wastage or error in production

Main Criteria and w Methods for producing medicine

Appendix

Attached to the Ministry of Public Health announcement

is the determination of details regarding the criteria and procedures. Method of production and

Current traditional medicine and amendments to add criteria for methods of production

traditional medicine according to the law.

2016

Appendix 1

Production of sterile medicine

Principle

The manufacture of sterile medicines requires special additional requirements to minimize the risk of contamination.
of microorganisms, particles, and pyrogens, with emphasis on the correct skills, training, and attitude of
Related personnel Quality assurance is especially important. and the production of this type of drug product must be carried out
Strictly following the prescribed preparation methods and procedures that have been verified. Reliability depends on every process. at the end of
in the absence of trace quality of work the production or testing
elements Ready-made pharmaceutical products only

Note: The regulations in this appendix do not detail methods for detecting microorganisms and levels of cleanliness.
of air and surface by referring to other documents such as standards of EN/ISO (International Organization for
Standardization)

General requirements

clause ÿ Sterile medicine production must be done in a clean area. Entrance for operators entrance for
Tools, starting materials or packaging materials must pass through the airlock. Clean areas must be maintained to a standard of cleanliness.
appropriate and the air supplied must pass through a filter with appropriate efficiency.

Item 2: Work in preparing components Product preparation and packaging must be done in an area that
Separated into separate areas within a clean area. Production operations are divided into two types. The first type is also production.
The process of making the product sterile in the final step (Terminally sterilized) and the second type is Production by a sterile process (Conducted
aseptically) in some steps or all steps of production.

Item 3: Clean area for the production of sterile medicines. Divided according to the specified characteristics of the environment.
Each production process requires an appropriate level of environmental cleanliness in the power state.
Work so that there is minimal risk of contamination of particles or microorganisms in products, objects or packaging materials.

Clean area for manufacturing sterile medicines Must be designed and verified to be level.
Air cleanliness as required by the state “At Operation (In operation)” The “In operation” status is a rest)” In order to achieve the status of "
condition in which the system is

installed and activated. along with work
of production tools But there were no workers in that area.

The “running” state is a state in which the installed system is activated according to the specified instructions.
along with the specified number of workers working on the job

Status must be determined. “Operating” and “Not Operating” status for clean rooms

Each room or group of clean rooms

The sterile drug production area is divided into 4 levels.

Level A: This is a specific area for high-risk operations, such as packing areas,

Container for rubber stoppers Area where the ampoule and vial are open The equipment assembly area is sterile as usual. This condition can be achieved by using Laminar Air Flow. The Laminar Air Flow system must have a constant wind speed.

Consistent in the range 0.36 - 0.54 meters/second at the working position which must demonstrate maintenance of the condition

The air flow is parallel and verified.

Isolators and work booths with gloves Air flow may be used in the same direction.

(Uni-directional air flow) and use a lower speed.

Level B: This is an environmental area for Level A areas used for preparation and packaging.

By a sterile process

Levels C and D: Clean areas for critical production of sterile medicines.

less

Classification of clean rooms and clean air equipment

Article 4 Classification of clean rooms and clean air equipment Classified according to EN/ISO 14644-1, with cleanliness levels clearly separated from monitoring of environmental conditions while work is in progress. Quantity

The maximum allowable airborne particles at each level are shown in this table.

	Maximum number of particles allowed in 1 cubic meter of air that are the size of a frog or larger than specified.			
level	**Not operating (at rest) In operation (in operation) 0.5 micrometers5.0 micrometers**			
	0.5 micrometers 5.0 micrometers			
A	ÿ,ÿÿÿ	ÿÿ	ÿ,ÿÿÿ	ÿÿ
B	ÿ,ÿÿÿ	ÿÿ	ÿÿÿ,ÿÿÿ	ÿ,ÿÿÿ
C	ÿÿÿ,ÿÿÿ	ÿ,ÿÿÿ	ÿ,ÿÿÿ,ÿÿÿ	ÿÿ,ÿÿÿ
D	ÿ,ÿÿÿ,ÿÿÿ	ÿÿ,ÿÿÿ	Not specified	Not specified

Item 5: For Class A classification, the air sample volume must not be less than 1 cubic meter per

Sampling position

Level A The amount of airborne particles in accordance with ISO 4.8 is determined by the limits.

Particle size equal to or larger than 5.0 micrometers

Level B (No operations) Number of particles in the air of both sizes (0.5 and 5.0 micrometer) in accordance with ISO 5 standards.

Level C (No operations and operations in progress) The number of particles in the air shall be as follows. According to ISO 7 and ISO 8 standards respectively.

Level: Good (No operations) Number of airborne particles according to ISO 8.

For the purposes of classification according to the methods in EN/ISO 14644-1 specifying both Minimum number of sampling locations and sample size This depends on the limit of the largest particle size at each level and how the obtained data is evaluated.

Article 6 Classification of clean rooms and clean air equipment Portable with A particle counting machine should be used. short sampling pipe length This is because remote sampling systems with long pipes will have a high retention rate. of particles with sizes equal to or larger than 5.0 micrometers. Systems with air flow in the same direction should be used. Isokinetic sample heads. Item 7. Classification in state. “Operating” may be

displayed during normal simulation operations.

Operation or during the creation of a media film by simulating the worst case scenario. The requirements of the EN/ISO 14644-2 standard include test data to demonstrate continued compliance with specified cleanliness levels.

Monitoring of clean rooms and clean air equipment

Item 8: Clean rooms and clean air equipment must be inspected regularly while work is in progress. and the location of monitoring depends on the risk analysis study. and the results obtained during the classification of

Clean room and clean air equipment

Item 9: For Level A areas, particles must be monitored throughout the duration of the critical process, including Assembly of tools Unless there is reason to support that in cases where contamination in the process may cause the particle counter Damage or danger, such as danger from living microorganisms And the danger from radiation in such cases must be monitored. During tool assembly, before commissioning, before exposure to risks Must be monitored during

Simulation of operations as well The appropriate frequency and sample size must be determined for monitoring. Level A area for work interruption events Events with temporary interruptions, such as power outages and in the event that the system is damaged Detection and alarm shall be provided in case the particle exceeds the warning limit. During packing, it may not be possible to control particles equal to or larger than 5.0 micrometers to a low level. The filling position is achieved due to the formation of small liquid particles or droplets from the product itself.

clause 10 A similar system shall be used to monitor particle size in level areas. B. Although the frequency of Random inspections may be reduced. The importance of a particle monitoring system depends on its effectiveness in separating the area. Between adjacent Levels A and B, Level B areas shall be monitored with appropriate frequency and sample size.

that can detect changes in contamination levels and system damage and sending warning signals

In case the particles exceed the warning limit

clause 11 An airborne particle monitoring system may consist of particle counting equipment of a type separated into

An independent, or sampling point type is a series of networks connected to a single particle counting device.

or use both types together System selection must be appropriate to the particle size to be measured. In the case of using the system

Long-distance sampling requires consideration of length. and the radius of curvature of the pipe which causes the residue of particles in the pipe

Choosing a monitoring system must take into account the risks arising from starting materials used in the production process, such as starting materials.

related to living microorganisms or radiopharmaceuticals

Item 12 The sample size for automated monitoring depends on the sampling rate of the system in use. The sample volume is not

necessarily equal to the cleanroom classification volume, and

clean air equipment

clause ÿÿ In Level A and B areas, monitoring the number of particles equal to or larger than 5.0.

Micrometers are an important indicator of early failure in cleanliness levels. Sometimes the test results

The number of particles equal to or larger than 5.0 micrometers may be incorrect. due to electrical noise

Abnormalities of the light beam or the aggregation of small particles Continuous detection of small amounts of particles or

regularly is an indicator of the possibility of contamination. and must investigate to find the cause. Such cases may indicate

Air system failure Failure of the filling machine or inappropriate practices during setting up the machine and

Routine work performance

Article 14 After completing work and there were no workers in that area. The particle count must return to its normal state.

“No operations” as specified in the table Within a period of 15 - 20 minutes (Clean up period)

Item 15: Inspection and inspection in Level C and D areas while performing work. To be carried out by taking into account

Principles of quality risk management. Requirements, warning limits and operating limits depend on the nature of

Operation but must be able to return to the status “No operations” within 15 – 20 minutes (Clean up period)

Article 16 Determination of other characteristics such as temperature and relative humidity depends on the product and its characteristics.

Operation These parameters must not affect the required cleanliness standards.

It

Article 17. Performing work in each area Each level of cleanliness Shown according to the table below

level	operation of the final product. This steps in the that
A	Pack products when there is more risk than normal.
	Prepare solutions when there is more risk than usual and product packaging
CD	Prepare solution and components for filling.

level	Operations for commercial products treated by a sterile process
A	Prepared and packaged using a sterile process.
	Prepare the solution before filtering.
CD	Handling components after washing

Clause 18 Work operations using sterile activities must be inspected regularly. which can be done

There are many methods, such as placing petri dishes. air sampling and surface sampling, such as the swap method.

(Swabs) and the use of contact plates

The sampling method used must not affect the level of cleanliness of the sampling area. The results from

Monitoring shall be taken into account when reviewing production records for release of finished drug products.

Monitor surfaces and workers after working in critical areas. and must be monitored

Chapter additional work beyond production operations, such as after system validation,

Cleaning and disinfection

Article 19 Limits for microbial monitoring of clean areas during work.

Limits for microbial contamination (g)				
level	Random weather sampling Colon/Licot u m.	Placing food plates culture (Center diameter 90 mm) colon/4 hours (b)	touch plate (Center diameter 55 millimeters) Colon/Nijan	Print Tongmu Quantity: Nwi 5 colonies/glove
A	<ÿ	<ÿ	<ÿ	<ÿ
B	ÿÿ	ÿ	ÿ	ÿ
C	ÿÿÿ	ÿÿ	ÿÿ	
D	ÿÿÿ	ÿÿÿ	ÿÿ	

Note: This (g) is an average.

(b) Each petri dish may be exposed to air for less than 4 hours.

Article 20: Warning limits must be set. and appropriate operating limits for particle monitoring results.

and microorganisms if these limits are exceeded. Corrective action must be specified.

Isolator Technology

Item 21: Using isolator technology to reduce the need for workers to be in the production process area.
which results in products produced by the process being sterile. Can reduce the risk of microbial contamination from
environment significantly Isolators and equipment for passing objects into and out of the isolators to reduce
There are many types of contamination. The isolator and surrounding environment must be designed to ensure consistent air quality.
with the requirements of the said area Isolators are made from a variety of materials and are subject to varying degrees of cracking and
leaking. There are many different types of equipment for delivering objects into and out of the isolator. From a single door to two doors designed to
It is a completely closed system. along with a mechanism to make it sterile

Point 22: Care must be taken when transporting goods into and out of the isolator, which is one of the causes of contamination.
In general, the area inside the isolator is a high-risk area for operations. Because of the area
The operation of all these devices may result in improper air flow. Laminar No. 23 The level of

air cleanliness for the environment in which the isolator is located depends on its design.
and the use of isolators which must be specifically controlled. For isolators in sterile processes
Must be located in an area with at least a good level of cleanliness (D).

Article 24: The use of isolators must be properly verified. By considering the factors
All the crises of isolator technology such as Air quality inside and outside of the disinfection isolator
Loading and unloading process isolator and the integrity of the isolator

Article 25 The use of the isolator must be inspected regularly. and must have a leak test.
Isolator and glove system regularly

Blow molding technology Packing and sealing. Item

26. Blow molding machine for packing and sealing. It is a machine built for the purpose of performing work.
continuously within one machine Since the introduction of thermoplastic pellets into It must be formed into containers and then packed.
and sealing, all operated by one automatic machine.

A sealed filling blow molding machine used for aseptic process production which has a spray shower.
Air with efficiency level A may be installed in rooms with at least a level of cleanliness. C by the operator to use
Clothing used for Level A or B levels of germs and particles in the environment while “No operations” must be within specified limits.
For the current environment "Working" only includes the number of germs. Must be in
set limits Blow molding, filling and sealing machines used for production with final sterilization.
Must be installed in a room with at least a good level of cleanliness.

Item 27: Blow molding technology Filling and sealing Must take at least the following matters:

27.1 Design and verification of equipment

27.2 Verifying the accuracy and repeatability of spot cleaning

Clean-in-place and sterilization at the point of use (Sterile-in-place) 27.3 Environmental conditions of

the clean room where the equipment is located.

27.4 Training and clothing of workers

27.5 Check for interruptions in critical areas of the equipment. Including assembly

parts by aseptic method before starting packaging.

Final sterilization products

Article 28 Most preparation of components and products must be done in an environment of at least a good level.

So that there is little risk of microbial and particulate contamination. including being suitable for filtration and purification
Continue to be sterile.

If the product is more at risk of microbial contamination than normal, e.g. Products that cause microorganisms
Easy to grow or must be kept for a long time before being sterilized or production processes that are not made in containers

Closed areas must be performed in a Class C environment.

Article 29 The final packaging of sterilized products must be done in an environment of at least level C.

Item 30 Products that are at higher than normal risk of contamination from the environment, such as packaging operations that

Must do it slowly or the container has a wide mouth or need to be exposed to environmental conditions for more than 2 - 3 seconds

before sealing Must be contained in a Class A area in a Class A environment. C at least

Preparation and packaging of ointments, creams, suspensions and emulsions shall be done under

Environment level C before sterilization in the final step.

Products prepared by a sterile process Washed components

clause ÿÿ must be stored in at least a good environment. The starting material and
Sterile components, if they are not sterilized or filtered for sterility in further processing, must be

in level A cleanliness in a level B environment

Item 32: Preparation of solutions that are sterilized by filtration during the production process must be done in

Environmental conditions C, but if not filtered, the starting materials and products must be prepared at level A cleanliness.
In a level B environment

Article 33 Processing and packing of products prepared by the sterile process must be done in a clean manner.

Level A in a Level B environment

Point 34: Before closing the rubber stopper tightly. Moving products packed in containers that are not completely closed, such as in the case of freeze drying. Must be done in level A cleanliness in a level A environment. B or if placed in a tray for Closed transport must be done in Class B environment.

Clause 35 Preparation and packaging of sterile medicines such as ointments, creams, suspensions, and emulsions when the product has been exposed to air and has not been filtered afterwards. Must be done in a level A cleanliness environment in a level B environment.

Personnel

No. 36: The number of workers in a clean area must be kept as low as necessary. especially During production by the sterile process, inspection and control must be done outside in a clean area as much as possible. Article 37: All workers Including

cleaning staff and maintenance staff working in the area Cleaners must receive regular training in the discipline related to correct manufacturing methods for the product. Sterile medicine Training should include knowledge of hygiene. and basic knowledge of microbiology, if any. Outsiders who have not received such training, such as those hired to maintain the building It is necessary to enter a clean area. Special care must be taken in giving advice and supervision. Item 38 prohibits workers whose work is related to the process of preparing laboratory animal tissue. or

cultivation Microorganisms not used in the ongoing production process enter the sterile drug production area. In addition to having practice According to the strictly and clearly specified procedures.

Article 39: There must be high standards regarding hygiene and cleanliness of workers. Related workers Personnel involved in the manufacture of sterile medicines must be instructed to report all conditions that may cause the release of contaminants. that have an abnormal amount or type, including periodic health examinations in such cases Action must be taken. with workers who may spread excessive microorganisms to the point of causing danger based on the decision of the assigned

expert. Article 40. Do not wear a wristwatch. decorations And do not use cosmetics in clean areas.

Article 41 Changing clothing and washing hands must follow the written procedures to reduce contamination. of work clothes used in clean areas or the introduction of contaminants into clean areas. Article 42 Work

uniforms and the quality of work uniforms must be appropriate for the process and level of cleanliness.
of the work area Work clothes must be worn in such a way as to protect the product from contamination. Item 43

Details of work clothes required for each level of cleanliness. are as follows

43.1 Level: Good, wear hair and beard covering. Wear appropriate coveralls and shoes. or use shoe covers Appropriate measures must be taken to avoid foreign contaminants from entering the clean area.

43.2 Level C: Wear a covering over the hair, mustache and beard. Wear a shirt and pants together or two separate shirts and pants. The shirt must fasten the wrists and cover up to the neck. Wear appropriate shoes or shoe covers. Clothing must not release fibers or particles.

43.3 Level A or B wear a head covering to keep hair in check. The mustache and beard should completely cover the tip of the head covering. It must be inserted into the neck of the shirt. Wear a mouth and nose cover. Wear sterile plastic or rubber, powder-free gloves. Wear foot covers that have been sterilized or sterilized. The bottom of the pant leg must be tucked into the foot cover and the bottom of the sleeve into the glove. Clothing must not emit fibers or particles and retain particles released from the body. Item 44 Clothes used outside of the work area must not be brought into changing rooms that

lead to Level B and C rooms. All workers in Level A or B areas must change into clean, sterile clothing that has been adequately sterilized or disinfected each time they work. Gloves must be periodically used with disinfectant. during work Mouth and nose cover And gloves must be changed at least every time you go to work.

Article 45 Clothing used in clean areas must be cleaned. and take action to prevent contamination which will was released later Such operations must be carried out according to the procedures. Separate washing and cleaning equipment is required. Improper washing methods cause damage to the fibers. and increases the risk of particle release.

Buildings and

premises No. 46 Surfaces within clean areas must be smooth. Does not absorb water and not broken To reduce the release or accumulation of particles or microorganisms and must be resistant to cleaning fluids and disinfectants used.

Item 47. To reduce the accumulation of dust particles. and to be easily cleaned, there must be no corners that can be cleaned No, and wrinkled edges from walls, shelves cabinets and tools should be kept to a minimum. The door should be designed so that there are no corners that allow entry. cannot be cleaned, so sliding doors should not be used. No. 48:

The ceiling must be welded and closed tightly. To prevent contamination from the space above the ceiling.

Article 49 Delivery pipes, air pipes, and other open-ended pipes must be installed without creating corners. Openings that do not close completely, and Do not use materials with surfaces that are difficult to

clean, Section 50, in Level A or B areas used for production by sterile processes. There must be no sink for washing hands and drainage pipes. In other levels, air trapping devices must be installed between machines. or sink and wastewater pipes In clean areas lower than A or B, floor drains must be equipped with devices to prevent backflow.

Item 51 Changing rooms must be designed to be airlocks with separation for each step of changing. change clothes So that the clothing is contaminated by microorganisms and particles as little as possible. Must have a system Efficiently removes air from the room with filtered air.

The final changing room must be clean and in good condition. "No operations" equals the area where operations will be undertaken. In some cases, it may be necessary to separate the entrance and exit of the changing room, and hand washing equipment must be provided in the first step of the changing room only. Item

52: Do not open the airlock doors on both sides at the same time. Use an interlock system or a visible warning system or an audible warning system. To prevent opening more than one side of the door at

the same time, No. 53, air that is filtered and distributed into the room to maintain a higher room pressure level must have a direction of air flow to surrounding areas that have a lower level of cleanliness. In all conditions where work is being done and the air in the room must be expelled effectively. Adjacent rooms with different levels of cleanliness must

The difference have an air pressure of 10 - 15 pascals, especially in areas with the highest risk, namely in the surrounding environment where is in contact with the product and the cleaned components that come into contact with the

product. Recommendations regarding the air supply and differences in air pressure may need to be

Adjust as necessary in the case of certain substances, such as disease-causing substances and highly toxic substances. radioactive substances or starting object or products that contain live viruses or bacteria. It may be necessary to take action to dispose of the material. Contamination of facilities and treated air released from clean

areas. Item 54 must demonstrate that the air flow pattern does not create a risk of contamination, for example, care must be taken to ensure that the air flow does not cause dispersion. Particles from the source produce particles from personnel. Operation or machinery to areas where there is a higher risk to the product

be installed. Item 55: There must be a system to warn of abnormal hat is paid in, a difference measuring device must operation of the air. of air pressure between areas where the pressure difference in the area is important Including the need record differences in pressure. to regularly

tool

Item 56: The conveyor belt must not pass through the partition wall between the air cleanliness level A or B area and the production area with a lower level of cleanliness. Unless the belt is continuously sterilized, such as in a sterilization tunnel, item 57, the equipment must

be designed and installed. Connection equipment and service systems to be able to work Maintenance and repairs can be carried out from outside in a clean area as much as possible. If you

want to make it sterile. If possible, they must be assembled completely before being processed. Sterile. No.

58. Maintenance of tools within a clean area. If unable to maintain cleanliness standards Can be determined during maintenance. The area must be cleaned. Disinfect or sterilize before starting. continue working

Article 59 Water production and distribution systems must be designed, installed, and maintained to ensure that water can be produced. suitable quality Including must not use more than the designed capacity of the

system. Water for the manufacture of injections must be produced, stored and distributed to the point of use in such a way as to prevent growth. of microorganisms such as There should be regular circulation

at a temperature higher than 70 degrees Celsius. Item 60: All types of equipment, including sterilizers, air systems and air filtration, ventilation holes and gas filters. Water preparation and production system Water storage and distribution Must be checked for accuracy. and plans Yes maintenance and must be certified before returning to use.

Hygiene No.

61 Hygiene of a clean area is important. Cleaning must be done according to a written schedule when available. The use of more than one type of disinfectant must be rotated and regularly monitored to ensure that There has been no development of strains that are resistant to the disinfectant. Item 62: Disinfectants and cleaning

agents must be monitored to ensure that they are not contaminated with microorganisms. The diluted solution. Must be stored in clean containers and stored only for the specified time. In addition to being sterilized, for disinfectants and cleaning agents used in Level A and B areas, they must be sterilized before use. Section 63: Fumigation of clean areas. May be useful in reducing

microbial contamination in areas where
Difficult to get in and clean

process

Item 64 Care must be taken to minimize contamination during every step of the process. including steps before sterilizing

Article 65 Do not produce or package products derived from microorganisms in the same area used for the production process. Other medicinal products But what if it's a vaccine of dead microorganisms? or bacterial extracts after the effect has been exhausted It may be packed in the same area as other sterile drug products. Item

66: Verifying the correctness of production by the sterile process. Must include testing Simulate the process using culture media or media. The selection of culture media must be based on the type of culture. Product and its specificity, clarity, concentration and suitability for sterilization.

Article 67 The process simulation test must be replicated as closely as possible to the production process. Free from routine germs and includes every critical production step. This must include the things that cause the interruption. Operation during normal production and worst case scenario

Article 68 First verification of accuracy Three consecutive process simulation tests must be performed. Shift work until the results are satisfactory. and repeat at the specified time. Including after there has been an important improvement of

Air systems, tools, processes, and number of shifts. Normally, process simulation testing is repeated.

Twice per year per work and process shift. Clause 69 The

number of containers used for media fills must be sufficient to allow evaluation of the production batch.

Small quantity The number of containers for the media fill must be at least as large as the container. Number of production models The goal must not be infected.

Using the following criteria:

69.1 When containing less than 5,000 units, no contamination must be found.

69.2 When packing 5,000 to (1) ÿÿ,ÿÿÿ unit

found contamination (2) 1 Unit must investigate to find the cause and consider redoing the media film.

found contamination in 2 units, the cause must be considered in order to re-check the accuracy.

After investigating the cause

69.3 When containing more than 10,000 unit

(1) contamination is ÿ The unit must investigate to find the cause.

found (2) contamination is found in 2 units, the cause must be considered in order to re-check the accuracy.

After investigating the cause

Article 70 The occurrence of contamination of media for any production scale during certain periods of the media fill inspection may

Shows the level of contamination low levels which must be investigated to find the cause

The investigation to find the cause of the media fill failed. Must include trends affecting insurance.

Sterility of the production model since the last media fill.

Article 71 Any verification must not cause damage to the process.

Item 72: Water sources, water preparation tools. And water that has been prepared must be monitored for chemical contamination and

Biology on a regular basis and monitor endotoxins as appropriate. and maintain records

monitoring including corrective actions

Article 73 Activities in clean areas must be kept to a minimum. Especially while being produced by the sterile process.

and worker movement must be controlled and guidelines in place to avoid the release of particles and

Microorganisms due to hastily conducted activities. Item

74: Temperature and humidity in the room must not cause discomfort. Due to the characteristics of the clothing worn by the worker

wear

Article 75 The starting material must have minimal microbial contamination. The requirements for the starting material must be determined.

Microbial quality and identification by monitoring

Article 76: Containers and objects in clean areas must release as little fiber as possible.

Article 77: There must be appropriate measures. To minimize particle contamination in the final product.

Clause 78 Components, containers and tools after the cleaning process has been completed must
Take steps to prevent re-contamination.

Article 79 The time between washing and drying and sterilization of components, containers.
and tools The time between sterilization and use must be as short as possible. and must be specified
Time limits appropriate to storage conditions.

Article 80: The period of time between starting to prepare the solution and sterilizing it. or filtering through a filter
To get rid of germs, it must be as short as possible. The longest acceptable storage time must be determined for each type of product.
Consider the ingredients in the product and provide recommendations for storage methods. You must check for existing infections first.
Make it sterile. and establish limits for the bacteria present before sterilization begins, which depends on efficiency.
of the sterilization method used The amount of germs present in each production batch must be analyzed. Both products are packaged
Sterile and final sterilization products For products that are sterilized in
The final step in overkill sterilization may be to check for existing bacteria at intervals of time.
only appropriate For the parametric release system, the analysis of the amount of bacteria that
It has to be done for every production model. and is considered a test during the process Endotoxin levels must be monitored.
(Endotoxin) as appropriate All solutions, especially large volume injections, must be filtered through a sterile filter.
and if possible, place the filter in a position as close to the filling as possible.

Article 81 Components, containers, tools, and other things required in a clean area for the process.
Sterile It must be sterilized and transported into a clean area through a door sterilizer.
Two sides, which are embedded in the wall. or by other means that achieve the objective of not introducing contaminants. non-flammable gas
that passes for use must be filtered with a sterile filter.

Article 82 The effectiveness of the new methods to be used must be checked and verified. determined based on history of
This It
Periodic verification of accuracy performance or when there is a change
Important parts of the process or tool

sterilization

Article 83 Every sterilization process must be checked for accuracy. Including methods to make it sterile.
that are used that are not specified in the current Pharmacopoeia as specified by the Minister. or methods used for products that are not
Is it a solution in water or only one type of oil (Simple aqueous or oily solution) and, if possible,
Choose a method to sterilize with heat.

In all cases of the disinfection process The product must be in accordance with the drug registration and drug

production license, Article 84. Before using any sterilization process, it must be proven that the process is appropriate.
for the product and is effective in thoroughly sterilizing each type of item according to conditions
Yes
desired by physical measurement and the use of visual indicators (Biological indicators) as appropriate

The correctness of the process must be verified at specified intervals. At least once a year
and when there are important modifications to the tools Including the results of the inspection must be recorded and kept.

Article 85 Effective sterilization All materials must be sterilized according to
Defined process And the process must be designed to ensure that it can achieve the desired sterility.

Article 86: A format for arranging items must be specified that has been verified for accuracy for every process. Make it sterile.

Article 87 Biological indicators should be used as a supplementary method for monitoring and monitoring the
Sterile, must be stored and used according to the manufacturer's instructions and the quality is checked by testing.
Positive control (Positive control) if biological indicators are used. Strict caution must be taken to prevent
Microbial contamination of biological indicators

Item 88: There must be a clear method for separating unprocessed and sterilized products. Baskets
Trays or other containers used to hold products or ingredients must be clearly labeled. Indicates the name of the product or object.
Model number and whether it has been sterilized or not.

Using indicators such as bars for autoclaves It can only say that the model or sub-model has passed.
Sterilization process But it is not a reliable indicator that the model is sterile.

Article 89 Each sterilization operation must be recorded. and certified as part of the practice method
In releasing the production model

Sterilization by heat

Article 90 Sterilization with each cycle of heat Must be recorded on available time and temperature diagrams.
A sufficiently large scale or by using accurate equipment requires locating the Yongtrong and Mae properly during the inspection.
temperature measurement equipment used for control. and records should be audited.
with another independent temperature measuring device in the same location

Article 91: Chemical or biological indicators must be used. But it must not be used as a substitute for physical measurement.

Article 92 There must be sufficient time for all items to reach the specified temperature before starting the cooling period.
Sterile. You must find this time for each type of item that goes through the process.

Item 93 During cooling down after a high temperature period in the sterilization cycle. Care must be taken that sterile items are not contaminated by the cooling liquid or gas that comes into contact with them.

The product must be sterilized first. Unless it can be shown that any containers are leaking they will not be certified.
For use

Moist heat

No. 94 Monitoring of the moist heat sterilization process must measure both temperature and pressure by
Control equipment must be independent of monitoring equipment and recording diagrams if automatic control and monitoring systems are used.
Validation is required to ensure that critical process requirements, system failures and cycles are met.
of sterilization The record must be displayed in the system and can be observed by the operator throughout the operation.
Make it sterile. The readings from independent temperature indicators must be checked periodically against recorded values.
In the diagram, for a sterilizer with a drain pipe at the bottom of the cabinet it is necessary to record the temperature.
at this position throughout the working period Keep it free of germs. If in the sterilization cycle there is a period of sterilization
It is a vacuum. The cabinet must be tested for leaks regularly.

Article 95 If the item to be sterilized is not a product packed in a sealed container. must be wrapped with an object that
Allows air to pass through and water vapor to pass through and can prevent contamination after
Sterilization Every part of the article must be exposed to water or steam at a specified temperature for a specified time.

No. 96 Care must be taken to ensure that the steam used for sterilization is of appropriate quality and does not contain
Contaminants at levels that cause product or equipment contamination.

dry heat

Article 97 The dry heat sterilization process used must include air circulation.
inside the cabinet and the pressure is maintained higher than outside to prevent non-sterile air from entering inside. The air that
Entry into the cabinet must pass through a high-efficiency air filter (HEPA filter). If this process is used
to remove pyrogen, testing must be done using endotoxin.
(Endotoxin) is also part of the validation.

Sterilization with radiation. No. 98.

Sterilization with radiation is mainly used with objects and products that are not resistant to heat, pharmaceutical products.
Many types and packaging materials are sensitive to radiation, so this method can only be used if experiments confirm that radiation has no effect on decay.
of products, ultraviolet irradiation is an unacceptable method for It is sterile.

Article 99 The amount of radiation must be measured during the sterilization process. Using indicators (Indicators) to measure
Radiation dose, which is independent of the dose rate used but is a measure of the amount of radiation received by the product. Requires measuring equipment
A sufficient amount of radiation remains on the product container and is sufficiently close together. To make sure there is equipment
The radiation dose is measured in the radiation machine. The plastic dose measuring device must be used within the time limits of calibration.
The absorbance value from the dosimeter must be read within a short period of time after exposure to radiation.

clause 100 Biological indicators may be used as an additional control method.

Item 101 The accuracy verification method must take into account the effects of variations in the tightness of the package. Item 102

There must be a procedure to prevent mixing between objects that have been irradiated and objects that have not been irradiated.

Irradiation may be done using a radiosensitive dye. (Radiation-sensitive color disk) is placed on each package container to

Separate between irradiated and unirradiated package containers.

clause ÿÿÿ The total amount of radiation must be administered within a specified period of time.

Sterilization with ethylene oxide

Article 104 This method is used only when other methods cannot be used during the verification of the correctness of the process.

Sterilizing with ethylene oxide must demonstrate that this method does not result in product damage. and show the condition with

Time taken to remove gas To reduce residual gases and unwanted reaction products to acceptable limits.

for each type of product and object

Article 105 Direct contact between the gas and microbial cells is necessary. Therefore must be careful by avoiding

Do not allow microorganisms to be encapsulated in certain objects such as Whether the protein is crystalline or dry, the type and quantity of the packing material affect the process significantly

No. 106 Before the object comes into contact with the gas. Must be adjusted so that humidity and temperature are in balance with the specified values. In the ethylene oxide sterilization process, the benefits and disadvantages of the adjustment period must be considered.

Balanced with the requirements for a shortest period of time before sterilization.

Article 107 Each cycle of sterilization must be monitored with appropriate biological indicators using an appropriate number of test specimens distributed throughout the item to be sterilized.

The information obtained is part of the production record.

Article 108 During each round of the sterilization process Must record the time used, pressure and temperature.

Humidity inside the cabinet, concentration and quantity of all gases used must be recorded, pressure and temperature throughout the upper cycle.

Diagram This record is part of the production record.

Article 109 After sterilization Items must be stored in controlled conditions with ventilation.

so that the residual gases and undesired products from the reaction are reduced to the specified level. This process must be verified.

correctness

Filtration of drug products that cannot be sterilized in the final container. Using filtering methods alone is not enough.

clause ÿÿÿ If the product can be sterilized in

The final container can be sterilized with steam, which is the most common method used today. If the product cannot be sterilized

Sterile in the final container. The solution or liquid can be filtered through an available sterile filter.

Hole size 0.22 micron or smaller Or at least the size of the holes is equal to the microorganisms that can remain on the filter.

Filter into a container that has been sterilized. Such filters can eliminate bacteria and mold. Most can, but cannot eliminate viruses or mycoplasma. Therefore, it is necessary to consider using the filtration process together with the use of heat.

clause ÿÿÿ Filtration methods are more risky than other sterilization processes. Therefore, there should be a second filtering. With the sterile quarantine filter again immediately before packing, this final filtration must be as close to the point of packing as possible. Clause 112 The

filter must have characteristics that release the least fibers.

clause 113 The integrity of the sterile filter must be checked before use and immediately after. Filtering is completed by appropriate methods such as bubble point test, air diffusion test.
(Diffusion flow test) or pressure hold test (Pressure hold test). During verification, the time required for filtration of a known volume of solution must be determined. and find the pressure difference between Filter used to filter In the production that is done regularly If during filtering it is found that these values are different from those determined significantly The cause of the investigation must be recorded and investigated. The results of the inspection must be included in the production record. The integrity of the gas filter and critical ventilation holes must be verified after use for the filter. Other filters should be verified in a timely manner.

Article 114: The same filter must not be used for more than one working day. In addition to checking the accuracy

Article 115 The filter must not affecting the product by filtering out product components or releasing certain substances into the product

The final stage of the sterile medicinal product

Item 116 Products packaged in vials that will be freeze-dried that are not completely sealed with rubber stoppers must be kept. Under level A conditions at all times until the rubber stopper is completely closed.

Article 117 Containers must be closed using a method that has been properly verified. Containers that are closed by fusing, such as glass or plastic ampoules. Every container must be checked for completeness. Other types of containers must Verify completeness using appropriate methods from collected samples. Item 118: The container and sealing

system for vials packed using the sterile process is not yet complete. until the aluminum cover is sealed. and must be done immediately after closing the rubber stopper. Item 119: Tools used to seal the

aluminum cap of a vial. Can produce a large amount of particles and should therefore be located separately and equipped with an adequate exhaust system. No. 120 Sealing the aluminum cap of the vial.

Can be carried out by a sterile process using Sterilized aluminum lid or operate outside the rubber stopper area. with a clean process The vial must be protected under Class A cleanliness up to the point where it leaves the rubber stopper area. After that, the vial has a rubber stopper. It must then be protected with a supply air of Class A cleanliness until sealed with an aluminum cover.

Article 121 Vials without rubber stoppers or incomplete closures must be removed before sealing with aluminum caps. If there is an activity that requires an operator to enter the aluminum cap sealing area, Appropriate technology should be used for protection. Direct contact with the vial and reduce microbial

contamination to a minimum. Article 122 Restricted access barriers system, which is a technology Modern production machines and isolators may be useful in ensuring the desired conditions are achieved and reducing the need for operators to enter the sealed area with aluminum caps. Section

123 Sealing so that the inside of the container It's a vacuum. Must test maintaining vacuum condition. according to the appropriate period specified.

Article 124 Every container containing injection drugs must be inspected for contamination or other defects. if checking Visual inspection must be performed under properly controlled lighting and background conditions. During inspection You must stop your eyes periodically. This worker must undergo regular eye exams. If the worker wears glasses, they must Eye check with glasses If using other methods of inspection, the accuracy of that process must be verified and the performance of the equipment must be checked periodically. and record the inspection results

Quality control

Article 125 Sterility testing of finished products is the final measure of control. To insure sterility Testing for each product must be validated.

Article 126 In the case of approval to use parametric release, special emphasis must be given. To check the correctness and monitoring of the entire production process. Article 127 Samples

used for sterility testing must be representative of the entire batch. In particular, it must include Examples from the part of the batch that is considered to be most at risk of contamination, such as 127.1

Products that are packaged using a sterile process. A sample of the container must be collected. contained in the beginning and end of the edition. and after there is an event that has a significant work interruption

127.2 Products sterilized by heat in the final container. Must collect samples The product is placed in the area with the lowest temperature in the cabinet.

Appendix 2

Production of biological medicinal products for human use

scope

The process used to produce a bioactive substance or biopharmaceutical product is a critical factor in determining Appropriate legal controls Active substances and biopharmaceutical products are therefore broadly defined with reference to: with the production process This appendix sets out the criteria for active ingredients and medicinal products classified as biological substances. all around

This appendix is divided into two main chapters:

Chapter 1 contains additional criteria for the production of bioactive substances and biopharmaceutical products. Controlled from the production of germline models and the source of cells used for culture. or production from the starting material until finished end of process as well as testing methods

Chapter 2 contains criteria for certain types of bioactive substances and biotherapeutic medicinal products. This appendix as well as other related appendices from this Ministry of Public Health announcement will supplement the Other criteria included in the criteria and methods for producing drugs, Part and Part 2 of the announcement of the Ministry of Public Health. This appendix covers 2 main topics as follows:

1) Production process of bioactive substances in the production process before entering the sterilization process. The main criteria are in the rules and procedures for producing drugs, Part 2 of the Ministry of Public Health announcement. Criteria for the subsequent production process steps to obtain a biopharmaceutical product. Specified in the criteria and methods for producing drugs, Part 1 of the Ministry of Public Health announcement. Some types of biological products (such as Advanced Therapy Medicinal Products (ATMP) obtained from cell culture) must be processed with a sterile process at every stage of production. 2) Types of Products This annex establishes comprehensive criteria for all aspects of the

production of biologics. both active ingredients and biological medicinal products The two main topics mentioned are shown in Table 1. The information presented in

this table is presented in only one level This does not mean that it can be covered in precise detail. And you must understand that Not only has the level of stringency in the rules and procedures for drug production increased in detail since The initial to subsequent steps in the production of bioactive substances must still follow the principles of The rules and procedures for producing medicines are always strictly in accordance with this announcement. which is consistent with other tables at involved as shown in the rules and procedures for drug production, Part 2, while the initial production steps The fact that the processes are covered in this appendix does not mean that they are subject to audit. regularly by officials of the Food and Drug Administration Antibiotics are not classified as biological drugs. However, in cases where there is a production process involving biological substances, the requirements in this appendix can be applied. Criteria for the production of medicinal products prepared from separated human blood or plasma are specified in

Appendix 13 and for products produced from medicinal plants that are not genetically modified are specified in Appendix 6

In some cases, other laws may be used to regulate the following groups of starting materials for the production of

biological materials: 1) Tissues or cells used in the production of industrial products (such as medicines), donation, procurement. and the quality inspection of tissues and cells may be regulated by national law.

2) Blood and blood components that are also used as starting materials for products for the treatment of certain diseases. modern technology Existing national legislation may establish technical requirements for donor selection and blood collection and quality testing. and blood components

3) The production and control of genetically modified organisms must comply with specific regulations within the country. Quarantine must be established. and maintain it in facilities used to handle genetically modified microorganisms. The guidance of national law must be followed to determine and maintain an appropriate level of biosafety, including measures to prevent cross-contamination. However, this must not conflict with the requirements according to the rules and regulations. Methods for producing drugs according to this announcement

Table 1 Criteria **Computers used in production activities that fall within the scope of Appendix 2**

Types and sources of objects,	Product samples	Using the criteria according to the Ministry of Public Health announcement. in the various production steps shown with an asterisk (*).			
animal sources or plants (that have not been genetically modified)	Heparin, insulin, enzymes, proteins, extracts, Product allergy to Advanced therapy, immunosera, vaccines from	* The process of collecting plants, tissues, and parts that are liquid	* Trimming blending and/ or process At the beginning of manufacture	* Separating and making pure	* Setting up recipes and Packing
2. Viruses or bacteria / fermentation / cultivation of cells	viruses or bacteria, enzymes, proteins.	* Creation and maintenance Master cell bank (MCB), active cell bank (WCB), master virus strain (MVS), active strain (WSL)	* Tissue culture and/or ferment	* Making the infection ineffective related If need separation and purification	*Setting the recipe and Packing
3. Fermentation / Cultivate cells with Biotechnology	Products obtained by the method Recombinant monoclonal antibodies, allergens, vaccines, antibiotics (viral and non-viral vectors, plasmids), recombinant	*Creation and maintenance Master cell bank (MCB), active cell bank (WCB), master virus strain model (MSL), active strain model (WSL)	*Culture of other tissues and/or fermentation	*Separating and making Purification and modification	*Setting the recipe and Packing
4. Animal sources genetically modified	proteins, medicinal products. for advanced treatment (ATMPs)	*Bank of modified substances Basic genetics and those used work	*Collection, trimming, mixing and/or processing At the beginning of manufacture	*Separating and making Purification and modification	*Setting the recipe and Packing
5. Plant sources genetically modified	Proteins obtained by the method Recombinant Vaccine	*Bank of modified substances Basic genetics and those used work	Growth and harvesting	*First extraction, separation and purification and modification	*Setting the recipe and Packing
6. Human sources	Allergens Hormonal enzymes obtained from urine	*Collection of liquids	*Mixing and/or processing during Start of production	*Separation and making pure	*Setting the recipe and Packing
7. Human or animal source	Gene therapy: genetically modified cells	donation, procurement and inspection The quality of the tissue or cells used as the starting material for production	*Production of carriers and cell purification and passing process	*Genetic modification of cells outside the body Creation of a master cell bank (MCB), working cell bank (WCB), or primary cell model. *Separation	*Setting the recipe and Packing
	cell therapy body	donation, procurement and inspection The quality of tissues or cells used as starting materials for production.	*Creation of master cell bank (MCB), active cell bank (WCB) or production version of primary cells or combinations of cells	of cells Let the cells grow. pure combination with components that are not cells	*Setting the recipe Mix products and Packing
	Tissue engineering products	donation, procurement and inspection The quality of tissues or cells used as starting materials for production.	*Production process Early separation and purification Create master cell bank (MCB), active cell bank. (WCB) or production model of primary cells or combining cells	*Separation of cells Let the cells grow. a combination of non-cellular components.	*Setting the recipe Mix products and Packing

Principle

The manufacture of biopharmaceutical products involves specific considerations arising from the nature of the product. and production processes. Therefore, the methods for producing, controlling, and administering biopharmaceutical products require precautions.
some special things

Traditional generic pharmaceutical products, which are produced using chemical and physical techniques, are highly uniform, while the production of active ingredients and biopharmaceutical products involves biological processes and materials, such as cell culture or extraction of substances from living substances. life These biological processes may show variations according to Nature causes variation in the scope and nature of the product. For this reason, risk assessment Quality is therefore of paramount importance for this type of material and should be used to develop product control strategies in every production step to reduce variance to a minimum and reduce the chance of contamination and cross-contamination. This is because the objects and process conditions used

in cultivation are designed to have conditions suitable for Growth of specific cells and microorganisms Therefore, there is an opportunity for contamination from microorganisms. In addition, many products may have limited tolerance to purification techniques, especially those designed to inactivate or eliminate foreign contaminants. The design of the production process, tools, and facilities Production support system state of preparation and adding buffers and reagents Sampling and operator training It is an important consideration for Reduce the occurrence of such contamination events to a minimum.

Product specifications (such as those listed in a drug book) according to the drug registration and according to the documents permitting the import or production of drugs for clinical trials) will be an indicator that the active ingredients and Must the materials used be determined for the level of microorganisms present or not? Or does it need to be sterilized or not? At what stage of the biomaterial manufacturing process must the process be performed that cannot be sterilized by heat (that is, requires sterile filtration)? The process must be performed under aseptic techniques to minimize contaminants. little Proper control and monitoring of the production environment Whether it is cleaning in the production area and the sterilization system combined with the use of a closed system Can reduce the risk of contamination and accidental cross-contamination. Quality control, which is normally done using bioanalytical techniques, is often subject to variability in methods. rather than

detecting quality using chemical-physical methods. Production process that is consistent and reliable

(Robust) is considered very important. Moreover, quality control during the production process is extremely important. In the production process of bioactive substances and biopharmaceutical products Biological

medicinal products that contain human tissue or cell components, such as Products for advanced treatment National requirements for donation, procurement and quality inspection procedures must be met. collection and inspection of these products must be carried out according to system standards. suitable quality and according to domestic regulations In addition, national regulations regarding Re-use verification begins with the donor. (while maintaining the confidentiality of the donor) through various steps related of the tissue service agency and continuously under drug law until the institution that uses the product

Active ingredients and biologic medicinal products must meet national recommendations for risk reduction.
of the transmission of substances that cause spongiform encephalitis from animals through medicinal products used in
humans or animals

Chapter ÿ General guidelines

personnel

clause 1 All personnel (including cleaning staff Maintenance staff or control staff
quality) entering the production and testing areas must receive training. and training is repeated periodically.
in matters specific to the products produced and to the work performed This includes the specific measures taken to prevent it.
Work personnel products and environment

Item 2: The health status of personnel working to ensure product safety must be considered in the case
It is necessary to receive appropriate specific vaccinations. and regular health check-ups for personnel whose duties include
production department, maintenance department, testing department, and laboratory animal

care and inspection department. Item 3: Changes in the health status of personnel that may have an adverse effect on the quality of
The product must be separated from operations in the production area. and to keep health records carefully
Appropriately, production of BCG vaccine and tuberculin products must be limited to:
Personnel whose health is carefully monitored By checking your immune status or by doing a chest x-ray.
Regularly examining the health of employees must be considered along with work risks. In case of having to work
with dangerous creatures Must receive advice from medical personnel.

Item 4 Where necessary to reduce the chance of cross-contamination. Areas for movement of personnel must be limited.
(consisting of quality control personnel Maintenance department and cleaning staff) using the principles of
Quality risk management In general, personnel working in areas that come into direct contact with microorganisms that
Live, genetically modified organisms, toxic substances, or laboratory animals must not enter areas where other products are handled.
Products that are lethal or other living things In cases where passage cannot be avoided, measures must be taken.
Control contamination using the principles of quality risk management.

Premises and tools

Item 5: Levels for controlling particle contamination. and microorganisms in the production area, which is one control strategy,
must be adjusted appropriately according to the product and production process. Taking into account the level of contamination
of raw materials and risks to products if there are indications according to the risk management process
Quality aspect: Work environment monitoring plan In addition to those specified in Appendix 1, sterile must be supplemented Pharmaceutical production
with methods for examining existing specific microorganisms (such as microorganisms native to the area, microorganisms that
does not require air) where identified by the quality risk management process

Item 6: Places and facilities for production and storage of products must be designed and organized.
Types of work areas, both in the work process and in the environment, to prevent contamination of the product.

from outside Although contamination occurs in some work processes such as fermentation and cell culture, There may be evidence that is easily identifiable. But preventing contamination is more than just Inspect and dispose of later. Environmental monitoring and a program for testing for germs present in objects used in production is a step intended to verify the condition of control. In the case of the production process It is not a closed process. This gives the product a chance to come into contact with the environment within the room, such as Adding supplements Culture medium gas buffer solution Operations during the production of medicinal products for advanced therapy therefore require measurement measures while working. This includes engineering and environmental control measures. According to the principles of quality risk assessment In this regard, the principles of quality risk management These principles and requirements specified in Appendix 1, Sterile Medicine Manufacturing, should be taken into account, as appropriate, when selecting levels for the working environment. and measures to

Related controls Clause 7: The production site must be separated specifically for handling live cells that are stable in The environment of the production site until the process of inactivation must be separated specifically for the production site. Organisms that

can cause severe disease in humans. Item 8: Production of several biological medicinal products in the same area may be permitted if there are considerations or The following or equivalent measures are effective. which is part of the control strategy Using the principles of Quality risk management To prevent cross-contamination By considering Product type

8.1 Knowledge about the important characteristics of microbial cells and contaminants that come from outside (e.g. pathogenicity of bacteria Detectability, persistence, and susceptibility to inactivation) within the same facility.

8.2 In cases where the nature of production is determined by the number of small production models produced from different materials or starting materials (e.g., cell-derived products), donor health factors and/or risk of loss of total yield of the product and/or patient-specific factors should be taken into account. During the development of production control strategies in order to accept the work at the same time.

8.3 Must protect living creatures. or prevent spores from entering the area or tools that are not available Relevance Control measures to eliminate organisms or spores before producing another product. Next, consideration must be given to the air control system (HVAC), cleaning. and eliminating contamination for Disinfectants and spores must be verified. 8.4

Environmental monitoring specific to the microorganisms being produced must be carried out. In adjacent areas both during production and after cleaning and decontamination, attention must be paid to the types of equipment used (e.g. airborne particulate matter meters) in areas that handle live microorganisms. and/ or spore-forming microorganisms

8.5 Tool products and additional tools (e.g. tools used for calibration or Verify correctness) and disposable items Must be brought into or removed from the area in a manner that prevents

Contaminate other areas Other products and other product steps (such as protection of sterilized products

or has already destroyed the toxins from products that have not yet been destroyed)

8.6 Continuous production with separate production times (campaign-based manufacturing) that is carried out

After the cleaning method and validated decontamination.

Item 9: For the process of formula making, filling and packaging, it is necessary to organize

A separate area shall be provided based on the above considerations. together with consideration of necessity

specific to that biological product and characteristics of other products This includes non-biological products that

the same production location Other control measures regarding the The above steps may include specific needs. Produced within

sequence of production steps Mixing speed, duration and temperature control limits.

exposure to light and storage as well as cleaning methods in the event of spillage of the germs produced

clause 10 Measures and procedures necessary for containment (such as the safety of workers and

environment) must not conflict with product safety measures.

clause ÿÿ Air handling equipment must be designed, installed, and maintained. To reduce the risk from

Minimizing cross-contamination between different production areas and may be system specific.

with production area Consider using a single-flow air system based on management principles.

Quality risk

Item 12: Areas with positive pressure must be used in the production of sterile products, but may be accepted.

Negative pressure conditions can be achieved in specific areas that are in contact with pathogens to contain them. In the case of using in areas with pressure

Negative or safety cabinets for the sterile processing of objects of special risk (e.g. pathogens) must

Surrounded by an area with an appropriate level of cleanliness and positive pressure. cascade of pressure levels

of the area must be clearly specified and there is continuous monitoring and installation of warning signs at

appropriate

clause 13 tools used to handle living microorganisms and cells, including tools used to collect random samples.

Must be designed to prevent contamination from living things. and other cells during the production process

Article 14 Primary containment must be designed. And there are periodic tests to ensure that it can

Prevent the escape of biological substances into the environment in the work area.

Article 15: The system “automatic cleaning (clean in place)” and “making

Automated sterilization” (steam in place/sterilization in place) wherever possible, valves are closed and opened.

The contents of the fermentation tank must be of a type that can be completely sterilized by steam.

No. 16 The air filter must be a type that does not absorb water. and must be verified according to

Specify the lifespan along with checking the integrity of the filter set at appropriate times according to the principles

of quality risk management

Item 17: The waste drainage system must be designed so that the waste that is to be drained is completely eliminated of toxicity.

(neutralised) or effectively destroys germs To minimize the risk of cross-contamination.

Must comply with the regulations of the relevant agencies. To reduce the risk of further contamination the external environment according to the risks associated with the biological hazard characteristics of the waste

Article 18 Due to the variability of biological products or production processes. You may need to measure or weigh. Additive weight or certain compounds that are relevant or critical during operations In this case, these substances may be stored within the production area for a specified period of time, for example for the duration of the production of the batch. or during continuous, split-time production These objects must be preserved.

appropriately

Experimental animals

Clause 19 Production of biological medicinal products or produce objects/biological substances using various species of laboratory animals By dividing experimental animals into 2 types according to their source as follows:

19.1 Live herds of animals, such as animals used in the production of polio vaccines (monkeys), serum with immunity to snake venom and tetanus (horses, goats and sheep), allergens (cats), rabies vaccine (rabbits, rats and hamsters) genetically modified products (goats and cows) 19.2 Tissues of laboratory animals or cells obtained from dead animals after an autopsy or from tissue

service agencies such as animal slaughter units. Examples in this group include: Cells of different species that come from tissues or Animal cells, feeder cells, used to support cell growth for food products advanced treatment From the source of the animal slaughter unit to obtain cell enzymes from sheep and pigs that are used to produce protective substances.

Blood clotting and hormones

In addition, laboratory animals may also be used to check quality, whether for general analysis such as the detection of fever-causing substances or specific analysis to determine potency, such as testing the potency of Whooping cough vaccine (guinea pig), fever-inducing substance test (rabbit), BCG vaccine test to prevent tuberculosis (guinea pig).

Article 20 In addition to having to comply with the regulations of Transmissible Spongiform Encephalopathy (TSE), other external contaminants such as animal diseases that can be transmitted to humans must also be monitored. Disease of origin from animals with a continuous animal health inspection plan and must be recorded with advice from experts to prepare a health examination plan for such animals In the event of a health problem occurring Must investigate Suitability of source animals or suitability of further use of animals with health problems, such as for production. To be a source of raw materials for production For quality control and safety testing along with recording the decision as a document There must be a retrospective approach to work. To inform the decision-making process regarding the suitability of medicinal substances. or medicinal products used or available The components of the medicinal substance This decision-making process includes repeated testing of samples stored at Obtained from a previous collection from the same donor. In order to establish the most recent donation source that is not infected, the period of withdrawal of treatment for the animal that was the original source must be recorded. and use it to consider eliminating those animals from program according to the specified period

Article 21 Special care must be taken to prevent and monitor infection in animals that are the source of infection. or donated laboratory animals with comprehensive measures such as procuring sources Facilities, animal husbandry, methods for biosafety, testing methods, control of animal bedding and animal feed. This is considered very important for animals that are free from pathogens that must pass the requirements according to the topic of the drug book. The organization of animal housing and health monitoring of other types of laboratory animals (such as flocks) must also be specified. healthy animals)

Article 22 Products produced from genetically modified animals. A traceability system must be maintained. (traceability) in the production of genetically modified animals from the source

animals. Article 23 Animal raising facilities, animal care and quarantine must be in accordance with national regulations. The accommodations of animals used in the production and quality control of biopharmaceutical products must be separated from Production area and

quality control, Article 24: For experimental animals of different species, important criteria must be established, such as information on the age, weight and health status of the animals

must be monitored. and record in writing. Clause 25: Experimental animals, biological substances, and tests used must be specified appropriately in order to prevent the risk of mixing. and to control all listed hazards.

Document operations

Article 26 Requirements for biological starting materials may require additional documentation regarding their origin, distribution chain, production methods and controls used to guarantee an adequate level of control. appropriate, including the microbiological quality of raw materials

Article 27 Some products may require specific identification of the constituent materials of the batch, in particular human body cells in the context of advanced therapy products. In a situation where there is Use your own cells or tissues and is compatible with donor cells Products produced in this way must be counted as one production model

Article 28 In cases where human cells or tissue from a donor are used, they must be fully traced back. From the starting materials and raw materials used, including various substances that come into contact with cells or tissues. throughout the confirmation of Receive the product at the point of use while maintaining individual privacy. and maintain the confidentiality of health information. Records must be maintained for traceability for 30 years after the product has expired. Special care must be taken to preserve product traceability information in the case of specific uses, such as matched donor cells. National regulations must also apply. Products that are components of blood When it is necessary to use this to support or as raw materials in the process Production of pharmaceutical products For medicinal products for advanced therapy Traceability requirements regarding Human cells and blood cells must comply with the principles specified in national legislation, the management required for traceability and the period of storage of samples. must be included in Technical contract between each responsible party

Production operations

Article 29 Due to the variability of biological substances and biological products, the steps to increase
Of course, process consistency reduces the level of variability in the production process and improves
The ability to produce reproducibly at different stages of a product's life cycle, e.g. Production process design
Reassessment must be made during product quality reviews.

Item 30: Due to the conditions of cultivation Culture medium and various chemicals are designed to be used
Supports the growth of cells or microorganisms in normal conditions. Therefore, special attention must be paid to strategy.
Controls to ensure consistent procedures are in place to prevent or reduce the chance of existing germs and metabolites
and related toxins Biopharmaceutical products for advanced cell-derived therapeutics, often available in small batches.
Procedures and requirements must be in place to control the risk of cross-contamination during preparation.
Cultured cells obtained from donors of different health status.

starting object

clause ÿÿ The origin, origin, and suitability of starting materials and biological raw materials (e.g., freeze-dried protective
agents, culture cells, reaction reagents, Culture medium serum buffer solution Cytokine enzyme
Factors for growth must be clearly defined. In cases where testing requires a long period of time, it may
It is allowed to use the starting material before the test results are known. You must be aware and understand the risks from using it.
Initial objects whose properties do not meet the requirements and the impact that may have on other production models By evaluating under the principles
of quality risk management In such case Emissions through the finished product depend on
Conditions of various test results according those are satisfactory The identity of all reactants must be verified.
to specifications appropriate to the production process. Additional guidance for biologic medicinal products is available in the guidelines.
and methods for producing drugs, as 1 and Appendix 8 Production of medicinal liquids, creams and ointments and recommendations for substances.
for bioactive ingredients, are in the criteria and methods for producing drugs, Part 2 of this announcement.

Article 32 The risk of contamination of starting materials during transit along the supply chain must be assessed.
With special emphasis on TSE, substances that come into direct contact with production equipment or products, such as Culture medium
used to test the accuracy of the filling process and lubricants which may be exposed to environmental effects. products must be taken into consideration
together with

Article 33 If the risk of bringing contamination is specified as well as the impact on the product
It is the same regardless of the production process. Therefore, a control strategy must be developed to protect the product and
To prevent solution preparation Buffers and other additives According to the principles and recommendations on appropriate topics.
of appendix 1 Production of sterile medicine In this announcement, various controls necessary for the quality of
Raw materials and sterile production processes, especially for products made from cultured cells that cannot
can achieve final sterility and have limited ability to eliminate waste germs. It is considered to have
Even more important In the case where the drug registration and supporting documents permit the import or production of drugs for
Clinical trials allow for the type and quantity of microorganisms in the active ingredient production process to determine control strategies.
Methods must be mentioned to keep the type and amount of bacteria present within specified limits.

item 34 If it is necessary to sterilize the starting material. Use the method to sterilize with heat, but If necessary, other appropriate methods may be used to sterilize the biological material, such as irradiation and filtration.

Article 35 Reducing the amount of microorganisms associated with the procurement of living tissue and cells. Other measures may be necessary, such as the use of antibiotics early in the production process. In some situations where it is appropriate to use antibiotics, such as to maintain plasmids in extraction systems and in fermentations, their use should generally be avoided. antibiotics in humans due to the possibility of drug resistance and the use of antibiotics is not an effective mechanism for Control microbial contamination, although this method should be avoided if necessary. This method may be used if there is appropriate and carefully controlled and antibiotics must be removed from the production process in As specified in the drug registration or supporting documents granting permission to import or produce drugs for clinical trials. Article 36: Tissues and cells of human

origin used as starting materials for biological medicinal products.

36.1 In some countries there are regulations regarding procurement, donation and testing, so the source of supply must have appropriate approval from the national regulatory authority. which must be done Verify that approval. It is part of the management of the original material suppliers. 36.2 In the case of importing human cells or tissues,

they must pass standard criteria for Domestic quality and safety National laws may have traceability requirements. and reporting of symptoms or serious adverse events. 36.3 There may be cases in which a process uses cells or tissues used as starting materials for Biopharmaceutical products are

processed at tissue services, for example to pre-cure cell lines or cell banks.

Prepared to be a master cell bank

36.4 Tissues and cells must be approved for release by the person responsible for the tissue service unit before being delivered to the drug product manufacturer. This requires controlling the starting material of the drug product. The tissue service unit must have all tissue or cell test results to deliver to the product manufacturer for use as information. In deciding on the separation and storage of substances In cases where production must begin before receiving test results From the tissue service unit Tissues and cells may be sent to product manufacturers under control to prevent cross-contamination with tissues or cells that have been released by the responsible person of the tissue service unit.

36.5 The transport of human tissues and cells to the production site must be controlled under A written contract by responsible parties of all parties. However, the production factory must have evidence in the form of documents showing Compliance with specified storage and transportation conditions.

36.6 Continuity of verification requirements. Starting with the tissue service unit up to each recipient And vice versa. This includes the storage of objects that have come into contact with cells or tissues. 36.7 There must be a technical

agreement between the responsible parties of each relevant party such as the manufacturer, tissue service agency, sponsor, drug registrar. This must clearly specify the responsibility of each party, including the person responsible for releasing it through tissues or cells. Section 37, in the case of gene therapy,

has the following considerations:

37.1 For products containing virus carriers The raw material of the product is the component that is derived from the virus carrier, such as the host virus strain. or plasmids that are genetically transmitted to contain cells and banks. Master cell of a packed cell line

37.2 For products containing plasmids Non-viral carriers and microorganisms Genetically modified non-viral or viral vectors The raw materials of the product are Components used in production production cells, that is, plasmids, host bacteria, and a master cell bank of cells from Recombinant microorganisms 37.3 for genetically modified cells The raw materials of the

product are Components obtained from

Genetically modified cells, that is, the raw materials used to produce vectors. Medicinal products are prepared from human or animal cells. The

ÿÿ.ÿ principles of the criteria and methods for producing drugs according to this announcement are applied to the system. Banks used in the production of vectors or plasmids used in gene

transplantation. Item 38: In the case where cells from humans or animals are used in the production process as co-culture cells. Appropriate controls must be in place regarding procurement, testing, transportation and storage. This includes Controlled human cells that meet national regulations

Seed lot and Cell bank system (Seed lot and Cell bank system) No. 39 to prevent undesirable

changes in properties that may occur from repeated cultivation or propagation for many generations. Production of bioactive substances and biopharmaceutical products obtained from microbial cultivation. Cell culture or multiplication in embryos and animals must be based on a virus generation system. The host and virus versions used and/or cell banks. Such systems may not be applicable to medicinal products for All types of advanced treatment. Article 40. Number of generations [(multiply the number of

copies, increase the number of generations (passage)] between generations of germs. or cell bank medicinal substances And finished drug products must comply with the requirements specified in the drug registration or documents accompanying permission to import or produce drugs for clinical trials.

Clause 41 Preparation of germline models. and cell banks, including master and working strains, as part of product life cycle management, must be conducted under conditions that demonstrate their viability. This includes a properly controlled environment to prevent the reproduction of germs. cell bank and Personnel performing work During the establishment of the germline model and cell bank, no other organisms or infectious materials [such as viruses, cell lines, or cell strains] may be processed in the same location. or by the same person for the steps preceding the generation of master germplasm or cell banks that may apply the principles of Applied drug manufacturing criteria and methods must be documented to support traceability, including issues related to ingredients used during development that may affect product safety. (e.g. reagents used that are of living origin) from the original source. and genetic development resources To be used for vaccines, follow the requirements of the drug book.

Article 42 After creating the master cell bank and the cell bank in use and the master germline model and generation Inactivated germs must follow quarantine and release methods. This includes characterization and testing. adequate contamination Suitability for continuous use must demonstrate consistency of Characteristics and quality of products in each model continuously Evidence of the stability and recovery of strains and banks must be documented and kept in a manner that can be used for evaluation.

product trends

Article 43: The germline models and cell banks must be kept. and used in a manner that minimizes the risk of contamination or alteration (e.g. storage in the vapor section of a sealed container). liquid nitrogen) control measures must be in place to prevent mixing for the collection of germplasm. and/or different types of cells together in the same place or on the same tool and consider the nature of infection from various objects to prevent cross-contamination.

Point 44: Cell-based medicinal products are usually produced from cell stocks with a limited number of inoculations per period, which is different from the two-tiered system of master cell bank and active cell bank. The amount of production that Processing from cell stock is limited by the number of cells divided after replenishment and does not cover the entire life cycle of the product. Cell stock changes must be performed according to the protocol. Checking the correctness of work, No. 45:

Containers must be sealed. Label it clearly. and stored at an appropriate temperature. Records of receipt and distribution must be kept. The temperature at which they are kept must be recorded continuously. and if liquid nitrogen is used for storage The level of liquid nitrogen must be monitored. Record any deviations from the established limits, including Take steps to solve and prevent

problems. Item 46: Cell stocks must be divided into sections and the divided cell stocks stored in different locations. To reduce the risk of loss all at once, controls at the storage location must be guaranteed accordingly. The criteria specified in the previous section,

item 47, must manage storage conditions. and maintenance of the cell stock according to the same methods and parameters. As soon as the containers are removed from the germline management system / cell bank, they must not be removed. Those containers are back in stock again.

Operating Principles No. 48

Change management must be done periodically. and take into account the impact on the quality of Finished drug products as well as the cumulative impact of changes on the process.

Article 49 Critical process parameters or other import parameters that affect product quality. There must be an indication of authenticity. and prepared as a document and shows that these parameters remain Maintain it within the requirements. Article 50.

Strategies for controlling the entry of items and raw materials into the production area must be carried out according to the principles. of quality risk management to reduce contamination risk Items and raw materials that are resistant to heat

that is transported into a clean area or clean containment area The sterile process must be carried out through a high-pressure autoclave or a two-way openable heating cabinet. Items and objects that are not resistant to heat shall be transported through Airlocks with doors that open on two sides, such items and objects must undergo an effective disinfection process on the outer surface. Items or materials that must be sterilized before use must be encapsulated in several layers to suit. Number of levels of import into the clean area and transmitted through an airlock that destroys germs on surfaces. appropriately

Item 51: It must be shown that the culture medium has the properties of stimulating the growth of microorganisms. suitable for its intended use. If possible, the media must be sterilized in the area where it is used. There is direct work. A sterile filter must be installed to sterilize the routine. to fill gas Culture medium, acid or alkali, foam reducing agent, etc., into the fermentation tank as far as possible.

Clause 52 Adding raw materials or cultures to fermentation tanks or other mixing tanks. and collecting samples must be done with caution. and under controlled conditions to prevent contamination Care must be taken to ensure that the mixing tank Connection is made correctly when filling. or sample

collection, item 53, if necessary Some production processes may be continuously monitored (e.g. inoculation in fermentation tanks) and the information collected is part of the batch record. When continuous cell cultures are used, special consideration must be given to quality control requirements in the case of such production methods.

Item 54 It is necessary to use the centrifugation and mixing process of products to create aerosols. Limit these activity areas to reduce the risk of cross-contamination.

Article 55 When there is an accidental spill, especially of living things. It must be handled quickly and safely. Valid decontamination measures must be available for each species. If it involves bacteria of the same type but different species or viruses that are very similar. Use the process that has passed. Validation is for one type only. unless there is sufficient reason that the bacteria or virus may Resistant to significantly different substances used. Item 56 If contamination is clearly

found from spillage or dispersion as aerosols, or the use of dangerous living things. Production operations and raw materials controlled Including production documents Must be adequately sterilized or have the information transferred by other means. Item 57: Methods used for

sterilization, disinfection, virus elimination. or making the virus ineffective Must be verified for accuracy. Article 58 In cases where there is a

virus inactivation or virus removal process during production, measures must be taken to reduce the risk of recontamination between products that have undergone the treatment. The virus has been classified with the product. Haven't gone through virus removal yet.

Item 59 Products that inactivate microorganisms by adding chemicals (such as microorganisms used in the production of vaccines) must have a process to ensure that those living microorganisms have been inactivated in mixing microorganisms. Cultures with inactivating substances must be considered to have been carried out thoroughly, especially

The surface area of the mixing tank that comes into contact with those living microorganisms. and the connecting part for moving to another mixing tank

Article 60: There are many types of instruments used in the chromatography process. Therefore, the principles of management must be applied. Use quality risk management in developing separation material control strategies. Encapsulating equipment and other related equipment when producing continuous products in separate production times and in locations used to produce multiple products. Do not support the reuse of materials used in separation. Even though it is used in Different steps Acceptance criteria must be established. operating conditions How to restore Lifespan and methods of disinfection or sterilization of the column

Point 61: When irradiation is used in the process of producing pharmaceutical products, study additional instructions in the appendix. ÿÿ Use of ionizing radiation in the production of pharmaceutical products

Article 62: There must be a system to guarantee complete sealing of containers after the filling process. In the case of finished products or products in process of production that represent risks. as well as how to work when Leaks and spills occur. Filling and packaging processes require procedures to preserve the product. within specified limits, such as time and/or temperature

Article 63 Activities related to containers used to contain living biological substances must be carried out to prevent contamination of other products. or the escape of living things into the work area or into the outside environment. The ability of living things to survive and the biological classification of living things must be taken into account. Compile the assessment of risks that occur

Point 64: Be careful with preparation. Preservation printing and labeling including specific messages

For products given to specific patients or there is an indication of the use of genetic engineering methods displayed on the label. Primary containers and secondary packaging of self-administered products must have patient-specific identification with the statement “For use only in specific patients” displayed on the label directly on the product.

Item 65: The compatibility of labels attached to containers must be verified in cases where they must be used in Very low temperature. Item 66: In the case of

receiving health information of the donor. and/or animals after purchasing, which has an effect on Product quality, such information should be taken into consideration in the work procedures for recalling products.

Quality control

Article 67 Quality control during the production process is important in confirming the consistency of the product. The quality of biopharmaceutical products is higher than those produced using traditional production methods. testing between Production process Proper production steps must be taken to control conditions critical to quality. of the finished product

Article 68 In cases where the storage time for products during production can be extended for another period (days, weeks or longer), the plan for continuous stability studies of the finished product must consider the generation. Manufactured from objects during production that are stored for a maximum period of time.

Article 69 Some types of cells, such as cells obtained from the same person used for biopharmaceutical products for advanced treatment Quantities may be limited and therefore may allow the development of adapted test methods. and strategy keep a sample Ready to document if specified in the drug registration or supporting documents. Permission to import or produce drugs for clinical trials

Article 70 Advanced therapeutic products produced from cultured cells must be checked Sterile cell culture or antibiotic-free cell bank To confirm that there is no contamination. Bacteria and fungi It can also detect other contaminated microorganisms as appropriate. Item 71 Products with a short lifespan that

require certification before testing for quality. Every final product completed (e.g. sterility testing) requires a strategy. Appropriate control in the work area These control measures must be based on an understanding of the product. and ongoing processes Taking into account the controls and properties of the materials used in production, a clear description of the methods of product release and the responsibilities of the personnel involved must be included. in production evaluation And analytical data is important. Continuous evaluation of effectiveness must be made. of quality assurance system This includes maintaining records that help assess trends. Testing cases of the final product cannot be processed because the drug life is very short. Alternative methods must be adopted. Consideration is required to obtain equitable information for issuing batch quality certification documents (e.g. rapid microbial detection methods). Procedures for certification and release of this product group It may be carried out in two steps: before and after the results of the complete process analysis test results have been completed.

71.1 Evaluation of production documents and results from environmental monitoring of production.

that are carried out by designated persons must cover production conditions. deviation from method Perform all normal tasks and analysis results for review and use in issuing conditional certificates. By the responsible person 71.2 Evaluation of

final analysis test results and other information before issuing Quality certificate of finished product Before the product is distributed by the responsible person, 71.3 there must be a documented

procedure that explains the measures to be taken when the results of the quality inspection do not meet the requirements (including coordination with the staff overseeing the clinical trial). from what has been spread already product This case requires a full investigation. and take relevant corrective and preventive actions to Prevent a repeat event and to prepare the results of operations. The work

procedures must describe the measures to be carried out by the responsible person. If it is found that the test results It is not satisfactory after the product has been distributed.

Chapter 2 Specific criteria for certain products

2.1 Products that come from animal sources

This guidance applies to products of animal origin as well as materials from service organizations such as slaughterhouses. This is because the supply chain is likely to be long and complex. Therefore, it is necessary to control according to the principles of Quality risk management and consider the appropriate topic of the drug book as well as the need for specific tests at each specified step. Documents must be processed. Demonstrate traceability in the supply chain system and clear roles of those involved in the supply chain, including adequate details of an up-to-date work plan. 1 There must be a program for

monitoring animal diseases related to human health. Organizations must take into account reports from sources. Reliable information on the prevalence of the disease and measures to control when doing Compiling the assessment of risk factors and mitigation of such organizations, such as the World Organization for Animal Health (World Organization of Animal Health), which must be supplemented with national and local health monitoring data and control programs. At the local level, it covers information on the source (e.g. farms, or fattening farm) of animals and control measures during transport to the slaughter unit. Item 2. In the case of the slaughter unit (abattoir) used as

a source of animal tissue production, it must show It is seen that strict standards are being followed. By considering reports from domestic regulatory agencies, which are agencies that verify compliance with food, safety, quality, and legal requirements regarding animal and plant health.

Item 3: Measures for controlling medicinal raw materials at service units, such as animal slaughter units, must have elements of Manage an appropriate quality system To guarantee that operator training is provided. checking back. control object and consistency is at a satisfactory level These measures may be based on external sources. In addition to the standards, criteria and methods for producing drugs according to this announcement, there must be a level of control that is equality

Article 4 There must be measures to control objects to prevent interference that affects the quality of objects. or at least evidence of activities carried out throughout production and the supply chain. This includes Move objects between initial collection areas. Partial or final purification. Storage location.
Maintain collection resources and distribution agents Details of such arrangements must be recorded in the traceability system and must be recorded, investigated and acted upon. If an error occurs

Article 5 Raw material suppliers must be inspected regularly to verify compliance with control measures. Objects at each stage of production Issues must be investigated in depth to a level appropriate to their importance along with complete documentation. In addition, there must be a system of practices in the agency to ensure that it is carried out. that is effective in solving and preventing problems

Item 6: Tissue cells And organs intended to be used to produce pharmaceutical products are derived from cells of different species. Must come from animals that are bred in a specific area. (a breeding building with a boundary fence) for this purpose and must not be used

tissue cells and organs from wild animals or animals from animal slaughter units are used. In the same way Do not use tissue.

Founder animals must also be monitored and documented.

Article 7: For cell therapy products obtained from cells of different species, follow other appropriate recommendations.
regarding the procurement and testing of cells of animal origin, such as the EMA Guideline document on

xenogeneic cell-based medicinal products

2.2 Allergen products

Allergens may be produced by extraction from natural sources or by DNA technology.
mixed line

clause 1 Must specify adequate details of the allergen that is the source. To ensure the

Regularity of the procurement of raw materials used, such as common name designation Scientific name of origin Residence according to

Natural contamination limits How to collect Animal allergens must come from healthy animals.

Strong. Appropriate biosafety control systems must be in place for raising colonies (such as mites and animals) that

It is used to extract allergens, which must be stored in specified conditions to minimize deterioration.

Item 2 must specify details. and check the correctness of the steps in the production process, which

Consists of steps before production. (pre-treatment) extraction, filtration, separation of substances through membranes,

concentrated or lyophilized

Item 3 must specify details of the modification steps in the production of modified allergen extracts, such as substances.

Modified allergen Conjugated allergens Products must be identified and controlled during production.

Item 4. Products that are mixtures of allergen extracts must be prepared from the allergen extracts.

Each type of allergy comes from a single source of material. The extract of each allergen is considered to be 1 active ingredient.

2.3 Animal Immunosera Products

clause 1 Special care must be taken in controlling allergens that originate from living things. to guarantee

Quality, consistency and free from external contaminants Preparation of substances used to stimulate the immune system of animals that

as source of origin (e.g., antigens, hapten carriers, adjuvants, stabilizers) and storage of substances

Before using these substances to stimulate immunity in animals, documented operating procedures must be followed.

Item 2 Immune stimulation schedule blood test and blood sample collection must be consistent

As approved in the drug registration or supporting documents for requesting permission to import or produce drugs for testing purposes

Clinical

Item 3: Manufacturing conditions for preparing antibody subcomponents (such as Fab or F(ab')) and

Modifications must be based on validated and approved parameters in cases where the enzyme used has

Many components must ensure that the enzyme is consistent in composition every time it is used.

2.4 Vaccines

clause 1 The production of vaccines from poultry eggs must guarantee the health of the entire poultry flock. (Although the poultry

Item 2: The correctness of the complete sealing of the

product container must be checked during production.

and check the accuracy of the storage period as well

Rule 3: Do not open the container. or sampling inactivated products in areas with live biological materials.

Item 4: Sequence of steps for adding active ingredients and auxiliary substances. and additives in the recipe development process

of products during production or final product Must be in accordance with the method specified in the production documents or

Production version record

Item 5: Using organisms that have a high level of biosafety (such as disease-causing vaccine strains).

outbreak) for use in production or testing, suitable storage facilities must be prepared. and must be received

Approved by the national regulatory authority. and must have approval documents for verification

2.5 Products obtained by the recombinant DNA method must maintain

clause ÿ operating process conditions in accordance with the parameters that have been verified.

Correct process of cell growth, protein extraction and the purification process for

Guaranteed product consistency by working process can reduce the level of impurities provided.

remaining at an acceptable level within the specified framework The type of cell used in production may require measures.

Something additional to guarantee that there is no virus contamination present. Production with multiple harvests, period

Continuous cultivation must be carried out within a specified period.

Item 2: Purification process of eliminating unwanted host cell proteins, nucleic acids.

Carbohydrates, viruses, or other impurities Must be within specified limits which have been validated.

2.6 Monoclonal antibody products

clause ÿ Monoclonal antibodies may be produced from murine hybridomas.

human (human hybridoma) or produced by hybrid DNA technology There must be appropriate measures to

control different starting cells (including culture cells, if used) and raw materials used in the production of hybridomas; or

Sales line to guarantee product safety and quality and must also verify that measures

While these are still within approved limits, special attention must be paid to being free from virus contamination.

Data obtained from products produced by the same platform technology may be accepted.

Yes, if the appropriateness of the production operation is demonstrated.

Item 2: Must verify that the criteria must be monitored after the production process is completed, and

For ending the production process early within approved limits

Item 3: Manufacturing conditions for preparing antibody fragments (such as Fab or F(ab')) and their modifications (such as radiolabeling, conjugation, chemical connection) must be in accordance with Validated parameters

2.7 Products obtained from genetically modified animals (Transgenic animal products)

The consistency of ingredients obtained from genetically modified sources is likely to be a problem. than biological sources that have not been genetically modified Therefore, it is necessary to have more requirements to show See the consistency of the products in every production batch in

every aspect. Item 1: The production of biologic medicinal products can be done in a wide variety of animal species. Biologics may be produced. or is created in animal body fluids (such as milk) before being collected and purified further. Each animal used in production must be clearly identified by a unique marking. and must prepare Backup method In the case of loss of the primary marker, Section 2, raising and caring for animals must

be arranged in such a way that the animals are exposed to pathogens and infectious agents. Can be transmitted from animals to humans to a minimum. Appropriate measures must be put in place to protect animals from external environment An animal health monitoring program must be prepared and the results must be recorded. Follow up and keep it. If unusual events occur, the cause must be investigated and the impact on the use of animals considered. continuous production and the impact on previous products produced In addition, care must be taken to ensure that no products used for treating animals are contaminated with biopharmaceutical products.

Item 3: There must be a record of the genealogy of animals from the first generation of animals used until the animals used in production. This is because genetically modified cell lines are derived from a single gene from the first generation animal. Therefore must be protected Do not allow substances from different genetically modified

animals to mix together. Section 4: Storage conditions for animal products must be consistent with those specified in the drug registration or Documents for requesting permission to import or produce drugs for clinical trials Storage schedule and handling conditions Animals removed from production must comply with approved standard operating procedures and acceptance limits.

2.8 Products obtained from genetically modified plants

Consistency of raw materials obtained from genetically modified sources More likely to cause problems than raw materials Derived from sources produced by biotechnology that does not undergo genetic modification. Therefore, it is necessary to have more regulations in order to Shows the consistency of products in every production model

clause Bank 1, measures must be taken in addition to those in every aspect. To prevent contamination of Modified Plant specified in Chapter 1, Master Genetics. and genetically modified plant banks that are used from exogenous plant materials. and contaminants coming from outside Including the need to monitor the stability of genes within the specified generation number range.

Item 2: Plants used in production must be clearly identified with different markings and must be inspected.

Confirm the important characteristics of the plants being grown. Including completeness and strength according to the specified time period throughout the period of

Cultivate to guarantee consistency of production.

Clause 3: Measures must be taken to protect and maintain the safety of the plants being grown. To reduce the risk from

Microbial contamination and cross-contamination with other unrelated plants must be kept to a minimum. In addition, there must be

Measures to prevent contamination of products from other substances such as pesticides and fertilizers require a program to be developed.

Monitor and must record the results of the monitoring if there are any unusual events. Must investigate to find the cause and

Consider the impact on using that generation of plants to produce further products.

Clause 4: Conditions for removing plants from production operations must be specified. and acceptance limits for substances

that may interfere with the purification process (e.g. host cell proteins) and the results must be verified.

within approved acceptance limits

Item 5: Environmental conditions (such as temperature, rain) that may affect quality characteristics must be recorded and

The yield of recombinant protein products produced by plants from the time they are grown. throughout the cultivation period until

Harvest and storage period of harvested things By setting criteria to consider according to the principles as

Document guidelines such as Guideline on Good Agricultural and Collection Practice for Starting Materials of Herbal origin

2.9 Gene therapy products

Gene therapy products are divided into two types: vectors and genetically modified cells. Requirements in this section

Covers these 2 types of products for gene therapy products derived from cells. Some of the requirements in Section 2.10 may apply to cell

therapy products derived from human body cells and other animal cells and engineered products.

Tissue comes into force

1 Because the cells used in the production of gene therapy products are derived from humans. (Coming from the same person

joints or different people) or from animals (different species) therefore there is a risk of contamination from substances that come from outside.

(adventitious agents) therefore special consideration must be given to separating substances derived from cells from the same person

receiving them. from an infected donor Durability of control measures and tests for starting materials, cryogenic stabilizers. Culture medium

Cells and carriers must follow the principles for assessing environmental risks.

Quality and consistent with drug registration documents or supporting documents for requesting permission to import or produce drugs

for clinical trials Cell lines used as vectors for viruses as well as control and testing measures

These cell lines must follow the same quality risk assessment principles. and use the system

of the virus strain and cell banking systems if relevant.

Point 2: Various factors such as the nature of the genetic material. Carrier type (viral or non-viral) and the type of cells used in

production are likely to be contaminated with impurities. Exogenous substances and contamination

that must be taken into account in preparing all strategies to reduce risks to a minimum. and to adopt this strategy

used in designing the production process Facilities and tools used in production and storage

How to clean and decontamination Packing, labeling and product distribution

Item 3: The production and testing of gene therapy products presents specific problems regarding safety and Quality of the finished product Including the safety of product users and related personnel, therefore, control products according to the classification of biological hazards, together with risk assessment methods. to be used to ensure the safety of workers, the environment, and patients, in accordance with national laws or international safety measures

Item 4: Principles of quality risk assessment must be used in personnel control. (including officials quality control and maintenance personnel), object flow direction, including storage and testing. (e.g. raw materials, samples of products in process and final products and samples from inspections environment) by using a unidirectional flow chart. In this regard, consider the case of moving between Areas that use various genetically modified organisms and areas that use non-genetically modified organisms.

Item 5: Venue design And tools used in performing work must consider cleaning methods. and the elimination of contamination that is necessary for the management of various species of organisms and, if possible, must be supplemented with methods that Detect specific organisms that have been bred for production in the additional environmental monitoring program. Item 6: There must be measures to prevent the original strain of virus from infecting the vectors used to multiply. Because it may lead to an increase in the number of violent carriers with hybrid technology occurring.

Article 7: There must be an emergency plan for dealing with accidents and leaks of living things. This plan must specify Methods and procedures for containment Operator protection cleaning, eliminating contamination and safety to reuse However, the impact on the product or other things should be assessed. in the incident area

Article 8: Areas for the production of virus vectors must be separated from other areas by specific measures. Manage the separation of areas to see that they are effective. If possible, it must be carried out in a closed system in the process. collect samples and transportation to prevent leakage of viral substances

Article 9 It is not allowed to produce vectors from multiple gene therapy viruses in the same area. and same time In the case of producing non-viral vectors, this may be done in the same area. By controlling using the principles of Assess quality risk It must be demonstrated that the practice of changing production from one product to another to another product on a time-separated, effective basis

clause 10 There must be sufficient detailed information on the steps in the production of genetically modified vectors and cells. To ensure that gene therapy products can be traced back to raw material information (plasmids, genes used and Controlled gene sequence Cell bank stock of virus vectors and non-viral) to the finished product.

clause 11 Transportation of products that contain and/or contain genetically modified organisms must comply with according to laws and regulations appropriately

Item 12. The transplantation of genes from outside the body (ex-vivo gene) into recipient cells has the following considerations:

12.1 Must be carried out in a place specifically designated for these activities, which must There is appropriate storage management.

12.2 There must be measures (including of Chapter 1, General Requirements) in order to reduce considerations in item 10, the possibility of cross-contamination and mixing of cells obtained from other patients This includes the use of methods Verified cleaning Using multiple virus vectors simultaneously Must be under Control according to the principles of quality risk assessment. Certain virus vectors (such as retroviruses) are not permitted. or lentivirus) used in the production of genetically modified cells. until it can be shown to be free of Increasing the number of severe contaminant vectors

12.3 Must maintain traceability requirements. and there is a clear definition of each production model From the source of the cells to the final product container. 12.4 Products that do not use

the transfer of genes to the recipient by biological means. must be tested and record evidence of the chemical and physical properties of the product.

2.10 Cell therapy products derived from human body cells and other animal cells and products Tissue engineering (Somatic and xenogeneic cell therapy products and tissue engineered products)

Products that are derived from genetically modified cells and are not classified as gene therapy products may Some guidelines and recommendations according to Section 2.9: Jeans Therapy Products Can be used as follows

clause ÿ The use of other substances (e.g. biological molecular cell products, biologics, support materials, matrix scaffolds) must come from an authorized source (e.g. authorized medicinal products). or medical devices that have been evaluated according to standard methods such as Medical devices with certification marks (marked CE) according to European standards)

Item 2: In the case of having (medical) equipment, including self-assembled equipment. that is included as part of Pharmaceutical products

2.1 There must be a written agreement between the drug product manufacturer and the medical device manufacturer. The agreement must provide adequate information about the medical device. To avoid changes Qualification of such tools during the manufacture of advanced therapeutic products which must also include Requirements to govern proposed changes for medical devices

2.2 There must be a technical agreement that stipulates the exchange of information related to Deviation in the production of medical devices

Point 3: Because body cells obtained from humans (from the same person or different people) or from animals (cells different species) are at risk of contamination from substances that come from outside, so special consideration must be given. Concerning the separation of raw materials that come from the same person as those obtained from an infected donor. or about cell collection The robustness of the control measures and tests used must be ensured. With these raw material sources, animals whose tissues or cells are used must be raised and processed according to Principles set out in relevant guidelines

Item Attention must be paid to specific requirements during the freezing process, such as the rate 4: Temperature changes during freezing or thawing, type of storage equipment and location.

and the reuse process must reduce the risk of cross-contamination. Maintain product quality and Facilitate accurate reuse. Written procedures must be in place regarding the safe handling and storage of products with positive serological indicators. Item 5: Sterility testing for cell cultures and cell banks that are

free of antibiotics is required. To show that it is free from contamination from bacteria and fungi. and take into account the detection of living things that can grow in some types of specific culture media as well

Item 6, if relevant A plan for monitoring the stability of drug products must be established together with Reference example and samples collected in sufficient quantities for further investigation.

Definition of words

Adjuvant means a chemical or biological substance that increases the stimulation of Immune system response to antigens **Advanced Therapeutic**

Medicinal Products:

ATMP) means medicinal products for human use that belong to the following groups: Gene therapy products cell products Therapy from human cells and tissue engineering products

Modified allergens (Allergoids) mean allergens that have been chemically modified to reduce Immunoglobulin E reactivity

Antigen means a substance that can stimulate an immune response . specific type (e.g. toxins, foreign proteins, bacteria, tissue cells) **Antibodies (Antibody)** means that proteins

produced by B lymphocyte cells can bind to antigens.
Specifically, antibodies may be divided into two main categories based on differences in production processes.

Monoclonal antibody (MAb) means a population of antibodies with similar properties produced from white blood cells, lymphocytes, or by technology. genetic engineering It has the specificity to bind only one specific site on the antigen.

Polyclonal antibody means an antibody obtained from Many types of white blood cells, lymphocytes Which is produced in the human and animal bodies in response to the position on antigens that come from outside the body

Area means a specific group of rooms within the same building related to production. One or more types of products which uses a common air management system

Bioburden means the amount and type of microorganisms present in raw materials, food, culture media, biological substances, products during production . or finished products It is considered contaminated when the quantity and/or type of microorganisms exceeds specifications.

Biological medicinal products means products that contain important substances. It works as a biological substance, which is a biological substance. Substances produced or extracted from biological sources and it is necessary to have

Characteristics and quality are checked using a combination of physical-chemical-biological tests. along with the production process and quality control

Biosafety Level (Biosafety Level: BSL) means the storage conditions used. Deal with organisms of different levels of danger by categorizing them starting from biosafety levels.

BSL1 (lowest risk does not cause disease in humans) up to BSL4 level (highest risk of causing severe disease There is a chance of spreading And there is no way to

prevent it. or an effective treatment method) **Campaigned manufacture** means the production of several batches of the same product continuously for a specified period of time. By following the measures Strict approved controls before changing production to other products There is no production. Many products at the same time But the same machine tools may be used in production.

Closed system means that the active substance or product does not come into contact with Room environment during production

Contained use means operations that use modified microorganisms. Genetics that are cultivated, preserved, and used for transportation and destroy or eliminate Using barrier protection systems (physical/ chemical/biological) to limit the contact of the organism with the general population and the environment. external

Deliberate release means the release of genetically modified microorganisms. Intentionally into the

environment **Outside the body (Ex-vivo)** means a procedure that is performed on cells or tissues outside the body. The body of a living thing is then transferred back

into the body of that living thing again. **Feeder cells** mean cells used in culture to maintain pluripotent stem cells. Culture of human embryonic stem cells normally uses a cell culture layer which Contains fibroblasts from mouse embryos or fibroblast cells from processed human embryos. To prevent stem cell division.

Fermenter means in the case of use with mammalian cell lines. The word “fermenter” means a biomass culture machine.

Gene means a DNA sequence that is the code used to produce one or several types of specific

proteins. **Gene transfer (Gene transfer)** means the process of transplanting genes into cells that involves with the gene expression system attached to a delivery system called a vector Which is obtained from a viral or non-viral source after a gene transplant? Genetically modified cells are called *Transduced* cells

Genetically modified organisms (GMO) means living things (except humans) whose genetic material has been modified in a way that does not occur naturally through breeding. and/or natural combinations

Hapten means a molecule with a low molecular weight that cannot be stimulated .
The immune response can be determined by its own size. unless combined with other molecules that are "carriers"

Hybridoma means a proliferating cell line that secretes (monoclonal) antibodies.
that is usually caused by the fusion of B lymphocytes and cancer cells together

Within the body (in vivo) means procedures performed in living things.

Look-back method means a procedure that is documented in order to Trace back bioactive substances or biological products that may have adverse effects from their use. or the inclusion of substances of animal or human origin that do not pass emissions testing. Because there is clearly a contaminated substance or there is concern about the source of the substance from humans or animals.

Master Cell Bank (MCB) means a source of a single type of cell which Prepared by taking selected cell clones and multiplying them under controlled conditions, dividing them into small containers and storing them under specified conditions. This master cell bank was taken. used to create All active cell banks **Master virus variant (MVS)** - same meaning as above. but related with the virus **Master Genetically Modified Substance Bank** – Same meaning as above. But is it used for plants? genetically modified animals **Monosesis**

(axenic) means the only type of organism used in Culture that is not contaminated with other species. **Place of production of many**

products (Multi-product facility) means a place used in production. Whether it is simultaneous production of many products or separate production times. Can produce biological substances There are many types of active substances and biological products. The tools used in production may or may not be separated. It can be specific to the production of

DNA. That is often active substances or products, meaning that plasmids are pieces of found in cells. **Plasmid (Plasmid)** Bacteria are circles that are separated from the cell's chromosomes.
which can be modified with molecular biology techniques, purified and separated from bacterial cells and used to transfer DN

Primary cell lot means a group of primary cells that have been expanded at least to have sufficient numbers for use.

Responsible Person (RP) means the person responsible for ensuring that each Manufactured versions of bioactive substances or biopharmaceutical products are produced. and check to ensure that it is legal and meets the specific requirements of the product. Products and specifications as registered. “Responsible person” is equivalent to “certified person” in EU terminology.

Responsible person for blood or tissue establishment means this term is equivalent to the term “responsible person” according to the EU terminology. **Scaffold means** a substance or matrix for

for helping support Helps with delivery, which may strengthen the structure. or facilitate movement Acts as adhesion or transport cells and/or biologically active molecules
biological

Somatic cells mean cells that are not reproductive cells that make up Human or animal body, these cells can be living body cells that come from oneself (from a patient) or from another person. or from cells of different species (for example, from animals), these cells are managed or modified through the process outside the body of living things and transferred back to the body again To make it effective for the treatment, diagnosis or prevention of disease in humans. Specified **pathogen**

free (SPF) means raw materials from animals (such as chickens, embryos, or cultured cells) used in production. or quality control of biological medicinal products that come from animal herds that are free from specific pathogens. The term herd or group of such animals refers to animals raised in the same environment. and being cared for by a shepherd who has not come into contact with animals that

are not free from germs **Genetically modified organism (Transgenic)** means an organism that has genes from another organism. Inserted into normal gene elements for the purpose of expressing the gene used to create the biomateria medicinal

Vector means a delivery agent which transmits genetic information from one or more cells . one living thing to another cell or living thing, such as a plasmid, liposome, virus,

viral vector means a **carrier** obtained from a virus and modified with techniques. Molecular biology in such a way that it selectively retains only part of its parent virus genes. If genes related to ability In virus replication is deleted. The resulting carrier will lack the ability to replicate itself.

Working cell bank (WCB) means a group of microorganisms or cells. Homogeneous which is distributed evenly into containers and kept stable for used in production These cells were obtained from the master cell bank. **Active virus version** Same as mentioned above But regarding the virus, **the genetically** - meaning **modified organism bank being used** - the meaning is the same as above. But it is used for genetically modified plants or animals. **Infectious animal diseases Zoonosis** means an

animal disease that can be transmitted to humans.

Appendix 3

Radiopharmaceutical production

Principle

The production of radiopharmaceuticals must be carried out in accordance with the rules and procedures for drug production. 1 and 2 of This Ministry of Public Health Announcement, this appendix details some practices specific to Radiopharmaceuticals

Note (1) The contents of this appendix do not cover the preparation of radiopharmaceuticals from generators and licensed equipment in radiopharmaceutical preparation units. (both in the hospital and radiopharmaceutical preparation unit Hospital) unless there are national regulations.

Note (2) According to the requirements for protection from radiation, the amount of medical radiation received must It is under the clinical responsibility of the practicing physician. (practitioner) in the nuclear medicine unit Even though it is used in diagnosis and treatment A medical physicist must be present.

Note (3) The contents of this appendix include radiopharmaceuticals used in clinical trials. Note (4) The

transportation of radiopharmaceuticals shall be in accordance with the requirements of the International Atomic Energy Agency and the regulations. Guidelines for protection from radiation hazards

Note (5) Production methods other than those described in this appendix are acceptable if inspected. accuracy and demonstrate a level of quality assurance at least equivalent to the methods described in this appendix.

Introduction

clause 1 The production and handling of radiopharmaceuticals can cause harm, with the level of risk depending on The type of radiation that is emitted The energy of that radiation and the half-life of radioactive isotopes must therefore be strictly controlled. Prevent cross contamination Contamination with radionuclides (Radionuclide) and radioactive waste management. 2. Some

radiopharmaceuticals have a short half-life. Therefore, it is necessary to let it pass before completing the test in order to Total quality control In such case There must be details of product release procedures including responsibilities. of those involved and it is necessary to evaluate the effectiveness of the insurance system continuous quality

Section 3. This rule applies to the production process of manufacturers in the industrial sector, institutes, or medical centers. Nuclear or Positron Emission Tomography (PET) center where the following products are produced and quality controlled.

ÿ.ÿ Radiopharmaceuticals

3.2 Radiopharmaceuticals that decay to positrons (PET Radiopharmaceuticals)

3.3 Radioactive Precursors for use in the production of radiopharmaceuticals.

3.4 Radionuclide generator (Radionuclide generator)

type of production	No need to follow GMP guidelines (Non-GMP)*	must be followed Criteria and methods for producing medicines. The part that ÿ and part 2 according to the principles. including relevant appendices In this announcement			
- Radiopharmaceuticals - radiopharmaceuticals that decays to positrons Effective starting materials radioactive	*Local production* *Atomic reactor or cyclotron*	*synthesis* *Chemical*	*Steps to make* *pure*	*Implementation of results* *Formula development* *Recipe and portion*	*sterilization* *or making it free of* *The germs in the final step*
Nuclide generator radioactive	*Production in the machine* *Atomic reactor or cyclotron*	*Production operations*			

** The reactants and the transport system from the cyclotron to the synthesis equipment may be considered.*

The first step in the production of the active ingredient

Section 4: Manufacturers must explain and provide reasons to support the production process of the active ingredient and the final medicinal product. and apply the criteria and methods for producing drugs, part ÿ or part 2 to be used in the production process/step that specific

Item 5: Preparation of radiopharmaceuticals must comply with the requirements for protection from radiation.

Item 6: Radiopharmaceuticals that are injectable drugs must meet the requirements for sterility for injection drugs and Sterile working conditions for the production of sterile drug products are specified in the Sterile Appendix of the rules and ÿ Pharmaceutical production procedures for producing drugs according to this announcement.

Item 7. Requirements and testing methods for quality control of radiopharmaceuticals that are widely used are specified. It is in the European medicine textbooks. or other related drug textbooks or that has received permission to distribute

clinical trials

Article 8 Radiopharmaceuticals that are investigational drug products in clinical trials must be produced in accordance with the requirements in Appendix 12. Production of research medicinal products of the rules and procedures for producing drugs according to this announcement as well.

Quality Assurance

Article 9: Quality assurance in the production of radiopharmaceuticals is very important. Due to the unique characteristics of the drug This type and production quantities are very small. Also, in some cases, medicine must be given to the patient before all tests are completed. complete

clause 10 An effective quality assurance system is extremely important. Because it must be prevented.
Product contamination and cross-contamination and must protect the environment and workers from radiation.

clause 11 Must record information regarding monitoring of production area conditions. and strict production operations and is part of the evaluation of the product release process.

Article 12: Apply the principles Regarding certification and verification for use in the production of radiopharmaceuticals. And risk assessment methods must be used to consider the scope of the certification examination. and verification Both rules and methods for producing drugs must be followed. and requirements for protection from radiation hazards

personnel

clause 13 Every step of production must be under the responsibility of personnel knowledgeable in prevention. Radiation hazards to personnel involved in production Controlling the analysis and release of radiopharmaceuticals must Receive appropriate training in quality management specific to assigned radiopharmaceuticals. Must be entirely responsible for product release.

Article 14 All personnel performing duties in areas where radioactive products are produced, including employees
Cleaning and maintenance staff Additional training is required on this type of product.

Article 15 If the production location must be used together with the research section. Research personnel must receive adequate training. Sufficient regarding the requirements of the criteria and methods for producing drugs according to this announcement. and quality assurance department Research activities must be reviewed and approved. This is to ensure that research activities do not cause harm to production.
Radiopharmaceuticals

Premises and tools

General Article 16 Production of radioactive products must be done in a controlled area. Both environmental and
Radioactivity All production steps must be carried out in a closed operating area specifically prepared for radiopharmaceuticals.

Article 17: There must be measures to prevent cross-contamination from personnel, objects, radionuclides, etc. Equipment must be used as a closed system. If it is necessary to use open system tools, special care must be taken. To reduce the risk to minimize contamination
The risk assessment must demonstrate that the level of cleanliness of the environment Production is appropriate to the type of product being produced.

Article 18: Accessing the production area requires changing clothes. and is limited to only those who are assigned.

Article 19: The work area including the environment must be monitored for radioactive particles and
Microorganisms as specified in the performance certification test.

Article 20 There must be a plan for preventive maintenance, calibration, and certification. which is carried out by those who have Knowledge to ensure that all facilities and equipment used in the production of radiopharmaceuticals are appropriate. and passed the certification inspection Including the need to maintain records and accounts.

Item 21: Be careful of radioactive contamination within the premises. and facilities must be properly controlled to measure radioactive contamination, which can be achieved by direct measurement with measuring instruments. Radiographically or indirectly by performing routine swab tests.

Article 22 The surface of the tool that comes into contact with the product must not react, stick or absorb to the point of having an effect. on the quality of radiopharmaceuticals

Article 23 Air that leaves the work area with radioactive products must be avoided. Go again unless there is a supporting reason. Ventilation routes must be designed to reduce particle and gas contamination. Radioactivity into the environment There must also be a system to prevent particles and microorganisms from entering the controlled area.

Item 24: The atmospheric pressure in the area in contact with the product must be controlled to be lower than the atmospheric pressure. surroundings in order to store radioactive particles and must prevent the product from contamination from the environment, which can be done By using blocking technology or there is an airlock with lower pressure than nearby areas

Production of Sterile Products Article 25

Sterile radiopharmaceuticals are divided into those produced by the sterile process and those that are sterilized in the final step. Places and facilities must maintain a high level of cleanliness. Environmental conditions appropriate to the type of production operation. Work area for sterile products where the product or containers exposed to environmental conditions must comply with the requirements specified in Appendix 1, Production of sterile medicine

Section 26. The production of radiopharmaceuticals must use a risk assessment approach to consider the differences in Pressure, direction of air flow and air quality

Article 27 In the case where an automatic system, which is a closed system, is used in various steps such as chemical synthesis. Purification, sterilization by filtration. To be carried out in a high-radiation laboratory cabinet (Hot-cell) in Ambient level C (C). However, high radiation operating cabinets must filter the air entering. And when closing the cabinet, there must be a level of cleanliness. High levels of air are suitable for activities inside the cabinet. The sterile process must be done in a clean area.

Level A (A)

Article 28: Assembling sterile tools and equipment before starting production must be done by Sterile processes such as assembling tubes and sterile filters Sealed sterile injection vial

Document operations

Article 29 All documents related to the production of radiopharmaceuticals must be prepared, reviewed, approved and Distributed according to written operating procedures.

Item 30: Requirements must be prepared in documents for starting materials, labels, packaging materials. Products in process Importantly, radiopharmaceutical finished products must have requirements for important items used in the production process. Including equipment or things used to help in the production process, masks, sterile filters because all of these things have an impact. All important to quality

clause ÿÿ Acceptance criteria for radiopharmaceuticals must be established, including acceptance criteria for product release. and product shelf life requirements such as Identification of the chemical identity of isotopes radioactive concentration Purity and specific radioactive activity (specific activity) No. 32 The main equipment used must have a record of

cleaning usage. Cleaning or sterilization, and

Maintenance The record must contain the name of the fruit. Product and model number Specify the date, time and signatures of those involved in that activity

Article 33 Records must be kept for at least 3 years unless national regulations specify a different time frame.

Production operations

Article 34: The production of different types of radioactive products must not be carried out simultaneously within the same work area. such as a high radiation laboratory cabinet or laminar air flow set To reduce the risk of cross-contamination or mixing of Produce less product

Article 35 Verifying accuracy is very important. Including checking the correctness of the system used Computers which must be processed according to the ÿÿ Computer-based system of rules and procedures for pharmaceutical production appendix New production processes must be validated before production for sale.

Item 36 Critical parameters must be able to be identified before or during validation and must Clearly define the range for repeatable operations.

Item 37: Products packaged using the sterile process must have the integrity of the filter checked. Sterile filters are used with consideration given to radiation protection and maintaining the sterility of the filter.

Item 38: Because it works with radiation, it is allowed to label the containers before production. Empty injection medicine bottles. Closed sterile products may be labeled with certain information prior to packaging, provided that such processing is Does not destroy sterility or the eye lens must be protected from radiation exposure if it must be inspected after packaging. Radioactivity in injection vials

Quality control

Article 39 Some radiopharmaceuticals may be used before chemical and microbiological testing has been completed. Completed by evaluating production version documents.

The release of radiopharmaceuticals can occur in at least two phases: before and after analytical testing.
complete

39.1 Relevant authorities must evaluate production records. which must cover the conditions
of production and analytical testing before transporting radiopharmaceuticals under quarantine conditions to clinical departments

39.2 Final evaluation of analytical data to ensure that all deviations from Normal procedures are recorded as evidence. There is a reason. and release it appropriately before giving evidence Documented certification by the designated person. Where certain test results have not been obtained prior to use of the product, the designated person must conditionally certify the product prior to use and finally certify the product after. All test results were received.

Article 40 Most radiopharmaceuticals are used quickly after production. Due to its short lifespan, it must be specified.
The period during which the product can be used is clearly stated.

Item 41: Radiopharmaceuticals containing radionuclides with a long half-life must be tested. to show that The product must pass the acceptance criteria before being released or certified by the designated person. Item 42 Samples can be stored to wait

for the radioactive substances to decay to an acceptable level before being taken.
Test, but everything must be tested. Including testing for sterility as quickly as possible.

Article 43 Must prepare written work procedures regarding production assessment and analysis data. which must be considered before transporting

Article 44 Products that do not meet acceptance criteria must be discarded. If an object is used for re-production, work procedures must be followed. prepared in advance and finished products must pass acceptance criteria before being released into the product market. Items returned must not be remanufactured. and must be stored in the form of radioactive waste. Article 45: Work

procedures must describe the measures that the assigned person must take. If later delivered Products that have not yet expired have been found to have failed the test results. Incidents like this must be investigated to find the truth, including
Take corrective action and prevent to prevent this incident from happening again in the future. and must be recorded. Item

46: Information must be provided to clinical practitioners. And to help facilitate information, bring the system

Checking back on radiopharmaceuticals

Article 47 There must be a system for checking and confirming the quality of the starting materials. Distributor certification must include an assessment. that guarantees that the initial object The quality of the procured products consistently meets the requirements for the purchase of starting materials. Packing material and important equipment in the production process from certified distributors

Reference samples and collected samples are also available.

Item 48: At least sufficient samples of radiopharmaceuticals of each batch of product awaiting packaging must be kept.
6 months after the finished drug product expires unless there is appropriate risk management reason

Item 49: Samples of starting materials that are not solvents, gases, and water used in the production process must be kept for at least 2 years after releasing them into the finished product. If the stability of the reactant as specified in the specification has a period of Shorter than storage, it can be shorter than two years.

Article 50 Other conditions may be specified by agreement with officials of the Food and Drug Administration.
About sampling and collecting samples of initial objects and finished products produced for specific patients or produce
in small quantities or there may be problems with storage

Drug distribution

Article 51 Radiopharmaceuticals can be delivered under controlled conditions before all testing is complete. on condition that the receiving institution will not use the product until test results have been received and evaluated by the recipient.

Assigned

Definition of words

Preparation means handling and radiolabeling equipment with nuclides.
Radioactivity that is emitted from the generator or radioactive precursors in hospitals Generating equipment and objects
Initially, it must be approved for sale in the market. or have a license

Manufacturing means production, quality control, release and transportation.
Radiopharmaceuticals from active ingredients and starting materials

High radiation work cabinet (Hot-cells) means a radiation shielded work area for producing and handling substances.
Radioactive High Radiation Work Cabinets do not need to be designed as separate work areas (isolators).

Authorized person means a person who has basic scientific knowledge.
and techniques and have experience assigned by the organization

Appendix 4

Production of animal medicinal products that are not immune stimulating drugs

Production of premixes for medicinal animal feed

clause ÿ Production of premixes for medicinal animal feed Requires the use of various parts of the plant in large quantities.

Attracts insects and rodents production site design Including the installation of tools and operations must be in accordance with

in a way that can reduce such risks There must also be an insect and animal control program that can be implemented regularly.

Point 2: The process of producing pre-mixed substances creates a large amount of dust. Therefore must be aware of the importance To prevent cross-contamination and facilitating cleaning. For example, consider installing a cleaning system.

sealed conveyor or a dust removal system as appropriate. However, even if such a system is installed However, regular cleaning of production areas is still necessary.

Item 3: Production processes that may have a significant impact on the stability of active drug ingredients, for example:

Using steam in pellet production Must be carried out in a consistent manner. And the same every time in each model produced

Point 4 Production of premixes within a specific area They are not designed to be part of the main production facility.

requires special caution. or a buffer zone must be provided around the said area. To reduce the risk of

Contamination to other production areas

Production of substances to eliminate external parasites in animals

Item 5. Chemicals used to eliminate external parasites in animals that are classified as veterinary drug products that must be registered on a medicinal formula can:

Production is different from the requirements specified in Section 3, Buildings, Premises and Equipment, Section 6, namely, it can produce

and packaged according to the principle of separation of production time Within the area used to produce pesticides, but must not produce other types of veterinary medicinal products in the same area.

Article 6 Must use procedures for cleaning that have been verified for accuracy. to be used for protection

cross contamination And there must be steps in the process that create success. Ensure This safe storage of veterinary drug products

As specified in this document

Production of veterinary drug products mixed with penicillin

Item 7: The use of penicillin in veterinary drug products has not been found to have a risk of hypersensitivity in animals.

As in humans, although data on the incidence of hypersensitivity in horses and dogs are available,

Caused by other substances which are toxic to animals. For example: Ionophore antibiotics in horses, although they are prescribed

The production of some medicines must be carried out in separate areas. Such requirements may be waived in the case of area separation.

for the manufacture of veterinary medicinal products only. However, all measures necessary for Prevent cross contamination

ÿ

and safety of workers It is still necessary to proceed as specified in this document, namely the production of products containing penicillin. Production must be carried out according to the principle of separating production time. and after production Validated procedures for cleaning and decontamination must be followed.

Sample collection

Clause 8: Collection of samples of certain veterinary drug products that are placed in final containers. or mixed in a mixture The advance has a large volume. It may be inconvenient for the manufacturer to choose to store the entire container, so only a portion of the sample may be stored. But you must ensure that there is a sufficient number of samples. and stored appropriately

Article 9: Containers used for storing samples must be made from the same material used for product packaging. Available

Sterile veterinary drug products

of 10 Production of veterinary drug products that must be sterilized in the final step. May be carried out in the area under “Production Sterile Medicines” but must be a clean area with Cleanliness that has a level lower than the level specified in Appendix 1, not lower than the level of Good (D), must be approved by the granting official first.

Appendix 5

Production of immune stimulating products for animals

Principle

The production of immune-boosting products for animals has special characteristics that must be taken into account. When using the insurance system quality into practice and evaluation

This is because there are many animal species and associated pathogens. Makes the products produced diversified and the production volume is small, therefore, work is generally done in separate production times. In addition, due to the specific nature of production (culture process Failure to sterilize in the final step, etc.) must therefore be prevented. Products from contamination and cross-contamination are special. and must protect the environment from contamination This is especially true when production involves the use of pathogenic agents or exotic biological agents. Including the need to protect employees especially. When production involves the use of biological substances that cause disease in humans These factors together with the variety of immune-stimulating products for animals and their inferiority

Especially effective in final product quality control testing In order to obtain adequate product information, the role of the quality assurance system is of utmost importance. The need to maintain control over Covers all topics of principles and methods for pharmaceutical production. Including other criteria mentioned in this announcement. So it's not too much of an emphasis. In particular, data obtained from audits in accordance with the criteria and procedures for pharmaceutical manufacturing (e.g. equipment, facilities, products, etc.) must be rigorously evaluated. and notify the decision to Take appropriate action along with recording

personnel

clause 1 all personnel (including cleaning staff and maintenance staff) who perform duties in the area Producing immune boosting products requires training. and receive information on hygiene and microbiology. Personnel must receive additional training. Especially regarding the products being worked on. Article 2: Responsible personnel must undergo formal training in some fields. or all the

following branches such as Bacteriology, biology, biometry, chemistry, immunology, medicine, pathology, pharmacy, pharmacology, virology, and veterinary medicine and must have sufficient knowledge in environmental protection measures. Section 3 Personnel must be protected against infection from biological agents used in manufacture In the case of biological substances used Can cause

disease in humans. There must be adequate measures to prevent infection of workers from biological agents or from laboratory animals. Relevant personnel must be vaccinated and undergo a health examination.

Item 4: There must be adequate measures to prevent personnel from being carriers of the biological agents used. in production outside the production factory area This depends on the type of biological agent used. Such measures may include: Change all clothes and must cleanse the body before leaving the production area. Section 5: Risk of

contamination. or cross-contamination from operating personnel is especially important. For immune stimulating products Preventing contamination from personnel

involved in production This can be done with a set of measures or methods. Practice ensuring that appropriate contamination protection clothing is worn during procedures.

Production process

Preventing cross-contamination by personnel involved in production operations. This can be done with a set of measures. or practice method This is to ensure that personnel do not pass from one area to another. unless appropriate measures are taken To eliminate the risk of contamination During the working day, personnel must not pass through areas that are likely to be contaminated by living microorganisms or where animals are raised in a place where working with other products or other living creatures, if the passage cannot be avoided, the procedures for eliminating contamination must be clearly specified. Including procedures for changing clothing and shoes and, if necessary, taking a shower, which employees involved in the area must follow.

Personnel entering a containment area that has not handled open-system organisms for at least twelve hours earlier To check that cultures in closed containers whose surfaces have been decontaminated are not considered to be at risk of contamination. Unless the creature used is an exotic species.

Premises No. 6

Premises must be designed in a way that controls risks to both the product and the environment.

Contamination can be controlled by using containment areas, clean areas, clean/containment areas, or control areas. Section 7:

Live biological substances must be handled in containment areas. The level of containment depends on the capacity. in the pathogenicity of microorganisms and whether they are classified as exotic

species or not. Section 8: Biological substances that have lost their effect must be processed in a clean area. and a clean area must be used for processing with uninfected cells isolated from living multicellular microorganisms and, in some cases, sterile culture media. Sterilized by filtration

Article 9: Open system operations involving products or components that have not been treated

Sterile in the next step. Must be operated under class A laminar airflow. which is in the B level area

10 Other operations involving the handling of live biological material (e.g. quality control, research, diagnostic services) must be properly contained and separated. If production is carried out in the same building, the level of containment must depend on the pathogenicity of the biological agent. and is classified as a species

Is it new or not? When carrying out diagnostic activities, there is a risk of the emergence of severe pathogenic organisms. Therefore, the level
Containment must be sufficient to manage all risks. May require containment if quality control or
Other activities are carried out in buildings close to the production area.

clause ÿÿ The storage facility must be easily disinfected. and should have the following characteristics

11.1 There is no direct ventilation to the outside.

11.2 Ventilate air with negative air pressure. The air must pass through a high-efficiency air filter.
(HEPA filters) and no air circulation except in the same area and the air is filtered through a filter
Another layer of highly efficient air (This condition is normally achieved by recirculating air through an air filter that
with high efficiency into the area). However, air circulation between the areas may be possible if the air
Through two sets of high-efficiency air filters, the first filter must be monitored for its integrity.
continuously and adequate measures must be taken to safely exhaust air in the absence of air filters.
perfection

11.3 Air from production areas used for exotic species There must be ventilation. Two sets of high-efficiency air
filters assembled in series. and there must be no air circulation
From the Yes fruit area ta

ÿÿ.ÿ System for collection and sterilization of released liquids Including from condensation that
Contamination of the sterilizer Biomass cultivation machines, etc. Waste in solid form Including animal carcasses must be disinfected.
Sterilize or incinerate as appropriate. Contaminated filters must be removed in a safe way.

11.5 Changing rooms must be designed and used as airlocks. and a sink was installed.
and facilities for washing the body as appropriate The difference in air pressure must be within
Characteristics where there is no air flow between the work area and the outside environment. or the risk of
Contamination from clothing worn from outside areas

11.6 Airlock system of tool passages which is created in such a way that there is no air flow at
Contamination between the work area and the outside environment or risk of contamination of internal tools
Airlocks Airlocks must be of sufficient size to effectively remove contamination on the surface of the objects being transmitted.
Consideration must be given to installing a timer device on the interlock door. To allow sufficient time for the elimination process.
Contamination is effective.

11.7 In many cases, an autoclave with doors on two sides must be used to remove unused objects and
Sterile items enter safely without mixing.

Item 12. Equipment passages and changing rooms must have an interlock system. or other systems that
Suitable to prevent opening more than one door at a time. Changing rooms must be filtered.
Air quality is the same standard as the work area. and has a system that provides sufficient air circulation and independent from the area

Normally, the passage of equipment must be ventilated in an air condition or an area where an air system is installed only may be acceptable.

clause ÿÿ Production operations such as cell culture, preparation of culture media Virus culture that are likely to cause contamination Must be carried out in a separate area. Animals and animal products must be managed. carefully as appropriate

Item 14: Production areas where biological substances are particularly resistantto disinfection, such as bacteria that can form spores. Must be separated and used only for this purpose until the biological substance loses its effect.

Item 15 Must deal with only one type of biological substance at a time in that area, except for mixing. Then start with packing.

Item 16 Production areas must be designed to allow for disinfection between separate batches of production. Using the method that has been checked for accuracy.

Article 17 The production of biological substances may be carried out in a designated controlled area. All closed system tools and made sterile with heat. All connections must be sterile. with heat both after connection and before separation. It may be acceptable if the connection is made under laminar. Airflow with a small number of connections and there is no risk of leakage. and use correct aseptic techniques Sterilization parameters used Before disconnecting, verification must be performed for living things that use Different products may be placed in different biomass growers within the same area, provided that There should be no risk of accidental cross-contamination. However, living organisms that have special requirements for containment should not be exposed. Must be in a separate area dedicated to that product.

Clause 18 Cages or areas for animals that have a purpose or used for production Must be quarantined at Appropriate and/or measures to clean the area and must be separated from areas for raising other types of animals.

Cages or areas for animals used for quality control related to the use of biological agents. Can cause disease, requires adequate quarantine.

Article 19: Access to the production area must be limited to only authorized persons. Procedures must be posted. In writing, Article clear font and be concise and accurate as appropriate

20. Documents related to the building must be in the main file of the factory.

The area around the production plant and the building It must be explained in sufficient detail (in the form of diagrams and written descriptions) to accurately indicate the conditions and conditions for use of all rooms. Including substances video taken in the area Personnel and product flow charts must be clearly marked.

The species of animal in captivity or in the production area must be specified.

Activities carried out in the area surrounding the production area must be specified.

Layout of the containment area and/or clean area The ventilation system must be explained.
Shows air inlet and outlet, filter, and filter specifications. Number of air changes per
Hours and gradation of pressure It must be specified which pressure gradient must be monitored from the pressure indicator.

tool

Article 21: The tools used must be designed. and created according to the specific requirements for the production of each product.

Before using the tool Must pass certification and verification And after that
need maintenance and check for accuracy regularly

Item 22: It must be ensured that the equipment can satisfactorily store primary biological substances as appropriate.

Equipment must be designed and constructed to eliminate contamination. and/or easily sterilized
and effective as appropriate

Item 23: Closed system equipment used for primary storage of biological substances. Must be designed and built to
Prevent leaks or the formation of water droplets and aerosols. The gas

inlet and outlet must be protected to achieve adequate containment, e.g. by using
Sterile filter that does not absorb water.

The import and export of materials must take place in a closed area that can be kept free from
can be infected or, if possible, under appropriate laminar air flow.

Article 24 If necessary, tools must be properly sterilized before use, especially
How to use high pressure dry steam Or other methods are acceptable if steam sterilization is not possible. Due to the nature
of the tool It is important not to overlook certain types of equipment such as centrifuges and water baths, tools used for purification, separation.

or concentration Must go through
Sterility or at least sterilization between uses for different products. The effects of the methods for making
Sterile effect and the completeness of the tools used to be able to determine the duration of their use.
tools

All sterilization methods must be verified.

Article 25: Equipment must be designed to prevent mixing between living things. or different types of products, pipes
Valves and filters shall have identification of each function.

Separate incubators must be used for infected and non-infected packaging. Including living things and different
types of cells. Incubators containing more than one type of organism or cell are acceptable if adequate steps are taken to close the container.

surface contamination and separating containers from each other Culture containers and others must be labeled separately.

Each batch, cleaning and disinfecting these things is very difficult. and must be given special attention

Equipment used for storing biological substances or products must be designed and used in a protective manner

Possible mix-up Stored items must be clearly labeled. and in a leak-proof container.

Cells and germ stocks must be stored separately in separate equipment.

Article 26 Related tools, such as tools that require temperature control, must be equipped with a recording system and/or Warning system

To avoid equipment breaking down and failing, a preventive maintenance system is required. Analyze together with

trends in recorded data

Article 27 Bringing items into the freeze drier must be done in a clean/safe storage area.

appropriate

Removing items from the dryer will contaminate the environment. Therefore, the dryer

The single exit type requires decontamination in a clean area. before bringing the models that will continue to be produced into the area, except

Using the same type of living thing and a drying machine with 2 types Doors must be sterilized after each use.

around, unless it is opened in a clean area

Making the lyophilizer sterile Must be done in accordance with Section 23 in the case of work.

Separate production time It must be sterilized at least after each separation period of production.

Animals and pet areas

Article 28 Animal raising areas must be separated from other production buildings. and must be designed appropriately

Article 29: The health status of animals used in production must be determined, inspected, and recorded. Some animals must

Be managed as specified in the topic (monograph) only according to the medicine textbook, such as herds free from specific pathogens.

Article 30 There must be a system for identifying pets, biological substances, and testing to prevent risks arising from

confusion and to control all possible sources of danger.

Disinfection - Waste Disposal

clause ÿÿ Disinfection and/or disposal of waste and sewage may be especially important. In the case of production

Immune-stimulating products therefore require careful consideration of methods and tools. to avoid

Environmental contamination Including verification and verification.

Production operations

Article 32 Due to the variety of products, there are often many steps involved in production. Immune boosting products for animals and the nature of biological processes Therefore, attention must be paid to practice. According to procedures that have been verified for accuracy. To regularly monitor production operations at every step and control quality during production.

Additional special consideration must be given to the starting material. Culture medium and use of the germline generation system

Starting Materials (Starting Materials)

Clause 33: The suitability of starting materials must be clearly specified in written specifications. Such requirements include details of the supplier, production method, geographic origin and animal breed. that is the source of the starting material This shall include controls applied to the starting material. Particularly important is the control of microorganisms. Item 34: The results of

the test of the starting material must be in accordance with the requirements. In cases where testing takes a long time (e.g., eggs from a herd free of a specific pathogen), it may be necessary to use the starting material before the results of the Quality control analysis are known. In such cases, release through the final product can be Only when the results from testing the initial object are according to specifications

Item 35 Special attention must be paid to the information of the supplier regarding the quality assurance system. to evaluate appropriateness of the source and the scope of quality control testing required. Item 36. If possible, the sterilization method of the starting

material chosen is The use of heat. If necessary, other sterilization methods that have been validated, such as irradiation, may be used. Culture media **No.** 37. The ability of the culture media to support culture must be verified in advance. action Growth of germs.

Clause 38. Culture

media must be made sterile in production. or in the production line The use of heat is the method that should be chosen. Gases, culture media, acids, alkalis, defoaming agents

and other objects must be sterile before being placed in the Biomass culture machine that has been sterilized

strain generation and the cell banking system,

item 39, in order to prevent undesirable characteristics from occurring. This may occur from repeated cultures or multiple generations. Germ strains The production of immune stimulating products for animals obtained from microorganisms, cell or tissue culture, or propagation in embryos and animals must depend on the system. strain generation and/or cell banking system

Article 40 Number of generations (exponential increase Number of generations of culture (passage) between generations of germplasm or Cell banks and finished products must comply with the registration kit for sale.

Item 41: Characteristics must be assessed. and adequately test for contaminants in the germline models and cell banks. Criteria for acceptance of new germline models must be established. Models and cell banks must be developed for storage and use in a manner To reduce the risk of contamination or changes during the preparation of germline models and cell banks, there must be no Handling live or other pathogenic objects, such as viruses and cell lines, in the same area. by the same operator

Article 42: The preparation of germline models and cell banks must be done in appropriate environmental conditions in order to prevent germline models and cell banks and, if possible, with the operator and the external environment

(seed, item 43, must completely explain the source and storage conditions for the starting material of the germinal variety and material form) and must have information on stability. and reusability of strains and banks, containers Packages for storage must be tightly sealed and clearly labeled. and stored at appropriate temperature conditions Storage must be properly monitored. Inventory must be maintained and make an inventory of each container

Article 44 Only the assigned person is allowed to record the registration. Handling of objects and must be done under the supervision of the responsible person. Different strains or cell banks must be stored in a way that avoids errors. Confusion or cross-contamination The germline models and cell banks must be stored separately. and stored in sections on site. different to reduce the risk of total loss.

Principles for working

Article 45 During the production process, the formation of water droplets and foam must be avoided. or cause To a minimum, centrifugation and mixing steps that allow for droplet formation must be carried out in the containment area. or a properly cleaned/contained area. This is to prevent the transfer of the stencil. living organisms

Article 46 When there is an accidental spill, especially of living things. Must be handled quickly and safely. Valid decontamination measures for each species. If it's about bacteria Same type but different breeds or viruses that are very similar Use a process that has been validated. For one type only unless there is sufficient reason that the bacteria or virus may be significantly resistant to different agents. Significance

Article 47 Work involving the transfer of objects such as sterile culture media. Culture or product, if possible, must be processed in a closed, sterilized system In the event that this is not possible, Prevents transfer operations under laminar airflow.

Article 48 The addition of culture media or cultures to the biomass culture machine and other containers must be carried out. under carefully controlled conditions To ensure that no contamination occurs. Care must be taken to ensure that Connect containers correctly when adding culture fluid.

No. 49 If necessary, such as when two or more fermenters are in the same area. Sampling connecting pipe
or fill and connector (after connection, before product flow and again before connector separation) must
Make it sterile with steam. In other cases it may be possible to disinfect the connecting pipe using chemicals and make the connection under laminar.
Airflow to prevent contamination is acceptable.

Item 50: Tools, glassware, external surfaces of product containers and other objects must be disinfected.
before transferring from the containment area using validated methods (see paragraph 46).
The documentation aspect of production models can cause problems only with documents that are required to be used in compliance operations.
Only minimum standards, criteria and methods for producing drugs may be imported into and out of the production area. If
Obvious contamination, such as from a spill or spray, or involving exotic species, must be disinfected.
Sufficient documentation through tools or transfer information using methods such as copying or faxing.

Item 51 Waste from production that is in liquid or solid form, such as scraps of eggshells and discarded petri bottles.
Culture or unused biological substances Must be made sterile. or disinfect before removing from the storage area. In some cases, other methods may
be used, such as Sealed container or tube

Article 52 Items, objects, including documents brought into the production room. must be controlled carefully so that
Ensure that only objects are involved in the production operation. There must be a system in place to ensure that objects brought into the production room
Corresponds to what is taken out of the production room. In order to avoid the accumulation of objects within the production area.

Article 53 Items and objects resistant to heat that are imported into clean areas or clean/containment areas must pass Autoclave or locker
with door, opening on both sides. Objects and items that are not heat-resistant must pass through an airlock with a closed door.
Interlocks that have been sterilized and sterilized objects from other areas must be double-wrapped. and through the airlock
with appropriate caution

Item 54: Care must be taken to prevent contamination or confusion during incubation. There must be a method of practice. Cleaning and
disinfecting the incubator Containers in the incubator must be carefully labeled, item 55, except for the mixing clear and clear

process. and continue with packing (or when using a completely closed system) will contain biological agents.
Only one type of organism is processed in the production room at any given time. Production rooms must be disinfected.
effectively during the implementation of exposure to different living biological substances

Article 56: Products must be made to lose their effect by adding substances that make them ineffective. with adequate stirring
The mixture must be transferred to a second sterile container. unless the container has a size and shape that can be toppled
and easy to shake and mix To wet the entire interior surface with Che's most amazing mixture. Culture media/inactivating substances

Item 57: Do not open the container of the inactivated product or collect product samples in the area.
containing living biological substances All subsequent processing of the inactivated product must be carried out in a clean area.
Level A-B (A – B) or within a separate closure device for inactivated products.

Item 58 Careful consideration must be given to checking the correctness of the sterilization method. Virus removal and inactivation, item 59, must be packed

as quickly as possible after production. Product containers are suitable and stored under specified temperature and labeled. Clause 60: There must be a system to conditions. Waiting for packing before packing must be sealed

guarantee the integrity and lid of the container after packing. Closing the cap of a

bottle containing biological substances must be done in a manner that ensures that there will be no contamination with other products, Section 61, or the escape of living things into other areas. or external environment

Article 62: There are various reasons that may cause delays. between filling into the final container and labeling and product packaging, procedures must be established for the storage of unlabeled containers to prevent confusion and to ensure satisfactory storage conditions. Special care must be taken in storage. Products that are not heat resistant or products that are sensitive to light The storage temperature, item 63, must be specified at each stage of production.

The yield of the product must be consistent with the expected yield.

From the production process If there is a significant difference in production Must investigate to find the cause.

Quality control

Article 64 Control during production plays an important role in ensuring consistency of quality. Biopharmaceutical products, controls that are important to product quality, such as Removal of viruses that cannot be carried out on the finished product must be carried out at appropriate steps during the manufacturing process.

Article 65: Samples of products during production must be collected in sufficient quantities. and stored under conditions appropriate for use in repeat testing or confirm production version control

Clause 66 may contain requirements for continuous monitoring of data during production, such as:
Monitoring physical parameters during fermentation

Article 67 Continuous cultivation of biological products is a common practice. and must be considered specially in the need for quality control requirements arising from this production method.

Appendix 6

Production of medicinal products from herbal plants

Principle

Medicinal plant medicinal products are complex and variable in nature, therefore Controlling the starting materials, storage and processing of products is important in the production of medicines from medicinal plants. In addition to having to comply with other categories Follow the additional criteria specified in this appendix.

The starting materials used in the production of medicines from medicinal plants may be medicinal plants, medicinal plant substances. or medicine preparation from medicinal plants These starting materials must be of appropriate quality. Including supporting information to deliver to manufacturers of medicine preparations or medicines from herbal plants. To ensure that the starting materials from medicinal plants are of consistent quality. must have Detailed agricultural production information includes seed selection, cultivation. and harvest conditions These are all important things that affect the quality of the starting material. and consistency of the finished drug product. Recommendations on appropriate quality assurance systems for cultivation. and a good harvest is prescribed in “Rules and methods for cultivation and harvesting” for medicinal plant starting materials. which is prepared as National or international guidance documents, such as European Medicines Agency guidelines.

(EMA) World Health Organization or other equivalent criteria

The criteria in this appendix apply to starting materials from all types of medicinal plants, including plants with medicinal properties. Starting materials from medicinal plants or medicinal recipes prepared from medicinal plants.

The table shows the application of the criteria and procedures. Good ingredients are used in the production of medicinal products from herbal plants.

activity	Criteria for good methods for cultivating snakeheads and harvest (GACP) (of EMA, World Health Organization or equivalent)	Part 2 of the criteria and methods for producing medicine+	Parts ÿ of criteria and methods for producing drugs+
Cultivation, collection and harvest crops Algae, fungi, and lichens and their storage collect secretions	x		
Cutting and drying of plants and seaweed Molds, lichens and exudates*	x	x	x
Extraction by crushing plants and distillation**		x	x
Grinding, processing of solid substances Sit Plant extraction, separation, purification Concentration or fermentation of starting materials from medicinal plants		x	x
The production process for pharmaceutical forms, including ÿ Packaged as medicinal products from herbs			x

Note:

Description

+ Classification of medicinal plant materials according to the principles and methods of drug production. Depends on the use of the object products produced by drug production licensees Medicinal plant materials may be classified as active medicinal substances. Products during production or finished products Manufacturers of medicinal products from medicinal plants are responsible for ensuring that the classification criteria are applied. Types according to the principles and methods of production are used appropriately.

* Manufacturers must ensure that these steps are carried out in accordance with the pharmaceutical registration or registration. Initial steps taken in the plantation as described in the registration or registration shall Standards, criteria and methods for cultivation and harvesting of starting materials from domestic medicinal plants. or international standards. In addition, the rules and methods for producing drugs are also used in the cutting and Make it dry as well.

** In relation to the extraction by pressing plants and refining, if these activities are an important part of Harvesting to maintain product quality according to approved specifications is acceptable for these activities. It is carried out in the plantation area. If the cultivation is carried out according to the standards, criteria and methods for cultivation and harvest (GACP) within a country or internationally (e.g. EMA, World Health Organization or equivalent). This situation must be considered a special exception that must be described in the drug registration document or registration.

Activities carried out on plantations must be guaranteed to be documented, controlled and verified. Appropriate accuracy in accordance with the principles of the rules and procedures for drug production, Office The Food and Drug Administration may conduct audits of these activities to assess compliance with the law/ Criteria

Building, storage

area 1.

clause Starting materials from medicinal plants must be stored in a separate area. There is protection from insects or other animals. In particular, rats are not allowed to enter the said area. And there are effective measures to prevent the spread of animals. and microorganisms that may be mixed in with the starting materials. Prevents fermentation or mold growth and prevent cross contamination. A separate area is required for the quarantine of received medicinal plant precursors. and for storage Base materials from herbal plants that have been approved

for use. Item 2. The storage area must have good ventilation. The storage is in a way that allows air to circulate

easily. Item 3 must be given importance. Special in cleaning and maintenance for the storage area Especially in the case of dust and dust formation.

Item 4: Storage of starting materials from medicinal plants. or medicinal recipes prepared from medicinal plants that have been prescribed for certain conditions Special storage in terms of humidity Light protection temperature Must organize operations and monitor co as mentioned as well

Production area No.

5 must have special management methods during sampling, weighing, mixing and following operations. Procedures for medicinal plant precursors and medicinal plant preparations in the event of dust formation. This is to help. Easier to clean and avoid cross-contamination, such as providing a vacuum cleaner There is a separation of specific places in the process. such etc.

tool

Article 6: Tools, filter materials, and others used in the production process must be compatible with the solvent used in the extraction. This is to prevent the release or absorption of unwanted substances that may affect the product.

Document operations

Specific requirements for starting

materials No. 7 Manufacturers of medicinal products from herbal plants must use herbal starting materials produced in accordance with the criteria and methods. In the production of drugs according to this announcement and as specified in the drug registration documents, an assessment report must be provided. A complete supplier of herbal starting materials which has been evaluated by manufacturers of medicinal plant medicines or by another organization assigned Evidence of the active substance inspection is an important basis for the quality of the starting material. The manufacturer must verify, as appropriate, that Suppliers of medicinal plant precursors have followed the rules and procedures. To plant and harvest? If the above criteria are not followed. There is appropriate control. According to the quality risk management guidelines or not?

Clause 8 In order to comply with the rules and procedures for drug production, Part 1, Section 4, “Operations in

Document” Specific requirements for starting materials from medicinal plants or medicines prepared from medicinal plants must specify information.

As follows:

8.1 Scientific names of medicinal plants

8.2 Details of origin, such as country or region of origin. and other related information such as

Cultivation information Harvesting time, storage methods, pesticides used, contamination from radioactive substances, etc.

8.3 Parts of medicinal plants used

8.4 Process for drying medicinal plants

8.5 Physical characteristics of medicinal plants including visual inspection or microscope

8.6 Checking the identity of the active drug or analogue Special inspection is required in cases where

Medicinal plant substances may be adulterated or otherwise substituted. Including having to have a reference sample ready to be used for comparison.

unique

8.7 The amount of water in the starting materials from medicinal plants is checked according to the relevant drug textbooks.

8.8 Methods for analyzing or testing the components of active ingredients in treatment or analogues. Methods

Check for pesticide contamination in starting materials from medicinal plants. and determine acceptance criteria using the following methods

Related medicine textbooks or methods that have been verified for accuracy

ÿ.ÿ How to check for mold contamination Microorganisms include aflatoxins. Other mycotoxins

parts of animals and insects and determine acceptance criteria

ÿ.ÿÿ Methods for detecting toxic heavy metal contamination and adulteration of substances

8.11 Methods for checking for foreign objects

8.12 Other inspections according to general requirements or specific requirements according to the relevant drug textbooks for

This

Objects originate from that herb

uh

Reducing contamination must be recorded. of fungi, microorganisms, or anything else as documentary evidence. There are specific requirements.

and procedures specifying details of the process, test methods, and acceptance criteria for residues in

starting object

Additional recommendations in the production process

Item 9: Prepare instructions for the production process to explain various operations with starting materials from medicinal plants.

such as cleaning steps Drying, grinding, mineralization, drying time and temperature. Method used

To control portion size or the particle size of the starting material

clause 10 Prepare a manual and written work record. To ensure that the starting materials are from medicinal plants.

Every packaged unit is carefully inspected for adulteration/adulteration. or foreign objects such as scrap metal

Broken glass, parts or animal droppings, stones, gravel, sand, etc., including signs showing deterioration of the original material.

clause ÿÿ Prepare manufacturing process instructions that explain mining methods. or other methods used to separate foreign objects Methods

for cleaning/sorting plant parts before approved starting materials are stored. or before starting

production

Clause 12 for the production of medicinal preparations from medicinal plants. Prepare production process instructions that include

Details of the solvent Extraction time and temperature Details of concentration in different steps and methods used

Quality control

Sampling

clause 13 Medicinal plants or medicinal plant precursors often have non-homogeneous characteristics.

so natural Sampling of these starting materials must therefore be carried out with extreme caution by personnel with specific expertise. For each model, a

model-specific document must be prepared.

Item 14: Reference samples of plant starting materials must be provided. especially In the case where the starting object does not exist

Information is in the relevant drug book. A sample of the unmilled plant material must be obtained. In the case of using the starting object

Powdered form

Article 15 Personnel in the quality control section must have specific expertise and experience in starting materials.

from medicinal plants Medicine prepared from medicinal plants and/or medicinal products from herbal plants To be able to proceed

Test for identification and check for adulteration Contamination from fungal growth contamination of

animals and insects, inhomogeneity of the rough starting material received, etc.

Article 16 Identification and quality inspection of starting materials from medicinal plants. Prepared medicine recipe

from medicinal plants and medicinal products from herbal plants must be processed according to national standards or

International standards for quality and specifications or according to specific topics of related drug textbooks

Appendix 7

Sampling of starting materials and packing materials

Principle

Sampling is an important operation. Because it is only the starting material or packaging material. Only a small portion of each model is used as a representative test. Correct conclusions cannot be drawn from Testing a sample that is not representative of the entire model. Accurate sampling is therefore an important part of the quality assurance system. Note: Sampling Must comply with the requirements

specified in Section 6, Quality Control, Section 1. The additional requirements mentioned herein apply ÿÿ Up to 14 of materials and packaging materials. to sampling of Principles and methods for producing drugs, only the starting

personnel

1 Those responsible for sampling must be trained in correct sample collection and have training. continuously Training must at least cover the following points.

1.1 Sampling plan 1.2 Written

procedures for sampling 1.3 Techniques and tools used in sampling

Risk of cross contamination

ÿ.ÿ

1.5 Precautions regarding unstable substances or sterile substances 1.6

It is important to consider and examine the characteristics of the starting material. Packaging materials, containers and label visually

1.7 The importance of recording unexpected or unusual conditions that occur.

Initial

object number 2: Samples were collected from every container of the entire batch. and take each sample for testing The identity of the starting object Samples may be taken from certain containers if these are followed. Procedures that have been verified to ensure that the initial contents in the container are correctly labeled.

Item 3: Checking the accuracy of the method for collecting samples in some containers must at least consider the following points.

3.1 Type and status of producers and suppliers of starting materials. and understanding of the requirements of Rules and procedures for drug production at drug production sites

3.2 The quality assurance system of the manufacturers of the

starting materials. 3.3 The conditions and controls of the manufacturers used in

the production of the starting materials. 3.4 The types of starting materials and

the medicinal products that use the starting materials. Under the management as mentioned above may accept procedures that do not require Test the identity of the starting material in each incoming container for the following

cases: 3.5 In the case where the starting material comes from the manufacturer. or a factory that produces only one

type of starting material. 3.6 The starting material comes directly from the manufacturer. or in a sealed manufacturer's container, which must be a manufacturer with a reliable history And the quality assurance system has been assessed by the pharmaceutical product manufacturer or by an official accreditation agency.

Such procedures have been validated. Not applicable in the following cases: 3.7 Initial materials delivered by

middlemen such as brokers who do not know the origin of production. or production source
That has not yet been certified.

3.8 Starting materials used for injectable drug

products, Section 4: Evaluation of the quality of each batch of starting materials. It must be obtained from testing a representative sample of the entire lot, which may be from the same sample as was used to test the identity of the number of samples to be used as representative of the lot. Must be determined using the statistical methods specified in the sampling plan. However, the number of samples to be taken must be determined. combined into a mixed sample The type of the starting object must be considered. Including the knowledge of the supplier and the sample must be mixed homogeneously.

Packing materials

No. 5 The sampling plan for packing materials must at least consider the quantity received. desired quality of packing material Types of packaging materials (such as primary packaging materials, printed packaging materials), production methods, and knowledge of packaging material manufacturers' quality assurance systems learned from inspection. Evaluate the quality assurance system However, the number of samples that will be used to represent the model. Must be determined using statistical methods. specified in the sampling plan

Appendix 8

Production of liquids, creams and ointments

Principle

Liquids, creams and ointments are products that are susceptible to microbial and other contamination during production. Therefore
Therefore, special measures must be taken to prevent contamination.

note : The production of medicine liquids, creams, and ointments must follow the rules and procedures for producing medicines and
Other additional requirements as shown in this announcement of the Ministry of Public Health. The following requirements are focused on
Only the parts related to production only.

Premises and tools

clause ÿ To prevent product contamination, a closed system must be used in the production process. This includes the process of loading and
unloading medicines. In production areas where clean products or containers are left open and directly exposed to the air, there must be
Effective air circulation with filtered air

Item 2: The design and installation of tanks, containers, pipes and pumps must be able to be easily cleaned and
Eliminate germs, especially the design of the tool. There must be a dead spot or area where residue can accumulate.
It is the least likely source of microbial growth.

Item 3: Equipment that has contact with the product. Using glass The handle is made of high quality stainless steel. and avoid
equipment

Production operations

Clause 4: Characteristics must be specified. and monitor the quality of water used in production Both quality
Chemistry and Microbiology Water systems must be maintained to avoid or reduce the risk of growth
This This ,
Microorganisms after eliminating germs in the water system with chemicals Chemicals must be washed away according to approved procedures. Verified To
ensure that those chemicals are effectively disposed of.

Article 5 Objects received in the form of large transport tanks must be inspected for quality before being transferred to
large volume storage tank

Point 6: Care must be taken to transport substances through pipes directly to the correct destination.

Point 7. Materials that release fibers or contaminants must not be used, such as cardboard or wooden pallets. Do not enter areas where clean
products or containers are exposed to air.

Article 8 Mixed medicines, suspensions and extended-release medicines The product must be controlled to be uniform throughout the packaging. The mixing and filling process must be validated. Special care must be taken at the beginning of Packing process After stopping during the process and the final phase of the process to make sure The product retains its uniformity. Item 9: Drug products awaiting packaging include drug products that have already been packed. But it hasn't been labeled or packaged yet.

The immediate box must indicate the longest period of time accepted for storage and the storage conditions.

Appendix 9

Production of aerosol preparations for Prescribed dose inhalation

Principle

The production of pressurized aerosol products for inhalation with a dosing valve must meet certain requirements. is a special condition Due to the specifics of this form of medicine The production conditions for this form of drug preparation must be prevented. Contaminated by microorganisms and particles Quality Assurance in Valve Components And the uniformity of the suspension drug formulation is considered to be of special importance.

Note: The production of aerosols with fixed doses must follow the rules and procedures for drug production. and other additional requirements as shown in this announcement of the Ministry of Public Health. The following requirements are focused on Only the parts related to production only.

General

requirements 1 The current production and packaging system has 2

ÿ.ÿ The following method Two-stroke system or packing under pressure The active drug is suspended in a high-boiling propellant. A predetermined amount of drug is loaded into a container, sealed with a valve, and the lower-should**b**oiling propellant is injected through the valve stem. to be a finished product. Therefore, the propellant suspension be stored in a cool, designated place to

prevent loss from evaporation. 1.2 One-stroke system or packing under cold The active drug is suspended in a propellant mixture which must be controlled under high pressure or low temperature conditions. The suspension is then placed in a container. directly within one time

Premises and tools

Item 2: Production and packing must be carried out under a closed system as much as possible. Item 3: The

air in the area in contact with the product or component is clean. must be filtered Moreover, it must be

According to the requirements of the area, the cleanliness level must be at least good (D) and entry or exit must be through an airlock.

Production operations and quality control

The valve for determining the dosage of aerosol is a more complex part than other components. It must have 4

Sampling Requirements. and proper valve testing Including the manufacturer must conduct an assessment of the insurance system. Quality of valve manufacturers

Section 5. All types of fluids, for example, liquid or gas propellants. Must be filtered for elimination.
Particles larger than 0.2 microns, if possible, must add a filtration step as close to the filling point as possible.

Item 6: Containers and valves must be cleaned according to procedures that have been verified.
It must be appropriate for the use of the product. To ensure that it is free from any contaminants such as production aids.
For example, lubricants or microbial contaminants from cleaned valves. Must be stored in a closed container.
clean place and be careful of contamination before use, for example, contamination from sampling The container
It must be taken to the packaging line under clean conditions. or cleaning in the packing line closest to the packing point

Item 7. Packaging of products in the form of suspension medicines must be done with caution. To ensure consistency
of the drug packaged throughout the packaging process

Point 8: Packaging in a two-stroke system requires ensuring that both strokes provide the correct weight and components.
Correct, therefore, in each step, the weight of every container must be checked.

Clause 9: All types of control after packing must prevent which causes a leak. The leak test must not
contamination from microorganisms or moisture. Wow!

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Appendix 10
computer based system

Principle

The guidelines in this appendix shall apply to all computer-based systems that are part of activities to:
Control according to standards, rules and methods in drug production A computer-based system consists of a set of
Software and hardware components that work together to perform a certain function.

Computer programs must be verified for correctness. and technological infrastructure
Information must be verified.

The use of computer-based systems in place of manual operations must not affect the quality of the work.
Process control products or quality assurance is reduced and must not increase the overall risk of
process

General chapter

Risk management

clause ÿ Risk must be managed throughout the life cycle of computer-based systems with security in mind.
of patients, completeness of information and product quality in risk management systems, decision making
About the scope of verification and data integrity control must be based on assessment.
The risks of computer-based systems are supported by appropriate reasons. and is recorded as documentary evidence

personnel

Article 2: All relevant personnel, such as those responsible for the process Person responsible for the system assigned person
and information technology departments must cooperate closely All personnel must have a level of qualifications.
Accessing the system and appropriate scope of responsibility to be able to perform assigned duties

Product suppliers and service providers

Section 3 In the case of providing to a third party (such as a product supplier The service provider) is the operator, such as
providing, installing, adjusting, configuring the overall connection. Validate, maintain (e.g., through remote access), modify, or maintain
computer-based systems or related services. or in order to process data there must be
Establish a formal agreement between the manufacturer and the third party. and in the agreement there must be a statement specifying
Clearly assume the responsibility of third parties. Information technology departments must be considered and treated in the same way.

Item 4: The ability and reliability of the product supplier is an important factor in selecting products or must depend on risk
ÿ
Service provider, need for inspection assessment.

Item 5: Documents accompanying ready-to-use products that are already on sale must be reviewed by users whose duties include:
Control to check that user needs are met.

Article 6 Quality system and inspection information related to product suppliers or software developers and
The installed system I have to This will be available for the auditor to review upon request.

Project range

Validation

Article 7 Documents for verification of accuracy and the report must cover the steps involved in the life cycle.
of the system, the manufacturer must be able to justify the standards, protocols, and acceptance criteria. Method of practice and
Producer's notes based on risk assessment

Item 8: The verification document must include a change control record (if
involved) and reports on deviations found during the validation process.

Article 9 A list of all relevant systems must be prepared. Including work related to criteria and
The system's drug production methods are kept up-to-date.

For important systems, there must be an up-to-date system description with details of the entire system arrangement.
physical and logical Data flow and connection to other systems or processes. Requirements.
Basics of required hardware and software, including security measures.

clause 10 User requirements must describe the desired functionality of the system used.
computers and are determined based on a risk assessment. and the impact on the criteria and procedures for
Produce medicines which are prepared as documentary evidence User requirements must be traceable throughout the lifecycle of the system.

clause 11 Users with control responsibilities must take all appropriate steps. to make sure
The system has been developed in accordance with an appropriate quality management system. Suppliers must receive
Evaluate appropriately

Item 12 is for checking the correctness of computer-based systems developed according to specific needs.
There must be a process in place to ensure that quality measures are in place. and work efficiency in every period
The system life cycle is evaluated. and report accordingly. difficult

13 There must be evidence showing that there is a testing method. and appropriate testing simulation situations.
Items must be especially taken into account. System (process) parameter limits, data limits, and management
Errors Automated test tools and test environments must provide documented evidence of their evaluation.
Sufficiency and appropriateness of the tools and environment

Article 14 If the data is transferred to another form or system. Validation must be
Verify that the data has not been altered in value. and/or meaning during this transfer process.

Operational

period: Data No. 15: Systems that use computers that exchange data electronically with other systems must have a system. Verify proper built-in installation. for the accuracy and safety of entering and processing data to reduce risks

Verification of accuracy

Article 16 Important information entered by the operator must be further verified to ensure that the information is correct. This app May be performed by a second operator. or by electronic means that have been verified. Significance and potential consequences of erroneous information. or has been entered into the system incorrectly There must be preparation. Protect under risk management

Data preservation

Article 17 Data must be protected from damage. Both by physical and electronic means. Retained data must be verified as accessible, readable and accurate. Access to information must be able to This can be done throughout the data collection period. Article 18:

There must be regular backups of all relevant data, completeness, and accuracy. The nature of the backed up data as well as the ability to restore the data must be verified during the backup process. validate and periodically inspect and follow up

Print work

Item 19 must be able to print and obtain clear printed copies of electronically stored data. Product

20 is for records supporting release. school for distribution of the system must be able to print printouts. Item Indicates if data has been changed after it was first entered.

Record to check login, item 21, from

risk assessment. Consideration must be created to create a system that can record all changes and deletions of information related to the rules and methods of drug production. (The system must be able to create "Save for review login") and the reason for the change is recorded. or deletion of information as evidence documents, records to verify login must be available and ready to use and can be converted into a format that is generally understandable and is regularly reviewed.

Change management and customization

Article 22 Changes to computer-based systems, including adjustments to system settings. Must be carried out under control and according to specified procedures only.

Periodic evaluation

Article 23 Computer-based systems must be evaluated periodically. To confirm that the system is in a usable state and is correct according to the rules and methods for pharmaceutical production. In that evaluation, consider (as appropriate) the current working period. Deviation record Events, problems, upgrade history, performance, reliability, security, and validation status reports
system

safety

Article 24: There must be both physical and and/or logically to restrict access to the systems used. Computers are provided only to those assigned to them. Appropriate methods to prevent unauthorized persons from gaining access to the system, such as keys, passes, personal ID plus password, biometrics, restricting access to the device. Computers and data

storage. Item 25. The scope of security control depends on the significance of the

computer system. Item 26. Changes must be recorded. and revoking permission to access

the system. Article 27: A data and document management system must be designed. To be able to record the identity of the worker logged in Changing, confirming, or deleting information

including date and time **Handling**

of incidents, Article 28: All incidents must be reported and evaluated. (Not only when the system stops working and data is inaccurate.) Significant events must be investigated to find the root cause. which will determine the method Continue corrective and

preventative action.

Electronic signatures Article 29 Electronic records may be signed electronically. Electronic signatures must have the following characteristics:

29.1 It has the same effect as a handwritten signature within the boundaries of the company.

29.2 Permanently tied to the relevant record.

29.3 Specify the time and date of the electronic signature.

Release of Product Releases for Sale

Article 30 Computer-based systems used to record certification and release of product releases for sale shall allow only designated persons to certify and release releases of product releases. The system must be able to clearly identify and record who authorized or certified the product version. Certification and release of the product version must be done using an electronic signature.

business continuity

clause 31 For the availability of computer-based systems, especially those supporting critical processes, provision must be made for the continuity of those support systems. In the event that an event occurs, the system stops working, such as a system that is operated by an operator. or other alternative systems Time required to complete the alternative system Can work instead will depend on risk. and the suitability of the system to the business processes it supports. These alternative system arrangements must be documented. and has been adequately tested

Storage

Article 32: Data must be stored. and the readability and completeness of the data are checked. If the system is changed (such as computer equipment or programs), testing must be done to ensure that Can also retrieve data from the system.

Definition of words

computer program (Application) means software installed on the platform/hardware that defined and provides specific functionality

Computer-based systems developed according to specific needs (Bespoke/Customised computerised system) means a system that uses computers that are specifically designed. To be suitable for the process specific business **Ready-to-**

use software that is commercially available (Commercial of the shelf software) means software that is commercially available. which suitability for use has been confirmed by Various users **Information technology infrastructure (IT**

Infrastructure) means hardware and software such as Network software and operating systems that make computer programs work

Life cycle means all steps during the life of a system. From the determination want from start to end of use Including designing and setting specifications. Programming, testing, installation, operation and maintenance **Process owner** means a person who is

responsible for the process.

business

The person responsible for the system (System owner) means the person who is responsible for the readiness to work and Maintenance of computer systems including the security of data

contained in those systems. **Third party** means a group of persons who are not under the direct management of the production licensee and/or licensee. import

Appendix 11

Use of ionizing radiation (Ionising radiation) in the production of pharmaceutical products.

Introduction

Ionizing radiation may be used during the manufacturing process for various purposes, including reducing the amount of contamination and sterilization of products, for example starting materials, container components or

Blood products and products

There are two types of irradiation processes. These include gamma irradiation from radioactive sources and radiation. High-energy electrons (Beta radiation) from particle accelerators

gamma irradiation Two different modes of operation may be used:

(1) Batch mode is the placement of products in fixed positions around the origin. Radiation without being able to Do not allow the product to enter or leave the area while in contact with a radiation source.

(2) Continuous mode is an automatic system that delivers products along a conveyor belt. Enter the radiation room along the designated route at an appropriate speed. Then pass out of the room.

Electron irradiation involves transporting a product along a conveyor belt through a beam of high energy electrons (beta radiation). The Continuously or intermittently radiation travels back and forth through the product's conveyor path.

responsibility

1 Radiation may be administered by the drug manufacturer. or an irradiation factory that has a production contract which the irradiation operator Item: Must obtain appropriate production license.

Article 2: Drug manufacturers are responsible for the quality of their products and for achieving the objectives of irradiation. This ensures that the dosage required by the drug manufacturer is obtained. The irradiation operator must be careful in disposing of containers. For radiation, that is. The outermost area of the container containing the irradiated product.

Item 3: Radiation amount and required limits Must be notified in the drug registration.

Radiation dose measurement

Clause 4: Measuring the amount of radiation means Measurement of absorbed radiation using a radiation dosimeter. Understanding and correct usage techniques are essential for verifying accuracy. Irradiation factory testing Before starting the operation and process control

Item 5: Each model of radiation dose measuring device in regular use must be calibrated. and can be traced back to national or international standards The calibration frequency must be displayed on the equipment and must be followed.

Item 6: Preparation of standard calibration curves for regularly used radiation dose measuring equipment and measurement of changes in absorbance after irradiation must use the same equipment. If different equipment is used The absolute absorbance value of each device must be displayed.

Item 7: The accuracy of the measured radiation amount depends on the amount of moisture. Time lapse temperature between irradiation and measurement of radiation dose rate and type of radiation measuring device

Item 8: Wavelength of the instrument for measuring changes in the absorption value of radiation. and thickness measuring tools measuring equipment must be calibrated regularly at specified intervals. Purpose and use of radiation Depends on stability Radiation dosimetry equipment

Process validation

good. Item 9. Validation of the product is to prove that the quantity of the plant is

Article 10 Verification of accuracy This must include the preparation of a diagram showing the distribution of radiation doses. absorbed within an irradiation container in which the product to be irradiated is placed according to a specified pattern.

clause ÿÿ Radiation process requirements shall include at least the following items:

11.1 Details of product containers

11.2 Product placement pattern in the irradiation container in the case of product Many types with different densities Ensure that no high-density products are exposed to low radiation doses. or products with high densities must not block the radiation exposure of other products. The format must be specified. Product placement and verification

11.3 Arrangement of containers for irradiation around the radiation source. (model type) or conveyor path along a conveyor belt(continuous)

11.4 Upper and lower limits of the amount of absorbed radiation in products and their relationship to measurements. The amount of radiation used regularly

11.5 Maximum and minimum limits for the amount of absorbed radiation in irradiation containers and Relationship with routine radiation dose measurement To monitor the amount of absorbed radiation.

11.6 Other process parameters include dose rate, maximum duration of irradiation, number of irradiation times, etc.

Testing the irradiation plant before starting operation

General

Requirements No. 12 Testing of an irradiation factory before starting operation is an operation to obtain evidence. Documentation that the irradiation facility is consistently operating within pre-established limits when meeting the process requirements in the content of this section.

Preset limits are the maximum and minimum radiation doses that are designed to be absorbed. By using a container for irradiation, the irradiation operator must be aware of various factors, including the variations that may occur. Effects on exposure to radiation outside the limits in the product

clause ÿÿ Chai Rong factory testing before starting the operation Contains the following topics

13.1 Design

13.2 Preparation of radiation distribution maps

ÿÿ.ÿ Document operations

ÿÿ.ÿ Requirements for retesting of irradiation plants

Gamma irradiation machine

design

Item 14: The amount of absorbed radiation received by each part of the irradiation container at any point from Irradiation depends on the following

factors: 14.1 The intensity and shape of the

radiation source. 14.2 The distance between the radiation source and the

irradiation container. 14.3 The duration. Irradiation controlled by setting the time or speed of the

conveyor belt. 14.4 Composition and density of materials and other products between the radiation source. and containers for irradiation.

Item 15. The total amount of absorbed radiation also depends on the transport path of the container through the continuous irradiation machine or the pattern of product placement in batches. and the

number of cycles of irradiation. Clause 16: Continuous irradiation machine with a definite transport path. or a model with a layout The exact product depends on the strength of the radiation source. and type of product specified

The main parameters that Controlled by the operator is the speed of the conveyor belt or the setting of the radiation time.

Preparation of radiation distribution maps

Item 17: The procedure for preparing a radiation distribution map must include a container for irradiation which is filled with a simulation product. or product agents with uniform density placed in the irradiation machine must be equipped with equipment Measure the amount of radiation throughout the inside of at least three irradiation containers that will pass through the machine. Irradiate and surround with similar containers or replica products. If the product placement is uneven, the radiation dose measuring device must be placed in more than three containers, depending on

dose measuring device. Radiation, for example, the size of the radiation container. Item 18: Location of the containers not larger than 1 x 1 x 0.5 meters must be arranged three-dimensionally, spaced 20 centimeters apart throughout the container, including the outer surface. However, if you know the location with the lowest amount of radiation and highest from previous use of the irradiation machine The radiation measuring device can be moved from the area where the radiation dose is. in the average criteria To be placed in the area with the highest and lowest radiation doses in a three-dimensional manner, spaced 10 cm apart.

Item 19 The results of the methods used in items 17 and 18 must give the minimum and maximum values of the absorbed radiation amount. in the product and on the surface of the container for irradiation according to the parameters specified by the factory. density of Products and product placement formats

Article 20 The principle for preparing a radiation distribution map must be to use a reference radiation dose measuring device for the preparation. The radiation distribution diagram is accurate. However, regular radiation dose measuring equipment can be used for measurement. However, a reference dose measuring device must be installed next to the location expected to be the point of receiving the lowest absorbed radiation dose. and highest from irradiation and at the location where it is regularly measured. There must be equipment installed. Measures the amount of radiation in the container. For other irradiations in the same irradiation cycle The measured radiation dose has measurement uncertainty, which can be estimated from the variance of repeated measurements.

Item 21: It must be ensured that every container for irradiation receives a radiation dose not lower than that specified by the Random fluctuations in data from routinely used radiation measuring equipment. Item

22: Parameters of the radiation equipment must be controlled to be constant. There is monitoring. and recorded throughout the period Preparing a radiation distribution map includes maintaining such records along with the results of radiation dose measurement and other records. All that has been prepared

Electron beam irradiation machine

design

Item 23: The amount of absorbed radiation that each part of the product receives. Depends on the following factors

23.1 Characteristics of the light beam include the energy of the electrons. Average beam current, width and uniformity of radiation.

23.2 Conveyor belt speed

23.3 Product composition and density

23.4 Composition, density, and thickness of the material between the passage of the light beam, electrons, and the product portion.

23.5 The distance between the electron beam passage and the product container. Section

24 An important parameter that the irradiation operator must control is the nature of the beam. and the speed of Conveyor belt

Preparation of radiation distribution maps

Article 25: The procedure for preparing a radiation distribution map must include a radiation dose measuring device between the layers. Homogeneous absorbent pad which is used as a model product or between layers of a representative product that has a uniform density, at least 10 points must be measured to cover the maximum electron content value.

Article 26: Parameters of the irradiation machine must be controlled to be constant. There is monitoring. and recorded throughout the period Preparation of radiation distribution maps and such records must be maintained. along with the results of radiation dose measurement and other records All that has been prepared

Retesting of the irradiation plant

Article 27: Testing of an irradiation factory must be repeated if there are changes to the process or irradiation equipment. which affects the distribution of radiation into the irradiation container, for example changes of Radiation source The scope of retesting of the irradiation plant depends on the change level of the irradiation machine. or the arrangement of product containers must be retested every time there is doubt.

building

Article 28 Buildings and premises must be designed. and take specific steps to separate containers that Has been irradiated and containers that have not yet been irradiated apart. To avoid cross-contamination, if the item is contained in a closed irradiation container, It may not be necessary to separate pharmaceutical items from Non-pharmaceutical items because there is no risk of contamination Including having to control and eliminate the possibility of Product contamination by radionuclides (Radionuclide)

process

Article 29 The layout of the product within the irradiation container must be specified during Verifying the correctness of the process No. 30 During the irradiation process, the

amount of radiation in the irradiation container must be monitored. Using a validated radiation dosimetry method. Including the need to define the relationship between

The amount of irradiated and absorbed radiation received by the product during process validation
and testing of irradiation plants

clause ÿÿ Radiation indicators must be used to help separate irradiated containers.
and non-irradiated vessels, but indicators should not be used as the sole means of differentiating irradiation.
or whether it has not undergone irradiation or is an indication that the process is satisfactory.

Article 32 Product irradiation process where different types of products are mixed together in containers for
Irradiation can only be carried out if there is clear evidence from the testing process of the irradiation plant before starting.
Take action or other evidence This can guarantee that each irradiation container receives the correct amount of radiation.
meets the specified criteria

Item 33 In the case where it is prescribed to re-irradiate the product more than ÿ times to get the required amount of radiation.
An agreement must be obtained between the irradiation factory and the drug registrar. which must be re-irradiated internally
time agreed upon in advance If the radiation process is extended beyond the previously agreed upon time period due to a force majeure event occurring
during the radiation treatment, the drug registration holder must be notified.

be separated from the irradiated products.Products that have not been irradiated from products that have been irradiated throughout the process, No. 34, must

Gamma irradiation machine

Article 35 Continuous radiation process At least 2 sets of radiation measurement equipment must be installed on the product.
Exposure to radiation throughout the irradiation process.

Article 36: Model irradiation process At least 2 sets of radiation measurement equipment must be installed on the product.
Exposure to radiation at the point corresponding to the location receiving the lowest dose throughout the irradiation process.

Article 37 The continuous irradiation process must have an accurate indication of the location of the radiation source, including
Interlock between the position of the radiation source and the movement of the conveyor belt. Including the need to have an inspection
Continuously monitor conveyor belt speed and record results.

Article 38: Model irradiation process Movement of the radiation source and duration of irradiation
For each production model The results must be monitored and recorded.

Article 39 In order for the product to receive the amount of radiation as specified must be set to adjust the timer or
The speed of the conveyor belt is related to its degradation. and the increase in radiation sources must be determined and
Record the period of time or speed adjustment.

Electron beam irradiation machine

Item 40: A radiation dose measuring device must be installed in every container for radiation. Item
41: The value of the average beam current must be recorded. electron energy The width of the radiation and
Continuous conveyor belt speed These variables, in addition to the speed of the conveyor belt, need to be

controlled within limits This is determined during testing of the irradiation plant before starting operation. Because these variables Easy to change every moment

Document operations

Article 42 Must check and record the number of products received for irradiation, the number of products that have been irradiated, and Quantity delivered to customers The amounts must be consistent. If there are discrepancies, they must be reported and the reasons found.

Article 43 The irradiation operator must certify in writing the results of the amount of radiation the product receives. The container of each batch that is irradiated or delivered. Article 44 The

process and control records for each batch of irradiation must be verified and signed by. Responsible person appointed and maintained, procedures and location or record keeping. must be received Agreement between the irradiation operator and the drug registration holder. Clause 45 Documents regarding the verification and testing of the irradiation plant before

starting 1 year after the expiration date. or at least 5 years after release
Processed must be kept for at least a period of time.

The final product leaving the factory is irradiated, whichever is longer.

Microbial monitoring No. 46 Microbial

monitoring is the responsibility of the drug manufacturer. Including checking and monitoring the condition Environment of the production site and monitoring of microorganisms in products before irradiation as specified in the drug registration.

Appendix 12

Production of research medicinal products

Principle

Investigational medicinal products must be produced in accordance with the principles and detailed recommendations for principles and methods for drug production. Other recommendations shall be used when they are relevant and appropriate to the product development process. Practices must be flexible to accommodate changes as process knowledge increases. and suitable for Product development process

Volunteers participating in clinical trials may be at increased risk. When compared to patients who received treatment with medicinal products available for sale Applying the principles and methods of drug production to the production of investigational drug products is The objective is to ensure that there is no risk to volunteers. and the results of clinical trials are not affected by insufficient safety, quality, and effectiveness of drugs. due to unsatisfactory production There is also The objective is to ensure consistency of the same investigational drug product across batches used in trials. same clinic or another clinical trial Changes that occur during the development of investigational drug products Must be recorded as documentary evidence and have sufficient reasons for consideration

The production of investigational drug products is more complicated than the production of marketed drug products due to the lack of clear steps similar to routine production. Diversity of clinical trial designs Necessary packaging design Sampling frequency and concealment of treatment Including the risks that increased due to cross contamination or product mix-up In addition, knowledge about the potency and toxicology of products may be incomplete and there may be a lack of full verification of the manufacturing process or products sold on the market may be used. which has been repackaged or modified in some manner

It requires personnel with thorough understanding. and received training in following the rules and Methods for producing investigational medicinal products and need to cooperate with research sponsors who is the most responsible in every dimension related to clinical trials Including the quality of research drug products to deal with the challenges of production
research drug products

complexity of operations This Processing results increasing demand for systems High quality, effective results,

appendix also includes instructions on the manufacture, transportation, and return of medicinal products used in medicines.

clinical trial It is an area that connects and complements good clinical research practices.

note

Products that are not It is not a research drug product.

Non-test products, placebos, or analogues may be administered to participating volunteers.

clinical trials These products may be used as support or as preventive, diagnostic or

Treatment and/or may be necessary to ensure that volunteers receive adequate care, including

Used as specified in the research protocol to induce a physiological response. However, these products They do not fall within the definition of

investigational medicinal products. These products may be supplied by the research sponsor or the investigator. Research sponsors must ensure that

these products comply with clinical trial announcements/approvals. and the products used are of standard quality appropriate for the purpose of use

in the experiment by considering

to the source of the product, whether it is a product that has been approved for sale or divided products

New recruits therefore recommend that those assigned should take part. and provide recommendations for this mission,

product licenses, and making people aware

Full-scale production of research drug products and some including a variety of processes division of packing or the product form must be

under a production license But this license does not include making

Reconstitution of a product for the purposes of this specification. Reconstitution means the general process of

- Dissolution or distribution of investigational drug products. To administer medicine to volunteers

Experiment or

- Dilution, or mixing of investigational drug products with other ingredients. to be used as a vehicle for medicine

for use in drug administration

How to make a return? It is not a combination of different types of ingredients, including important medicines, together. To carry out the results

It is a research product.

Investigational drug products Existing things go through a process that is defined as rejuvenation.

The process of restoring the shape must be prepared as quickly as possible prior to administration.

done The reformation process must be specified in the application for permission to import or manufacture drugs for clinical trials or kits.

Investigational drug product documentation and clinical trial outlines or other relevant documents available at the study location.

Definition of words

Concealing treatment (Blinding) means a procedure which causes one or more parties involved

With the experiment, the type of treatment the volunteers received was unknown. Unilateral concealment of treatment refers to the case of volunteers.

Only one side does not know what treatment they are receiving. and concealing the treatment of two sides means the case of both

Volunteers, researchers, research supervisors And in some cases, the data analysts did not know the type of treatment the subjects received.

Therapeutic anonymization with respect to investigational medicinal products means concealing the identity of the product in accordance with

Recommendations from research sponsors While disclosing treatment means disclosing the identity of the product.
Conceal treatment

Clinical trial means a research study on humans with the objective of
Research or confirm the clinical, pharmacological and/or other pharmacodynamic effects of investigational medicinal products and/or

To search for adverse reactions caused by research drug products. and/or to study the absorption, distribution, metabolism, and

excretion of one or more types of investigational drug products from the body. with the objective
To find safety. **Comparator:** and/or the treatment effectiveness of that product

product means a research drug product. or products that

Available in the market (i.e., the active control substance) or placebo, which is used as a reference product in clinical trials

research drug products (Investigational medicinal product) means the pharmaceutical form of
The active substance or placebo used to test or used as a reference product in clinical trials, including

Products that have been approved for sale but used or assembled (recipe or packaged) in a form that

It is different from a form that has been approved or used for a new indication that has not yet been approved or studied.

Additional information according to the approved format

Investigator means a person responsible for conducting a clinical trial at

Research site: If the experiment is carried out by a team of people at the research site, the responsible researcher is the team leader. This may be called a research site.

Principal Investigator

Manufacturer or importer of investigational drug products (Manufacturer/importer of Investigational Medicinal Products) means a person receiving a production license. or product import license

Order means an order for the production process. Packaging and/or transportation of specified quantities The exact nature of the research drug product

Product specification file means a reference document that

or refer to another document containing all the information required to outline the details of the written guidance.

Font for production process Packing testing Quality control Emissions through production and transportation
research drug products

Sampling (Randomisation) means the process that determines whether volunteers are classified into groups.

Treatment or control group By organizing volunteers There is an equal opportunity to be selected for any treatment.
One is to reduce bias in research studies.

Randomisation code means a list showing the type of treatment given to each volunteer.

Obtained from a random process

Transportation (Shipping) means the process of packing for transportation. and deliver the received pharmaceutical products
Production orders for clinical trials

Research sponsor (Sponsor) means the person, company, institution, or organization responsible for the initiative.
Management and/or funding clinical trials.

Quality management

clause 1 The quality system designed, established and inspected by the manufacturer or importer must be described in detail.
Written procedures for research sponsors in accordance with the principles of the principles and methods of production.
and other guidelines applicable to investigational medicinal products.

Item 2: Product standard specifications and production process recommendations may change between
development, but must maintain control and full traceability of changes.

personnel

Article 3: All personnel involved with research products must receive appropriate training. In terms of the regulations
specific according to the type of those products

Even in cases where there are only a small number of people involved with investigational medicinal products, Each model produced must have a separate responsible person.
in production and quality control are separated

Article 4 The assigned person must ensure that there is a system in place according to the rules and methods for producing
drugs. and has extensive knowledge in drug development. and the clinical trial process Advice for those who receive
Assignments related to the certification of investigational medicinal products are in the content of items 38-41.

Premises and tools

Item 5: Information on the toxicology, potency, and ability to induce allergic reactions of investigational drug products may not yet be available.
This is not fully understood, so it is important to minimize the risk of cross-contamination. Design
Tools and facilities, assessment or testing methods and acceptance limits after cleaning.
The nature of these risks must be reflected. The continuous production method must be considered according to the production time.
Suitability by taking into account the solubility of the product in deciding the choice of solvent for
Cleaning

Document operations

Requirements and recommendations

Clause 6 Requirements (in terms of starting materials Primary packaging materials for products in process Products waiting to be packed
and finished products), production formulas, instructions for the production and packaging processes must cover information and knowledge that
It is current and must be re-evaluated periodically during development. and updated as necessary.

Each new edition must reflect the latest information. Technology currently used, requirements
According to the law and regulations according to the drug textbook and must be traceable to previous documents Change must
Follow written instructions. This must specify the effect of the change on quality.
Products such as stability and bioequivalence

Item 7: The reason for the change must be recorded. and study and document the impacts.
of changes to product quality and effects on ongoing clinical trials.

production order

Clause 8: Production orders must specify the product. based on the needs of the production process and/or packaging in quantity
exact sample and/or transportation and delivered by or on behalf of the research sponsor to the manufacturer. production order
It must be clear and concise in writing to avoid ambiguity. (Even if the order is sent via
Electronic) Production orders must be officially certified. and must refer to the product specification document.
and appropriate relevant clinical trial outlines.

Product specification document

Article 9 Product specification document (See the meaning from the definition of the term) Must be continuously updated.
during product development by ensuring appropriate traceability to previous documents

This document must at least include: or refer to the following information

9.1 Requirements and analytical methods for starting materials. Product packaging materials during production
Products waiting to be packed and finished products

9.2 Method of producing results

9.3 Testing and testing methods during the feedback process

9.4 Certified copy of the label

9.5 Clinical trial outline and the corresponding sampling code as appropriate

9.6 Request technical agreement. a common strategy between the contracting parties involved as appropriate

9.7 Request stability information

9.8 Storage and transportation conditions

The above list is not considered exhaustive. However, the content will vary depending on the product and
development steps The information shall be used as a basis for evaluating suitability for certification and release.
Passed the production version by the designated person. and must be a person who has access to all information in the case of production.
Different production processes in multiple locations under the responsibility of multiple designated people may be collected.
Maintain separate documents based on information related to activities at Each production location

Production formula and product process recommendations

clause 10 Every production or delivery of a product must have a working method. and record every step written clearly and adequately If the operation does not need to be repeated There may not be a need for a formula. Masterplans and operating instructions Records and records are critical to preparing the final document. in regular production When product release is approved

Item 11: Information from product specification documents must be used to determine the details of written instructions. Font for production process Packing testing to control quality Storage and transportation conditions **Packaging instructions** No. 12 Investigational

medicinal products are

generally packaged in a specific form for each volunteer as specified in the clinical trials Before starting the filling process, the number of samples to be used must be determined, including Quantity required for quality control and keep it as a sample. Must check the consistency of adequate quantity To ensure that the quantity of each product is correct according to demand in every step of the process.

Carry out

Record the product for the manufacturing, testing, and packaging processes.

clause 13 Production model records must have sufficient details. In order for the next step to be performed correctly, these records must include comments used to evaluate the appropriateness of the step. and changes that occur, and increase knowledge related to products and development of production methods, record production versions. At least for the period of time

This Dke specified by law. Article 14 must:

Production operations

Packaging

materials, Section 15, Quality control requirements and inspections Must include measures to prevent disclosure.
products accidentally Due to changes in the appearance of the packaging materials of different production models.

Production operations

Article 16 Critical parameters must be specified during development. and control during the production process to control the process The parameters of the production process and control during the production process Temporary may be determined from previous experience. including those obtained from preliminary development work Key personnel must Consider with caution To provide necessary advice and continually apply that advice to Increased experience in production There must be reasons supported by knowledge at that time in setting the specified parameters and using them to control.

Article 17 The production process of investigational medicinal products does not require verification to the necessary level. For regular production But production buildings and equipment used must be inspected and certified. For sterile products The sterilization process must be validated to the same standards as the sterilized product. Approved for sale in the market Results of checking for virus inactivation or virus elimination. and contaminants from The biological origin of the material must be provided upon request. To guarantee the safety of products obtained from biotechnology process By following the scientific and technical principles specified in the guidance available in this field.

Yes

Article 18 Validation of the sterile process when producing small batches often presents special problemsIn this case, the number of units packed may be the largest in production. If possible and consistent with Process simulation The media solution must be packed into a large number of units. To increase confidence in the results Tests that include filling and sealing procedures performed by a person. or semi-automatic machines have a high risk of sterility, therefore increased attention must be paid to operator training. and validation of techniques Sterilization process of each operator

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Principles of operation **This applies to comparative products.**

Item 19: If the product is modified, there must be supporting information in various aspects (such as stability, solubility, comparison, bioavailability. (Bioavailability)) to show that the said change does not affect the characteristics The original quality of the product has changed significantly.

Article 20. The expiration date shown on the comparative product in the original container. May not be applicable to Products that are repackaged in new containers This may not provide equal protection or may not be compatible with the product. Therefore, it is important to specify use by an appropriate date. Taking into account the nature of the product and the nature of the packaging Including the storage conditions according to which the product is actually used. Must be prescribed by or on behalf of the research sponsor. However, use within the date must be appropriate. and must not exceed the expiration date specified in the original container. This expiration date Must be consistent with the duration of the clinical trial.

Concealment of treatment

Clause 21 for products with concealed treatment Systems must be in place to ensure that concealment is effective and maintained, while allowing disclosure of “concealed” products when necessary. Including revealing the production model number. of the product before concealing the treatment Must be able to reveal product quickly in emergency situations.

Random

code, item 22: The procedures must describe the model. Confidentiality, distribution, management and storage Randomization code used for packaging investigational drug products. and code disclosure mechanism and keep records appropriately

Packing

Article 23 While packing investigational drug products It may be necessary to handle different products in the filling line. same place same time Appropriate procedures must be used. and/or special equipment as appropriate, including Training relevant staff To reduce the risk of product mix-up This is the least.

Article 24 Packaging and labeling of investigational drug products is complex. and is legally liable to errors that occur more than products sold in the market (including more difficult detection), especially when Products that “mask” similar treatments are used, requiring increased caution against infection.

Label errors, such as label quantity inconsistency used by line inspection control check During the production process by appropriately trained employees

Item 25: It must be ensured that the packaging of investigational drug products remains in good condition during transportation. and storage in On the way to the destination The cause must be determined immediately if it is found to be open. or tearing of the outer container during Transportation

Labeling

Item 26, Table 1 The contents of topics 26-30 have been compiled. The following information must be included on the label. Unless there is a reason Appropriate in cases where such information is not available, such as using a centralized electronic randomization system.

26.1 Name, address and telephone number of the research sponsor. Organizations that undertake contract research or the researcher (primary contact for product information clinical trials and disclosure of information in the case emergency)

26.2 Pharmaceutical forms Drug administration route, drug dosage, and in the case of a double-blind trial Reveal treatment Must have name/identification code and Size/potency of medicine In the case of a blinded treatment trial The label must include the statement “Placebo or [name/indication code] + [dose/strength]” to identify the

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26.3 Model and/or code number 26.4ingredient. and packing process

Experimental project reference code that helps identify the clinical trial, research location, investigator and research sponsor If not disclosed elsewhere

26.5 Experimental volunteer identification number/treatment number and number of times receiving treatment 26.6

Name of researcher (if not shown in 26.1 or 26.4) 26.7

Method of drug use (References may be included in the package insert. or other explanatory documents prepared For volunteers or the person who provides the product to volunteers) 26.8

Contains the statement "for use in clinical trials only" or other words with the same meaning.

26.9 Storage conditions

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26.10 Period used (Use within the expiration date or analysis date as appropriate) in

month/year format and in a manner that avoids ambiguity

26.11 Statement "Keep out of reach of children" except when the product is used in experiments. where volunteers
Didn't take the product home.

Article 27 Address and telephone number of the main contact for information on clinical trial products.

And for emergency information disclosure, it is not necessary to specify it on the label. Because volunteers will receive medication documentation.

or card showing this information and are advised to keep this document in their possession at all times.

Article 28 Details must appear in the official language of the country in which the investigational medicinal product is used. Details

specified in item 26 must appear in both primary and secondary packaging. (except as described in points 29 and 30) Requirements for the

content of labels on primary and secondary packaging are summarized in Table 1, which may also include other languages.

Article 29 When providing products to volunteers or personnel who administer medicines in the desired form.

Primary packaging always co-exists with secondary packaging. and secondary packaging has details as specified in Section 26.

The following information must also be included on the label of the primary packaging. (or on any drug delivery device which includes a package

29.1 The name of the research

sponsor. Organizations that undertake contract research or researchers

29.2 Pharmaceutical forms and routes of drug administration (This may not include solid products given by

orally), dosage, and in the case of open-label clinical trials Please specify name/identification code and
Size/potency of medicine

29.3 Production model and/or code number to identify components and how to pack

29.4 Trial reference codes that help identify clinical trials, research sites, investigators and

research sponsor If not disclosed elsewhere

29.5 Experimental subject identification number/treatment number and the number of the time you received it

treatment

Item 30 If the primary packaging is in the form of a blister or a small unit such as an ampoule that cannot be specified

The details as specified in Section 26 must provide the same details as those labels on the packaging.

The outer layer, however, on the immediate container must include the following information:

ÿÿ.ÿ Name of research sponsor, contract research organization, or investigator

30.2 Channel of drug administration (may not include solid products given orally) and

In the case of an open treatment trial Please specify name/identification code and dosage/strength of medicine.

30.3 Model and/or code number to identify ingredients and packaging methods.

30.4 Trial reference codes that help identify clinical trials, research sites, investigators, and

research sponsor If not disclosed elsewhere 30.5

Experimental subject identification number/treatment number and the number of times received treatment

clause 31 Symbols or pictures may be used to make the information mentioned above clearer. May display information

Additional information, such as warnings and/or instructions regarding product handling, e.g. Labels for cytotoxic products

or products that require special storage conditions

Article 32 Clinical trials with specific characteristics The following information must be added to the original container, but must

Does not cover the original label

32.1 Name of research sponsor, contract research organization, or researcher.

32.2 Experimental reference code that helps identify the experimental location, researchers, and

volunteers. Item 33 If it is necessary to change the usage data within the date. Add supplementary labeling to investigational drug products.

This supplement label must state the new use by date. and use the original production model number It may be covered on the label for use within the date.

Original, but will not be covered over the original production model number for quality control reasons. Such operations must be done

In a licensed manufacturing facility, the correct medicine is produced, however, where appropriate, it can also be carried out at the study site.

By or under the supervision of a pharmacist or other health professional personnel of the clinical trial location

clinic in accordance with national law If this is not possible, this may be done by the clinical trial supervisor.

Clinics with appropriate training Operations must be consistent with the principles of the rules and procedures for

Manufacture medicines according to specific standards and work procedures and within the framework of the contract If relevant and must be correct

Second party inspection Supplementary labeling must be accurately recorded in both clinical trial documentation.

and record the production version

Quality control

Article 34 While the process has not yet been standardized. or has been verified for accuracy

Complete testing is important to ensure that each production model meets specifications.

Article 35 Quality control must be carried out in accordance with the product specification documents and according to the information provided.

If desired, must be preparedand Records of verification of the effectiveness of treatment concealment

Item 36 The collection of samples has two purposes: one is to use them as samples for testing.

analyze and two To be used as a representative of the finished product, therefore, samples may be classified into 2 types as follows:

Reference example : Example of the default object model. Packaging materials and packaged products

primary or finished products They are stored for analytical purposes. (When there is a need) in the case that medicine is available

Good stability requires reference samples to be taken at critical steps during production (e.g. where testing is required.

analyzed and released through products) or samples during the manufacturing process which is transported outside the control of the manufacturer

Retention sample: A sample of the packaging unit from the finished product. of the models produced for packing each time/trial period This sample is preserved for the purpose of Check identity for example Product format, packaging, labeling Medicine leaflet Production model number, expiration date

There are cases where the reference sample and the collected sample are the same, that is, they are packaged units. complete such case Reference samples and stored samples are interchangeable.

Reference samples and collected samples of investigational medicinal products Including products that conceal treatment It must be preserved for at least two years after the end of the trial. or after termination of the clinical trial project This is the last official time this product has been used. It depends on which period is longer.

Samples shall be kept until the clinical trial report has been prepared to confirm the identity of the investigational drug product. and is part of the investigation to find the cause in cases where the experimental results are inconsistent. Item 37 must specify the storage location for

the reference sample. and samples collected in technical agreement between
Research sponsor and manufacturer and must allow the Food and Drug Administration to access it in a timely manner

The reference sample must contain a sufficient amount of at least twice the amount used to control the analysis. Full version in the production version that meets the requirements of the investigational medicinal product documentation set used to apply for permission to import or manufacture drugs. for clinical trials

Storing information about the final packaging of the samples. Can be done in recording form in writing or recorded electronically if the record contains sufficient information. In the case where it is recorded as computer based system The electronic data storage system must comply with the requirements in Appendix 10.

product release

Item 38: Investigational medicinal products must not be released (see item 42) until the designated person has certified that the product Conforms to requirements By considering the details as specified in Item 39, Item 39:

Evaluating each batch of products produced to certify quality before releasing the product to Includes these topics as appropriate.

39.1 Production records Including production control reports Test report during production and a product clearance test report demonstrating compliance with the order product specification document. research outline and random code These records shall include records of deviations or changes to plans and subsequent further investigations must be completed and certified for use by employees with authority to act To comply with the quality system

39.2 Production conditions

39.3 Status of verification of production facilities, processes and methods.

39.4 Inspection of results Ready-made products

Results of analysis or post-testing after importing the product (if relevant) 39.5

39.6 Report on stability studies.

39.7 Source and verification of storage and transportation conditions.

39.8 Assessment report related to the manufacturer's quality system. 39.9 Documents

certifying that the manufacturer is permitted to produce investigational medicinal products. or comparative pharmaceutical products For export by the competent authority of the country of export

39.10 Legal requirements related to authorization to sell products on the market. Standards according to the principles and methods for producing related drugs. and official verification documents of compliance According to the rules and methods for producing drugs

39.11 All other factors that quality personnel know are related to the quality of the lot. The significance of the

above elements is affected by the country of origin of the product, the manufacturer and the market status of the product (has or has not been authorized for sale on the market in the European Union or in countries where Third) and the stages of development Research sponsors must ensure that these elements

which the assigned person considers when giving evidence Verify production model Is consistent with the specified information (see also item 43). Item 40 in the case of research drug products produced and packed at

different locations under the control of the receiving person
Different assignments Follow the instructions in the same way.

Item 41 If allowed, packaging or labeling is done at the researcher's premises. or under supervision of pharmacists clinical trials or other health professional personnel The designated person does not need to inspect. Certification of such activities But research sponsors are responsible for ensuring that activities are documented and
Properly managed and consistent with the principles of the rules and methods for producing drugs. and must seek

Instructions from those assigned to these steps

Transportation

Article 42 Research sponsors must take care of investigational medicinal products. Until the process is completely finished in 2 steps: Issuance of transcripts by the designated person and release of drug products under the regulations Completely placed Research sponsors must make to ensure that the details in the application for permission to import or produce drugs for

clinical trial and the consideration by the designated person is consistent with that received final acceptance by Food and Drug Administration Appropriate action must be taken to ensure compliance. In practice, this is most effectively achieved through a process that controls changes to product specification documents and is controlled. Specified in the technical agreement between the designee and the research sponsor. Both steps must be recorded. and kept in the related experimental document files. By/or on behalf of the research sponsor

Article 43 Investigational medicinal products must be transported in accordance with the specified instructions. By/or on transport orders Research supporter behalf of regarding

Article 44 Disclosure of passwords must be made to persons with appropriate responsibility. Before shipping research drug products Go to the research location

Article 45: Details of transportation by the manufacturer or importer must be kept. This detail must include the name of the recipient. clearly

Article 46 The movement of investigational medicinal products from one research site to another is considered an exception. Special cases. The movement must be specified in the standard operating procedures. Must review product history while not It is within the control of the manufacturer, for example from a clinical trial regulatory report. and record the condition stored at the first research site as part of an assessment of the suitability of product movement and Consider following the advice of the assigned person. Return the product to the manufacturer. or another designated manufacturer to reapply the label if necessary and issue a certificate of results by the person assigned Relevant records must be kept. and ensure that
Can be traced back completely

Complaints

Article 47 The conclusions of the investigation of complaints from product quality problems must be discussed between the manufacturer or importer and the research sponsor. (If not the same person) This step involves the designated person and the person responsible for the clinical trial. To assess the potential impact of clinical trials on product development and on volunteers.

Product recalls and returns

product recall

Article 48 Procedures for returning investigational drug products and return documents Must be approved by the research sponsor together with the manufacturer or importer. (If they are not the same person), the researcher and the research supervisor must understand their duties. In the process of receiving medicine back

Article 49 Research sponsors must ensure that the suppliers of comparative products or other medicinal products used in Clinical trials have a communication system with the research sponsor. When it is necessary to recall delivered products

Returning

Article 50: Return the results. Research drugs under conditions Yes I agree. This specified by the mixture supported by research and specified Clearly in approved work procedures

item 51, clearly identify the investigational medicinal products that are returned. and stored in a controlled, isolated area. Appropriate records must be maintained of returned medicinal products.

destruction

Article 52 Research sponsors have a duty to destroy unused and/or returned investigational medicinal products. Must not destroy research drug products until receiving written permission from the research sponsor

Item 53 must record and check the consistency of the quantity. and verify the quantity of products available Correct delivery, use and return by or on behalf of the research sponsor for each research site. and during each period of the experiment Destruction of investigational medicinal products not used for the investigational site or during Experimental period This must be done only after investigating differences in study drug dosages. with an explanation Satisfactory and the consistency of the drug dosage is accepted. Recording the process of destroying drugs must be done in a manner that all steps can be monitored, the research sponsor must maintain records

Article 54 When destroying research drug products A dated certificate of destruction must be submitted. or receipt for Destroy the research sponsor These documents must be clearly stated. or can be traced back to the production model and/or The number of the patient involved Including the actual amount of drugs that were destroyed.

Table 1 Summary of details on the label

In general

cases , for both primary packaging and secondary packaging (item 26), details on the label include:

(1) Name, address and telephone number of the research sponsor. Organizations that undertake contract research or researchers
(main point of contact for product information clinical trials and disclosure of concealment of treatment in cases
emergency)

Address and telephone number of the main point of contact for product information, clinical trials
Clinic and disclosure of treatment concealment information Emergencies do not have to be included. In the case that volunteers receive documents
medicine package or card showing this information and are advised to keep this document in their possession at all times (Section 27) (2) Pharmaceutical

form route of administration Unit quantity and in the case of an open experiment
Treatment: State name/indication code and dosage/strength of drug.

In the case of a blinded clinical trial The label must contain a statement that states "placebo or
[name/indication code] + [dose strength/drug strength]" (3)

Production model and/or code number in displaying details. and packing process

(4) Experimental project code that reveals the experiment, research location, researcher, and research sponsor, if not disclosed elsewhere.

(5) Trial subject classification number/treatment number. and the number of times received treatment

(6) name of the researcher [if not shown in (1) or (4)] (7)

method of use of the drug (references may be specified in the medication leaflet or other documents made to explain to
volunteers or personnel who manage pharmaceutical products)

(8) The statement "for use in clinical trials only" or other words Yes with a similar meaning.

(9) Storage conditions

(10) Period of use (Specify use within the date, expiration date, or retest date as appropriate) in the picture
month/year and in a manner that avoids ambiguity)

(11) The statement "Keep out of the reach of children" except when the product is used in an experiment. without the volunteers taking
Take home products

Primary packaging In

the case of primary packaging always coexisting with secondary packaging. (When the outer packaging shows details as Item 26) Details on the label include:

(1) Name, address and telephone number of the research sponsor. Contract research organization or investigator (main point of contact for product information, clinical trials and emergency treatment disclosures) Address and telephone number of main

point of contact for information. of clinical trial products and disclosure of treatment concealment information Emergency cases do not have to be included. (2) Pharmaceutical form. route of

administration Unit quantity and in the case of an open experiment
Treatment: State name/indication code and dosage/strength of drug.

In the case of a blinded clinical trial The label must contain a statement that states "placebo or [name/indicator code] + [dose/dose strength]"

number to display Dosage routes for all solid dosage forms (3) Production model and/or code

details. and packing process

(4) Experimental project code that reveals the experiment, research location, researcher, and research sponsor, if not disclosed elsewhere.

(5) Experimental subject classification number/treatment number. and the number of times received treatment

Blister case or small packing (When the outer packaging shows details as per item 26)
Details on the label include:

(1) Name, address and telephone number of the research sponsor. Contract research organization or investigator (main point of contact for product information, clinical trials and emergency treatment disclosures) Address and telephone number of main

point of contact for information. of clinical trial products and disclosure of treatment concealment information Emergencies do not have to be included.

(2) Pharmaceutical form route of administration Unit quantity and in the case of an open experiment
Treatment: State name/indication code and dosage/strength of drug.

In the case of a blinded clinical trial The label must contain a statement that states "placebo or [name/indicator code] + [dose/dose strength]"

part of the system Dosage routes for all solid dosage forms Granted through grants may not be

The drug form and dosage may not be

specified. (3) Production lot and/or code number in displaying details. and packing process

(4) Experimental project code that reveals the experiment, research location, researcher, and research sponsor, if not disclosed elsewhere.

(5) Experimental subject classification number/treatment number. and the number of times received treatment

Appendix 13

Production of medicinal products prepared from human blood or plasma

content

Definition of words

Blood means all blood collected from one blood donor (human) and passed through
The process for giving or receiving blood for treatment. or further production

Blood component means the components of blood used in treatment.

Blood cells (red blood cells, white blood cells, platelets, and plasma) can be prepared by several methods according to blood bank standards.
These include centrifugation, filtration, and freezing. But it does not include blood stem cells. (haematopoietic progenitor cells)

Blood service organization (Blood establishment) means an organization or agency responsible for in drilling and testing
human blood and blood components and used in the storage process
and payment to give or receive blood for treatment (intravenous)

Blood products mean products used for treating disease prepared from blood.
or human plasma

the process of separating components, the manufacturing facility for separating components (Fractionation, fractionation plant) means production operations in an industrial production site (production site for separating
components) by separating the plasma components or purified by various physical and chemical methods.
such as sedimentation, chromatography

Good Practice guidelines mean standards and
National requirements for blood agency quality systems

Medicinal products derived from human blood or human plasma means medicinal products prepared from blood components. prepared at the level
industry By government agencies or private
agencies, **plasma used in the separation process (Plasma for fractionation)** means part of
Human blood fluid after the cellular components have been separated from the blood that has been drawn and stored in a container, or
Blood bags containing anticoagulants or separated by filtration. or continuous centrifugation
from anticoagulants By the process of removing blood from the donor and separating its components.
The desired blood is then returned to the donor's body through apheresis. It is intended to be used in the production of medicinal products prepared from plasma. especially albumin Substances that help blood
coagulants and immunoglobulins of human origin, including those listed in section “Plasma used in the process
Separate components” of the European Pharmacopoeia or other
equivalent drug textbooks) **Plasma Master File (PMF)** means a specific document separated from
Drug registration documents Contains detailed information regarding the characteristics of all human plasma used as materials.
Starting in production and/or used as a starting material in the production of protein sludge. both products in process/secondary sludge
The composition of the additives and active substances that are part of the plasma Pharmaceutical products or medical devices that prepare

Processing means any step in the preparation of blood components that is performed.
Between blood collection and preparation of blood components is the process of separating and freezing the components.
of blood. In this appendix, process also means Operations that occur at a specific blood unit
with plasma used for the process of separating plasma components

Responsible Person (RP) means the person responsible for ensuring that each model or
Times of receipt/production of active ingredients or a (biological) medicinal product has been manufactured and has been inspected for compliance
Legal regulations and according to standard requirements and/or the requirements according to the drug registration
The responsible person here is equivalent to the word EU “accredited persons”

Responsible Person (RP) for blood establishment means the person responsible for ensuring that every unit of blood or blood components have been collected
and test, process, store and sell in accordance with legal regulations. which the person responsible for
Blood service agency equivalent to the word "Responsible person" of the European Union

Contract fractionation program means a production contract to separate plasma components in the manufacturer's domestic industry in order to
Separates plasma components using materials sourced from many countries and produces non-commercial products.

scope

clause 1 The provisions of this Annex apply to medicinal products prepared from separated human blood or plasma. Plasma sediment within the country or imported into the country This Annex also applies to starting materials such as human plasma. For these products, the provisions of this regulation may also apply to the production of products prepared from stable human blood or plasma (e.g. albumin) that included in medical equipment as well This is in accordance with national law.

Article 2 This appendix specifies the specific requirements of the criteria and methods for drug production. For drilling and storage Handling, storage, and transportation of human plasma used for plasma component separation processes. and for the production of medicinal products prepared from human blood or plasma. Article 3 This annex

describes specific provisions for importing starting materials from other countries. and for Enter into production contracts for separating plasma components with other countries. This appendix does not

apply to blood components used in giving or receiving blood for medical treatment in Section 4.

Blood vessels

Principle

Article 5: Drug products prepared from human blood or plasma (and active ingredients used as starting materials) must comply with the principles and guidelines of the criteria and methods for drug production. Including compliance with the drug registration These products are considered biopharmaceutical products and the starting materials consist of biological substances such as cells or liquids. Any substance (including blood or plasma) of human origin that has characteristics derived from the biological nature of the source material, for example, infectious agents. Especially viruses that may contaminate the material of origin. Therefore, and the safety of quality these products depends on controlling the material of origin. and the origin and production methods Including screening for infectious diseases, eliminating and destroying the effects of viruses.

Article 6: According to the principles, active substances used as starting materials for medicinal products must comply with the principles and Guidelines for principles and methods for drug production For starting materials prepared from human blood or plasma Blood agencies must comply with national legal requirements. or international regulations regarding drilling, preparation, and testing. Drilling, preparation, and testing must be carried out in accordance with appropriate quality system Including setting standards and regulations. In addition, any national or international requirements that require a traceability process must be implemented. Including notification of serious adverse reactions and serious adverse events from donors to recipients. This reference is in the chapter. in addition to international guidelines and must also comply with the details in the topic of the relevant drug book. Section 7. Starting materials for the production of medicinal products prepared from human blood or plasma imported from abroad. for use or distribution within the country

Must pass criteria according to national standards

Clause 8 In the case where a production contract is made to separate plasma components Initial objects imported from

Foreign countries must comply with domestic regulations. or equivalent in terms of quality and safety for

blood components Activities carried out within the country must comply with the rules and procedures for drug production.

All items are complete. National standards and regulations regarding the quality system for the organization must be considered.

Blood service. Requirements for traceability. and notification of symptoms and adverse events

serious, including the guidelines of the World Health Organization

Article 9: Every continuous step after drilling, storage and testing (including the process of separating components

Blood, freezing, storage and transportation to the manufacturer) must be carried out in accordance with principles and guidelines.

Principles and methods for producing drugs Normally, various activities are carried out under the responsibility of

Responsible person (RP) of the agency that is permitted to produce for sale In the case that action must be taken according to

Plasma-specific processes for separating blood components within a blood service unit. Appointment

This specific responsible person may not be required to have the same proportion of responsibilities as the responsible person.

of the blood service agency Clear identification of status and legal responsibilities of those responsible for

Blood service agencies must be completely specified. Production facilities for separating plasma components/manufacturers must provide

The contract shall be in accordance with Chapter 7, Employment, Production and Analysis of the Principles and Methods of Drug Production, the part

which is jointly with the blood service unit in determining the responsibilities of personnel. and details of the requirements.

To ensure compliance with the requirements Responsible person of the blood service agency and responsible person of the production location for

Plasma component separation/production facility (see point 15) must also participate in contract preparation. The responsible person must provide

Tracking inspection To confirm that the blood service unit complies with the contract established.

clause Specific requirements for document processing and other agreements related to the starting materials of

Medicinal products prepared from plasma are listed in the Plasma Master Datasheet. This depends on national law.

Management **Quality**

clause 11 Quality management must control every step from donor selection in the blood service unit.

until the delivery of the finished drug product by the manufacturer Checking back on each donor until delivery of plasma

To the production site for separation of plasma components, it must be guaranteed by the blood service agency that it has passed the identification method.

Accurately, records are kept. and have an appropriate labeling system according to national or international regulations

country and must be preserved during production. and distribution of the final product by the producer.

Clause 12 Blood or plasma used as a source material for the production of medicinal products must be punctured, stored, and passed through.

Process by blood service agency and testing in a laboratory that uses a quality system according to standards

within the country or internationally Blood service units must be licensed and regularly inspected by

Food and Drug Administration The manufacturer must notify the manufacturer of the production contract to separate the plasma components.

The Food and Drug Administration is aware.

clause 13 Plasma imported from abroad must be purchased from certified suppliers/sellers (i.e.
Blood service agency including external warehouses that store plasma) as listed in the regulations.

of the starting material as specified by the production site/manufacturer for separating the plasma components. and accepted by the office
Food and Drug Administration (i.e., audited) of the plasma importing country and by the person responsible
of production facilities for plasma component separation, certification, and plasma release (Plasma used in

Separated components) used as starting materials in production are specified in Section 36.

Article 14 Verification Including the assessment of the supplier must be carried out by the production site/manufacturer.
Separation of plasma components of finished drug products. Including laboratory tests that comply with
Procedures prepared in writing Suppliers must be re-certified at regular intervals using
How to assess risk

Item 15: Places for separating plasma components/manufacturers of finished drug products. A written contract must be prepared.
letters with the blood service organization that delivers At least the following important details must be included.

15.1 Determination of related duties and responsibilities.

15.2 Quality system and documentation requirements

15.3 Criteria for donor selection and testing

15.4 Requirements for separating blood into blood or plasma components.

15.5 Plasma freezing

15.6 Plasma storage and transportation

15.7 Checking back information and information after donation/blood collection (including events
undesirable)

Blood service agencies must provide test results for every unit of blood to the production site. to separate components
Plasma/Pharmaceutical Product Manufacturer Additionally, what is the process of separating the plasma components? arising from subcontracting
Must be made into a written contract.

Article 16: A formal change control system must be in place for planning, evaluating, and
Record every change that may affect product quality or safety or traceability.
The impact of proposed changes must be assessed. The need for testing must be considered.

and further check for accuracy Especially destroying viruses. and steps to eliminate viruses

Article 17 There must be an adequate safety strategy in place to reduce risks from infectious agents, and
Substances that cause In the face of emerging infections, such strategies must include the following risk assessments.

17.1 Determine the quarantine period before using plasma in production, that is, for separation.

Units that were infected during the period of traceability of past blood donation results

17.2 Consider all criteria for virus reduction. and/or testing for substances that cause infection
or representative substances

17.3 Consider the ability to reduce viruses, the production size of plasma and other related issues.
with the production process

Traceability and anti-hacking measures B

Article 18 There must be a system that can trace back every blood donation. Starting with blood donors and donations through blood service agencies as well as production versions of finished drug products. Including checking back
from the destination as well

Article 19 Responsibility for traceability of medicinal products must be defined. (There must not be any period that is not
can be checked back)

19.1 Starting with the donor and donations at blood service agencies to production sites for separation
Plasma components (This is considered the responsibility of the responsible person of the blood service agency.)

19.2 Starting from the production site for separating plasma components to the manufacturer of pharmaceutical products and Secondary production location Whether it is a manufacturer of pharmaceutical products or medical device manufacturers (Considered the responsibility of responsible

person) Article 20 Information necessary for full traceability shall be stored in accordance with national law.

Article 21 Contract (referred to in Article 15) between blood service agencies. (including laboratory testing) and production/manufacturer sites for separating plasma components You must ensure that there is a check back. and measures after
Complete comprehensive storage From plasma collection to all pharmaceutical product manufacturers responsible for release.
final medicinal product

Article 22 Blood service agencies must notify the production site/manufacturer that separates plasma components in events that may Affect the quality or safety of the product, including serious adverse events or reactions.
and other relevant information found after the donor consents to donate blood or releases it.
Plasma, for example, has information traceable back to the results of past blood donations. (Information after blood collection) if
The production site or manufacturer for separating the plasma components is located overseas. Information must be forwarded to the responsible manufacturer. in domestic emissions that are produced using such plasma. In both cases, if quality is involved or
Safety of final medicinal products This information must be forwarded to the Food and Drug Administration, which
Responsible for production facilities or manufacturers to separate plasma components as required by national laws.

Item 23 The notification process specified in Item 22 applies to the assessment of blood service units by
Food and Drug Administration This will lead to revocation of existing license/certificate/approval.

Article 24: Data management after hacking must be specified in the standard operating procedures. and must be taken into account Duties and procedures for notifying the Food and Drug Administration Must have measures after drilling and collecting. As specified in relevant national or international recommendations.

Blood service agencies and plasma component separation facilities/manufacturers Must inform information which Let each other know If the following symptoms occur after donating blood:

24.1 The blood donor does not pass the health screening criteria for blood donors.

24.2 The blood donor was later found to be infected with the virus. which previous donations were not found to have Viral infection in said blood donor

24.3 Virus infection testing does not follow the agreed upon process.

24.4 The blood donor has an infectious disease caused by pathogens transmitted from prepared medicinal products. from plasma (including hepatitis B, hepatitis C, hepatitis A and hepatitis viruses other than type A and B and human deficiency A virus C. and human immunodeficiency virus B and other pathogens discovered today)

24.5 Blood donors with Krutzfelt-Jakob disease (Creutzfeldt-Jakob disease, CJD or vCJD)

24.6 The recipient of blood or blood components develops an infection after receiving blood for treatment which Can be traced back to the donor

In the event of the above event Re-evaluation must always be done on the production documents. Revocation of production model Such matters need to be carefully considered. Considering criteria such as pathogens and production size. Time between blood donations and changes in blood samples (seroconversion) nature of Products and production methods used

Premises and tools

Article 25 To reduce contamination from microorganisms or foreign matter entering the production process, dissolution frozen plasma And combining the plasma units must be done in a grade D (D) clean room as specified in Appendix 1, at least sterile. Pharmaceutical production Personnel working must wear appropriate clothing and protective equipment such as masks. and gloves. Other manufacturing processes that are not performed in a closed system must be carried out under appropriate conditions. As stated in Appendix 1 Production of sterile medicine

Article 26 The environment during production must be regularly monitored. Especially during the opening Plasma container and during thawing of frozen plasma and plasma integration To be as specified in Appendix 1 Production of sterile medicine

Clause 27 In the production of medicinal products prepared from plasma There must be an appropriate method for destroying or eliminating viruses. There must also be a procedure to prevent cross-contamination in separating products that have gone through the virus removal process from

Products that have not yet gone through the virus removal process There must be a clearly separated location and equipment for Production steps before and after removing viruses from products

Article 28: Do not check the correctness of virus disposal methods in production locations. to avoid contamination of the virus into the production process during Validation study Validation provided

Take action as specified in international guidance such as CHMP/BWP/268/95 “Note for Guidance on Virus. Validation Studies: The Design, Contribution and Interpretation of Studies validating the Inactivation and Removal of Viruses”

production

Starting material (Starting material)

No. 29 Starting materials used must meet the requirements of the relevant monograph in the drug textbook. related and must comply with the conditions specified in the drug registration document set. (including master data sheet Plasma, if any). These requirements must be specified in the contract document (see Section 15) between the blood service organization and Blood component manufacturing facility/manufacturer written and control documents by the quality system

Article 30. Starting materials imported from abroad for use in contract production must meet the requirements specified in Article 8.

clause ÿÿ Plasma obtained by different methods of collection (i.e., from whole blood or obtained from the process apheresis) may have different application steps. All steps of the process used (e.g. centrifugation and/or separation sampling, labeling, freezing) procedures must be specified in writing.

Article 32 Must avoid mixing between each plasma unit. or between samples, especially especially in the labeling process and must avoid contamination in the process of cutting the plasma bag line and Steps for connecting and sealing wires

Point 33 Plasma freezing is an important step in preserving easily denatured plasma proteins. For European Blood Clotting Agents)example, plasma must be frozen as soon as possible after collection (see Pharmacopoeia monograph No 0853 “Human Plasma for Fractionation” and other related topics monograph No 1646 “Human Plasma pooled and treated for virus inactivation” or other drug texts that related) and there must be a way to check the accuracy of the plasma freezing process.

Article 34: Storage and transportation of blood or plasma at all stages of the transportation system to the production site in order to Separate blood components set and recorded at every step. If the temperature deviates from the specified limit, it must be Immediately notify the production site for separating blood components. Use certified tools. and methods of practice that has been verified for accuracy

Certification or release of plasma used as a starting material for fractionation production. Article 35 Plasma used for

fractionation production must be released from containment through systems and processes that guarantee quality for Accepting production of finished products This plasma must be supplied to the production facility. To separate blood components or manufacturers only After the release has been recorded by the responsible person. Blood service agency (or in the case of blood or plasma collected from abroad by responsible personnel and has equivalent properties) to confirm that the plasma emitted meets the requirements. and specific requirements Specified in the written contract and every step has been carried out in accordance with the principles and methods of drug production.

Clause 36 when admitted to a production site for separating blood components Plasma must be passed through for use in production. Under the responsibility of the responsible person The responsible person must confirm that the received plasma meets the specified requirements. Specified in all relevant topics in the drug textbook. and according to the conditions specified in the drug registration document set. (including plasma master data sheet, if any) in case of use in contract production Must meet the requirements specified in Section 8 **for separating components.**

in processing **Processing of plasma for use**

Article 37 The steps used in the component separation process vary according to product type and manufacturer. and often involves separation of components/purification methods. Some methods may also be used to neutralize the effect and/or remove contaminants that may be present in the plasma.

Article 38 Requirements for the plasma integration process. Collection of pooled plasma samples Separating components/ Purification and Destruction or eliminate viruses It must be specified and must be strictly followed.

Article 39: The methods used in the virus destruction process must be strictly followed. and must be a method that passes Verify the correctness of virus removal. If there is a failure in the virus eradication process, a thorough investigation must be conducted. Following a validated manufacturing process is extremely important, especially in the virus mitigation process. This is because the deviations that occur may result in the finished product being Safety risks, therefore, there must be a process to consider the risks that occur.

the risk Repeating the same process (reprocessing) or repeating with a new process (reworking), Section 40, must be done only after has been managed. Using the steps specified in the drug registration.

Clause 41 There must be a system used to separate products or products during production that have been purged of viruses. From the part that has not yet been clearly removed from the virus.

Article 42 When products from plasma from different origins are produced within the same production location. Must clearly plan the production operations at separate times (campaign) separately. Including cleaning methods. Verified for accuracy. Depending on the results of the risk management process (taking into account the possibility of epidemiological differences), the requirements for the use of such measures are based on international recommendations. The risk management process must consider to the necessity of using separate production tools In the case of contract production as well

Article 43 Products during production that must be preserved. The shelf life must be determined based on the results of the study. Stability

Article 44 Storage and transportation of products in process of production and finished drug products. Appropriate conditions must be specified and recorded at every step. By using certified tools. and procedures that have been passed Verified

Quality control

Article 45 Requirements for testing for viruses. or other pathogenic substances must be considered from new knowledge in pathogens and have appropriate testing methods and has been verified for accuracy The homogenized

validated plasma must be checked initially (i.e. after separating the protein precipitate from Section 46 pooled plasma) by a test method with appropriate sensitivity and specificity. As stated in the relevant topics in the medicine textbook

Emissions from products during production and finished products. Item 47

applies only to production models made from pooled plasma that is negative for virus detection. and passed inspection According to related topics in the medicine textbook Including passing the criteria for testing for specific viruses. and according to the requirements Only approved standards (such as the Plasma Master Data Sheet) may be released.

Article 48 Emission of products during production for use within the production site or export to other production sites. Including the release through finished products. Must be done by the responsible person. and as specified in the approved drug formula registration, Section

49, release through products during production. or finished products for contract production for separation Components from plasma must be made by the responsible person according to the standards agreed upon with the contract provider and according to the standards, rules and procedures for drug production. According to this announcement

Collection of pooled plasma samples

Article 50 Plasma from one production batch may be used to produce more than one production batch. and/or products Samples kept together and related recording documentation from all plasma generations must be maintained at a minimum. years after medicinal products The finished product has the longest shelf life of the product obtained from the combined plasma.

waste disposal

Article 51 There must be written procedures for the storage and disposal of waste and products that do not meet the criteria (such as contaminated blood or plasma. Blood or plasma obtained from infected donors Plasma products in process or pharmaceutical products Expired pre-printed products) safely and documented.

Appendix 14

Verification and Validation

Principles

This appendix describes the principles of verification and validation that apply to production facilities, equipment, and support systems. and processes in the production of pharmaceutical products and may be used as additional advice. For important drugs They are not considered additional requirements of Part 2. The criteria and methods for producing drugs stipulate that Manufacturers must control key aspects of their operations through verification and validation throughout. Product and process life cycle Planned changes to facilities, equipment, production support systems, and processes that may affect product quality must be formally documented and the impact assessed on the status of validation. and control strategies Computer-based systems used in production must be verified according to the criteria in Appendix 10 for computer-based systems. The related concepts and recommendations in ICH Q8, Q9, Q10, Q11 should be taken into consideration.

General chapter

Apply quality risk management methods throughout the life cycle of the drug product. Decisions regarding the scope and the amount of verification and validation. which is part of the system Quality risk management must be based on appropriate risk assessment. and prepared as Documents are provided for facilities, tools, production support systems, and retrospective validation processes. It is a method that is no longer acceptable. Information supporting certification studies and/or verification which is

obtained from the source In addition to the manufacturer's May be used as a reference but on condition that it must be appropriate. and has a guarantee adequately that there are thorough controls throughout the process of procuring such information

Management and planning of certification and verification. Item 1: There must be

a plan for verification and verification of every activity. By considering
Life cycle of facilities, tools, production support systems. Process and product

Item 2: Certification and verification activities must be carried out by persons who have received extensive training. Appropriate according

to the approved methods. Item 3: Personnel who provide certification and verification. Must prepare a report as specified in Pharmaceutical quality system Although it does not need to be at the level of quality management or quality assurance, appropriate quality monitoring must be undertaken across the entire validation lifecycle.

Item 4. Important elements of the facility certification and verification plan must be specified.
clearly and documented in the verification master plan. or equivalent documents

Item 5: Master plan document for verification of accuracy. or equivalent document must specify the inspection system Certification/Authentication and must at least contain the following information

5.1 Policy on certification and verification

5.2 Organizational structure Including roles and responsibilities in certification activities and Validation 5.3 Summary

of existing production facilities, equipment, systems, processes, and verification and validation status. 5.4 Change control and deviation management. of certification

and validate

5.5 Recommendations for developing acceptance criteria

5.6 References to existing documents

5.7 Verification and verification strategies Including re-certification If relevant, Section 6 is for large and

complex projects. Planning has become more important. and planning Separate verification of each project may increase clarity. Item 7: Quality risk management must be used in

verification and verification activities. If there is increased knowledge or understanding from changes between project or commercial production Repeat the risk assessment. Risk assessment to support verification and validation

This must be clearly documented.

Section 8: Appropriate review must be combined with verification and verification in order to
Ensure completeness of all information received.

Document operations Including the master plan for verification. Item 9: Criteria

and methods for preparing good documentation are important to support knowledge management throughout the life cycle. Product life

clause 10 All documents produced during verification and verification must pass. Approved and authorized by appropriate personnel as specified in the pharmaceutical quality system. 11 Links

clause between documents in complex validation projects must be clearly defined.
clear

Article 12 A verification protocol shall be prepared that defines critical systems, characteristics and parameters as well as relevant acceptance criteria.

clause ÿÿ Various certification documents may be combined as appropriate, such as inspection documents. Installation certification (IQ) with work verification (OQ) documents.

Article 14 If verification protocols and other documents are received from external service providers. Appropriate personnel at the production site must confirm suitability. and consistent with internal procedures before approval Protocols from partners This may be supplemented with additional documentation or testing protocols before it can be used.

Article 15: Significant changes to the approved protocol during implementation, such as acceptance criteria, operational parameters. They must be recorded as deviations and must be scientifically appropriate. Article 16 Results that

do not pass the predetermined acceptance criteria must be recorded as deviations and must be investigated in detail according to internal procedures. The report must discuss the impact of the results on validate

Item 17: The review and summary of the validation must be reported and the results compared with the acceptance criteria. Subsequent changes to the acceptance criteria must be scientifically valid and recommendations made. Finally, according to the results of the validation

Formal clearance for the next stage of the certification and verification process. Article 18. Validity must be approved by the relevant responsible person. Whether it is part of the approval of the report Check the correctness of the documents or separate summary documents. Conditional approval to proceed with further verification will be possible. Only when the acceptance criteria or the deviation has not been fully identified. and there has been a documented assessment that there is no Significant impact on next steps

Instrument certification process Facilities Production support systems and various systems. Article 19. Certification

activities must be considered at every step, starting with the issuance of requirements. of the user until the end of using the tool Facilities Production support system and system, important procedures and some recommended criteria. (although these will depend on individual project conditions and may vary) may be included in each of the following steps.

User Requirements Section 20 must

specify specific requirements for the tool. facilities, support systems, production and systems in the user requirements and/or in the functional requirements. Important components of Quality must be created in this step, including reducing risks in the principles and methods of drug production to a level. Acceptable user requirements should be a reference point throughout the validation lifecycle.

Design verification

Article 21 Design verification is a step after equipment verification. Facilities

production support systems and systems, which must demonstrate and document designs that comply with the criteria

and methods for producing drugs must be verified to meet user requirements during design verification.

Acceptance testing at the factory / Acceptance testing at the production site

Article 22. Especially tools that use new or complex technology. May be audited at the supplier's assembly site
Before delivery, if relevant

Article 23 Before installing the equipment It must be confirmed that the equipment meets the requirements of the user.
At the partner's location If relevant

Article 24 In appropriate and reasonable cases Must review documents and testing some topics for acceptance

at the factory or at another stage without the need to certify the installation/re-verify the operation at the production site.
If it can be shown that the transportation and the installation does not affect the working capacity. Item 25

Acceptance testing at the factory may be supplemented by conducting acceptance testing at the production site.
After receiving the tools at the production site

Verification of installation (Installation qualification (IQ)) No. 26 Must certify

the installation of equipment. Facilities Production support system or system
various

Article 27 Installation verification Must contain at least the following items.

27.1 Verification of component installation Equipment, tools, pipeline work and services

that is correct according to the drawings and engineering specifications

27.2 Verification of correct installation according to pre-determined criteria.

27.3 Collection and review of documents regarding operations and requesting solutions The supplier's maintenance

schedule. 27.4 Equipment calibration.

27.5 Verification of materials used in construction.

Verification of work

Article 28 Verification of work must follow the verification of installation. This depends on the complexity.
of tools which may be able to certify the installation/certify the operation together

Article 29 Work verification Must contain at least the following items.

29.1 Tests developed from knowledge of processes, systems, and tools. To ensure that The system works as designed.

29.2 Tests to confirm maximum and minimum operating limits and/or conditions. “Worst case” item

30, when the work verification has been completed. Can be used as a standard method specification. Work operations and cleaning methods Operator training and preventative maintenance

Competency verification

clause ÿÿ Normally, performance verification must follow installation verification and functional verification. In some cases, competency verification may be completed simultaneously with work verification. or checking the correctness of the process

Article 32 Competency verification Must include at least the following items.

32.1 Tests using materials in actual production Certified substitutes or simulated products that Equivalent under normal operating conditions using the worst-case production model size. Frequency of sampling for Confirm process controls must be appropriate.

32.2 Tests shall cover the specified process operating period unless documented. Evidence from the development process that confirms the range of work

Re-certification

Item 33: Equipment must be evaluated. Facilities production support systems and various systems at an appropriate frequency to confirm that they are still under control

time status When it is necessary to re-certify and must be carried out when the deadline is due The said limit, item 34, must be appropriate and must specify evaluation criteria. In addition, small changes that occur over time must be assessed.

Process validation

Yes
Next Chapter

Article 35 The requirements and principles specified in this section can be applied to the production of various forms of medicines, covering the initial validation of new processes. Checking the accuracy of Process that is later modified and ongoing process validation. This appendix suggests that having a robust product development process facilitates validation. The correctness of the process was achieved.

This

Article 36: Content in this topic shall be used. This should be used in conjunction with guidelines related to process validation.
As announced by the Food and Drug Administration

36.1 The process validation guidelines are intended to provide guidance. Concerning news and information that will be used for registration of drug formulas only. Requirements according to the principles and methods of drug production Process validation must also continue throughout the process life cycle.

36.2 This method must be used to link product and process development. To be confident in Validity of commercial production processes and maintaining processes in a controlled state during Commercial production that is carried out on a regular basis. Item 37. The production process may be developed using traditional

methods. or a continuous verification method. However, no matter which method is used The process must be shown to be consistent and marketable. The production process uses traditional methods. Ensure consistent product quality before releasing The product must be validated prior to

Location

Retrospective verification is no longer an acceptable method. Item 38. Validation of production for sale (if applicable) before the product can be certified. the production process of new products must cover all sizes and strengths. of drugs that will be released to the market Including the production location The use of a bracketing method may be appropriate for new products based on of extensive production

process knowledge This is derived from the development process along with the verification plan. appropriate continuous form

Article 39 Verification of the correctness of the process of products moving from one location to another or in the same area. The number of production lots used for verification may be reduced by using the method. Bracketing model But you must have knowledge about the product including details of previous verifications. The bracketing method may be used with different strengths, batch sizes, and packaging sizes/types of packaging materials.

If appropriate

Article 40 Moving the original product production location Production process and control must be in accordance with the drug formula registration and meet the current standards for that type of drug formula registration. If necessary, corrections must be submitted. Change of drug registration

Item 41 Process validation must prove that, through the production process, the quality characteristics of the product and process parameters remain consistent. which is considered an important thing that causes Confidence in the verification status and acceptable product quality are the basis used to indicate that Process parameters and qualitative characteristics, important or unimportant? Must be clearly recorded and considered. From the results of risk assessment activities

Article 42 Normally, the production model for checking the correctness of the process must have the same production size as the production model. For commercial use, the use of production models of other sizes must be appropriate. or as specified in other sections of the criteria and procedures in

ÿ

Article 43 Tools and facilities Production support system and the system used for inspection The correctness of the process must be verified. and the correctness of the test methods used are checked. All products, regardless of how they were developed Knowledge of the

Article 44 process gained from studies and development or from another source must be accessible at the production site. Unless there is another appropriate reason. and use it as a basis for Validation activities No. 45 Production models for validating production processes, development, or relocation of production

sites may involve personnel. Various production models must be produced by people who have received training in the field of production. Criteria and methods Only in the production of medicine using approved documents Therefore, it is expected that production line personnel will be involved in the production of production models. for checking accuracy To enhance understanding of the product. Item 46. Supplier of the starting material. And important packaging materials must be certified before

production of production models. Validation If different from this, evidence of appropriateness must be recorded using management principles. Quality Risk No. 47: It is very important to have process knowledge for the suitability of the design space. (if used) and for developing mathematical models (if

used) to confirm the control strategy

process

Article 48 The production batch for verification that is released into the market must be determined in advance, and the production conditions must be controlled to fully comply with the rules and methods for drug production according to the accepted acceptance criteria. Verified for accuracy. According to the criteria for continuous process verification. (if used) and according to the drug registration or according to the documents requesting permission to import or produce drugs for clinical trials.

Article 49 Verifying the correctness of the production process for investigational drug products. Refer to Appendix 12.
Production of research medicinal products

Checking the discussion The product must be ready for production

for sale. Item 50. Verification of correctness before production for sale. It may not be necessary to prepare an audit plan. Complete and correct before starting normal production. Consideration of checking accuracy along with production in order to Distribution must have a supporting reason. Document it in the verification master plan so it can be seen. and has been approved by an authorized person. Article 51. Verification of accuracy along with production for sale must contain sufficient

information. Support the conclusion that Production models are consistent. and pass the specified acceptance criteria. The results and conclusions must be officially documented and available to the designated person before certification of the production lot. **Checking the discussion of the traditional process,** item 52, according to the traditional method Many

versions of the finished product are manufactured under normal conditions.

To confirm reproducibility

Item 53: Number of production models produced. and the number of samples collected must be based on management principles.
Quality risk by allowing the establishment of normal ranges of variability and trend values. and prepare information
to be sufficient for evaluation Manufacturers must consider and adjust the number of production models appropriately to show that
The process can produce products of consistent quality.

Item 54 It is generally considered acceptable that the minimum number of production models is 3 consecutive models produced under the conditions.
As usual, the correctness of the process can be proven. Other production models may be appropriate. Considering that
Do you use standard production methods? and whether similar products or processes are used at the production site?
Initial validation using three production releases may need to be supplemented with additional data derived from the releases.
production that follows As part of the ongoing process verification

Item 55: A process verification protocol must be prepared by specifying parameters.
critical process Critical qualitative characteristics and related acceptance criteria which is derived from development data or
Documented process knowledge

Article 56 Process verification protocol At least the following items must be included.

results 56.1 Brief details of the process and feedback. Refer to the record of

56.2 Various duties and responsibilities

56.3 Summary of critical qualitative characteristics that will require investigation.

56.4 Summary of critical process parameters and relevant limits.

56.5 Summary of other qualitative characteristics (non-critical) and parameters to be investigated, or
Be vigilant during validation activities. and the reasons for that conclusion

56.6 List of names and calibration status of equipment/facilities to be used (including
Measuring/monitoring/recording

tools) 56.7 List of analytical methods and checking the accuracy of analytical

methods. 56.8 Proposal for control during the process. along with acceptance criteria and reasons
Choose to use these controls.

56.9 Additional testing must be carried out. along with acceptance criteria

56.10 Sample collection plan and reasons

56.11 Recording method and evaluate the results

56.12 Launch process and combat support. Production model (if relevant)

Continuous process verification

Article 57 Products developed Using scientifically proven qualitative design methods during

It has been developed that The established control strategy provides a high guarantee of product quality. Therefore, it can be used Verify the process continuously. Continuous verification can be used instead of traditional authentication.

Article 58: The method to be used for verification of the process must be specified. There must be a control strategy based on principles.

The science of data on specified characteristics of input objects. Critical qualitative characteristics and process parameters

crisis to confirm that the product can be produced and to regularly evaluate control strategies.

Process analysis technology may be used. and multivariate statistical process control for manufacturers.

The number of production models required must be determined. To demonstrate high guarantee that the process can produce

Consistent quality products

Item 59. General principles in items 35 – 48. This applies to this topic as well.

Mixed methods

Article 60 Hybrid methods between traditional methods and process verification methods

Continuously can be used if there is enough knowledge about the product and process. and understanding

Process derived from production experience and information on past production models

Article 61 This method may be used in other verification activities after the change or

The process is currently being verified. Although the product has been initially verified for authenticity,

with traditional methods

Verification of ongoing processes during the cycle. Item 62 for **life**

items 62 - 66 applies to the verification of the accuracy of the above 3 methods of process.

That is the traditional method. Methods for continuous process verification and hybrid methods

Article 63: Producers must monitor product quality to ensure that Control status is maintained throughout.

Stages of the product life cycle by evaluating related process trends.

Article 64 The scope and frequency of ongoing process verification must be reviewed periodically. and may modify the

requirements at any point in the product life cycle based on the level of understanding.

of the current process and process performance

Article 65 Verification of ongoing processes must be carried out according to approved protocols.

or equivalent documents and prepare a report to record the verification results obtained using statistical tools.

as appropriate to support conclusions about variance and the ability of the process and to

Confidence in control status

Article 66: Use ongoing process verification throughout the product life cycle to support The status of product validation as recorded in the product quality review document must Consider incremental change over time. and the need for additional measures, such as collecting additional samples, must be assessed.

Transportation Verification

Clause 67 Ready-made pharmaceutical products research drug products Pharmaceutical products awaiting packaging and samples Must ship from Place of production according to conditions specified in the drug registration on the approved label product specification file

or as specified by the manufacturer. Article 68 Transportation verification is challenging because there are many factors involved in the transportation route. must be clearly specified Must take into account seasonal variations. and other variances are taken into account in the inspection. Confirm transportation as well.

Article 69: A risk assessment must be made to consider the impact of variations in the transportation process. beyond the controlled conditions or continuous monitoring, such as delays in transit, monitoring equipment failure, liquid nitrogen overflows Product fragility and other related factors

Article 70 Due to the fluctuating conditions during transportation. Therefore must be careful and record the environment Crisis that may affect the product on an ongoing basis unless there is another reason

Checking the correctness of packaging

Article 71: Variability of process parameters of equipment. especially during packing Primary types can have a significant impact on the integrity and proper function of packaged items such as blister packs. and sterile containers. Therefore, primary and secondary filling equipment must be verified. For finished products and products waiting to be packed

Article 72 Verification of equipment used for primary filling must be carried out within the minimum operating period. and up to the specified critical process parameters such as Machine speed temperature and sealing pressure or other factors.

Verification of production support systems, Article 73:

The quality of steam, water, air, gas must be confirmed after installation. By following the certification steps in the topic “Equipment certification steps Facilities production support systems and various systems” above

Article 74: The duration and extent of the certification inspection must reflect seasonal variations. (if relevant) including the intended use of the production support system. Item 75 must assess the risk to

the product when it comes into direct contact, such as heating, ventilation and air conditioning (HVAC) systems, or indirect contact through heat transfer To reduce the risk to system failures

Verifying the accuracy of testing methods, Section 76, all analytical methods used in verification. Validation or cleaning Must be verified within detection limits. and measure the quantity appropriately, if necessary, as specified in Section 6 (Quality Control) of the Rules and Methods for Pharmaceutical Production, part of this Ministry of Public Health, Section 77. When testing microorganisms in products, they must be checked for accuracy.

The method must be used to confirm that
The product does not affect the recovery of microorganisms.

Item 78 When testing microorganisms of surfaces within a clean room. The correctness of the method must be verified. Test used to confirm that disinfectants do not affect microbial recovery.

Checking the accuracy of cleaning. Article 79 Checking the correctness of cleaning must be carried out to confirm its effectiveness. Cleaning methods for equipment in contact with the product may reasonably incorporate simulated cleaning agents. appropriate scientific The specific equipment used to verify cleaning accuracy must be Appropriate in cases where tools of the same type are grouped together.

Article 80 Visual inspection of cleanliness is an important part of the inspection acceptance criteria. Accuracy of cleaning But using this method alone is not acceptable. Repetitive cleaning methods and repeat testing until the desired residue level is achieved are also unacceptable.

Article 81 Verifying the accuracy of cleaning takes some time. and inspection Validation that is verified after completion of each batch may be required for certain products, such as investigational drug products. There must be sufficient information obtained from verification. To conclude that the tools are clean and ready. Next time use

Article 82 Verification must consider the degree of automation in the cleaning process. The normal operating range of the production support system must be verified. and tools as specified
If the automatic work process is used

the The entire cleaning process must be evaluated. In order to determine the variable factors that affect item 83, effectiveness of cleaning and the performance, such as the operator. Details of the method, such as rinsing time, if variable factors have been identified. The worst case scenario must be used as the basis for the validation study.
clean

Article 84 The limits of product residues must be based on toxicological assessment. Must record reasons of selecting limits in the risk assessment. including all supporting references Limits must be set. Removing residual cleaning agents used Acceptance criteria must take into account the potential for product buildup. Different items in the production line use the same tools.

No. 85 Large therapeutic molecules and peptides deteriorate when exposed to strong acids and bases and/or heat and may lose its pharmacological effect. Therefore, toxicological assessment cannot be used in this situation.

Item 86 If it is not possible to check the specific residues on the product, other parameters may be chosen instead, such as total organic carbon. and electrical conductivity.

Clause 87: Risks from microbial contamination and endotoxins must be considered during development. Protocol for verifying the correctness of cleaning

Article 88 The influence of the time between production and cleaning must be taken into account. and during the process Cleanliness and use in determining clean and non-clean periods of the cleaning process.

Article 89 In the case of continuous production of drugs with separate production times (campaign), convenience in the production must be taken into account. Cleaning at the end of production The maximum period in continuous production in a discrete production time (duration and/or number of batches) shall be the basis for validating the cleaning.

Article 90 When using the worst case method with a product as a model to validate cleaning accuracy, there must be scientific reasons for selecting the product to be used in the worst case scenario. and must do Evaluate the impact of new products on the production site. Criteria for determining the worst case scenario may include:
in solubility, cleaning ability, toxicity, and drug potency

Article 91 The cleaning verification protocol must specify or refer to the locations where samples will be collected and the reasons for choosing those locations. and specify acceptance criteria. Article 92. Sample

collection must be done by blotting. and/or leaching or other methods depending on production tools The material and method of sample collection must not affect the results. It must be shown that it is possible. that all product-contact materials sampled in the instrument by the The used sample will recover. Cleaning methods must be carried out an appropriate

Article 93 number of times. On the basis of risk assessment

and passed the acceptance criteria To prove that the cleaning method has been validated.

Article 94 When the cleaning process is ineffective or not suitable for certain types of tools, it must be used.

Production-specific tools or use other appropriate measures for each product as specified in Section 3 (Buildings location and equipment) and 5 (manufacturing operations) of the criteria and methods for producing drugs, part ÿ

Article 95: Cleaning tools by employees The effectiveness of the cleaning process must be confirmed.

with employees with appropriate frequency

change control

Article 96 Change control is an important part of knowledge management and must be managed within the system.

Pharmaceutical quality

Article 97: There must be written procedures to explain what must be done. If you wish

to change about the initial object Product components Process tools, facilities, product range, production or testing methods, production model size, design space or other changes during

Life cycles that may affect product quality or process repeatability

Article In the case of using the design space The impact of changes on the design space must be considered.

98 By comparing with the design area registered in the drug registration. and the need to be assessed for

Legal proceedings

Article 99 Quality risk management shall be used in evaluating planned changes.

To consider possible impacts on product quality, electrical systems, accuracy, legal medicines, document preparation, inspection status, calibration, maintenance. and other systems to avoid consequences that may occur by

unintended and to plan for necessary process validation. Verification or

Re-certification

100 Changes must be approved by the responsible person. or those performing related duties

Items are in accordance with the drug quality system.

clause 101 Review supporting information such as copies of documents to confirm the impact of

Changes before final approval

Article 102 After the change and if appropriate Evaluate the effectiveness of the change.

To confirm that the change was successful

Definition of words

Bracketing approach means a method for checking accuracy on the basis

The science and risks that apply only to certain production models are derived from appropriate and specified design factors.

Extremely advance (both minimum and maximum) such as drug strength, production model size, or package size that were tested during

Process validation The design assumes that intermediate validations are overridden.
with extreme levels of authentication (both minimum and maximum) when performing strength verification
Bracketing methods can be used if the strength is the same. or have elements that are very similar, such as
Tablets produced with different pressure loads are pressed into tablets from similar granular basis. or strong capsules
They are injection molded differently but have the same composition. To fill capsule shells of various sizes, the bracketing method is used.
Can be used with containers of different sizes. or different types of injection pumps but in the same container
and lid system.

Change control means a formal system consisting of:
Representatives from the appropriate agencies review proposals. or actual changes that may have an impact
to the status of the verification of the correctness of the facility, system, tool or process, with
The objective is to consider the necessity. for ensuring and documenting that the system remains
Verified status

Cleaning validation means
Documented evidence that approved cleaning methods are repeatable in removing previous versions of the product, or
Cleaning agents used in equipment must be kept at a residue level below the maximum allowable level as specified.

Cleaning verification means collecting
Evidence based on chemical analysis after each production/separate time production batch. To show that residue from the production model
or the amount of cleaning agent has dropped below the specified maximum allowable level.

Concurrent validation means that
Validation performed under special conditions It is appropriate on the basis of benefit to a There is
significant patient population, following a validation protocol. along with the sale of production models used in
validate

Continuous process verification means
Alternative methods of verifying the correctness of the process By monitoring and evaluating the performance of
Continuous production process (ICH Q8)

Control Strategy means a set of control plans derived from an understanding This
in current products and processes This gives confidence in the performance of the process and the quality of the product.
Control consists of parameters and characteristics related to the drug. and substances and components of medicinal products
Facilities and operating conditions of the equipment In-process control Standard specifications
of the finished product and related methods and frequency of monitoring and control (ICH Q10).

Critical process parameter (CPP) means a parameter.
The process by which variation affects critical quality characteristics. and must be monitored or controlled to ensure that
This process produces the desired quality (ICH Q8).

Critical quality attributes (CQA) means physical properties
physical, chemical, biological or microbiological or characteristics that should be within a limited scope, range, or distribution
Approved to ensure product quality (ICH Q8) **Design qualification**

(DQ) means verification and preparation
Documentation to confirm that the design of facilities, systems and equipment is fit for purpose.
desired

Design space means the multidimensional combination and interaction of
Input parameters such as object characteristics and process parameters demonstrate quality assurance. Operations within the design space are not considered changes. Moving out of the design area
It is considered that a change has occurred. and create a process for considering changes after approval
Drug registration The applicant for drug registration registration is the one who proposes the design area and must be evaluated and
Approved by the regulatory authority (ICH Q8)

Verification of installation (Installation qualification (IQ)) means verification and preparation
Documentation to verify that facilities, systems, and equipment have been installed or improved. correct with
Certified design and recommendations of the manufacturer

Knowledge management means a systematic method for ascertaining knowledge.
analyze, collect and disseminate information (ICH Q10)

Life cycle means every period of the product life cycle. or facilities
Convenience from the start of development or constant use until the termination of use

Verification of ongoing processes (Also called Verification of the process
Ongoing Process Verification (also known as continued process verification))
This means that documented evidence confirms that the process remains in a controlled state during commercial production.

Operational Qualification (OQ) means verification and
Create documentation to confirm that installed or updated facilities, systems, and equipment are operational.
achieved the intended purpose throughout the specified working period

Performance Qualification (PQ) means verification and
Create documentation to confirm that systems and tools can work The method is effective and reproducible.
of certified processes and product standard requirements.

Verifying the correctness of the process (Process Validation) means verifying and
Documentation to verify that processes operating within established parameters can produce drug products efficiently.
Effectiveness and can be reproduced according to specified requirements and quality.

Product satisfaction (Product realization) means getting products with quality that meets according to the needs of the patient health professional personnel and agencies with control power and needs of Internal customers (ICH Q10)

Prospective validation means checking the correctness that is routinely done before production for sale.

Quality by design means a systematic method that starts with specifying Objectives and emphasis on understanding products and processes including process control Based on science and quality risk management

Quality risk management means a systematic process for evaluating, controlling, communicating, and reviewing risks to quality throughout the life cycle (ICH Q9).

Simulated agents mean substances that have physical characteristics. and chemical characteristics For example, viscosity, particle size, pH. Similar to the product being validated.

State of control means a set of control conditions that guarantee the performance of Consistently acceptable process and product quality

Traditional approach means a product development method that determines the point and the operating range of the process parameters. to guarantee reproducibility.

User Requirements Specification (URS) means a set Requirements of both owners, users and engineers that are necessary and sufficient for the design to meet its objectives. of the specified system

Worst case means a condition or group of conditions covering an upper limit and Process lower limit and situations in which the product or process is most likely to fail. When Compare with perfectly normal conditions according to standard operating procedures, provided that such conditions do not cause the product to occur. or the process failed

Appendix 15

Parametric Emission

Principle

clause ÿ The definition of a parametric emission system used in this Appendix means a parametric emission system.

that guarantees that the product has the quality expected On the basis of information collected during production and in accordance with Specific requirements of the principles and methods for pharmaceutical production regarding parametric release.

Article 2 Parametric emissions must meet the basic requirements of the rules and procedures for

Produce drugs in the relevant annex. and according to the following criteria

Parametric Emission

Article 3: Testing and control during production is comprehensive. May provide guarantees on products

ready-made products that will pass the requirements rather than testing the finished product.

Section 4 may allow the use of parametric emissivity with some specific parameters. to be a choice

It
Instead of routine testing of finished products Those who receive rashes like evaluations.Product purchases together with officials on duty

Inspect and evaluate according to the criteria and methods for drug production. Must be the person who grants, refuses, or revokes the release through the form.
parametric

Parametric release for sterile medicinal products

Section 5: Parametric release of sterile medicinal products. Here it is related to letting go.

Ready-made products that are routinely made without sterility testing. cutting test
Sterilization can only be performed if it is clearly shown that it has been sterilized as specified and has passed inspection.

It's correct.

Item 6: Due to statistical limitations of the test method. Sterility testing is only a chance method.

only to detect critical errors in the sterility assurance system.

Article 7: Parametric release is allowed if there is information that accurately shows the production process in each

A production model that provides itself with adequate assurance that the manufacturing process has passed its and has passed

design. Verified To ensure the sterility of the product

Clause 8: Parametric release is allowed only for products that are free of ingredients in the product. onThe last step This

the final container

ÿ

Item 9: Method for sterilization according to the requirements specified in the drug book using moist heat, dry heat, and radiation.
Ions can be taken into account for parametric emissions.

clause ÿÿ Parametric emissions do not apply to new products. Due to the duration of the test results
satisfactory sterility It is considered part of the acceptance criteria. But there are cases where new products are caused by
Just a little change From the point of view of ensuring sterility including test data
Free from existing sterilization of other products may be considered in connection with each other

11 A risk analysis of the sterility assurance system must be carried out, paying attention to
Evaluation of sterile products Non-sterile emissions in

Article 12: The manufacturer must have a good history of following the rules and methods for producing drugs.

13 When evaluating compliance with the rules and methods for producing drugs You must bring the history of the encounter.
The product is not sterile. and the results of sterility tests performed on products, including manufactured products.
Under the quality assurance system for sterility that is the same or similar is taken into consideration.

Item 14: There must be an engineer with experience in certified sterility assurance and a microbiologist.
certified Residing at the place where production is carried out and make it sterile

Item 15: The design and verification of products must ensure that they can maintain
Complete under all relevant conditions

Article 16: The change control system must review changes. by insurance personnel
Sterile

Article 17: There must be a system to control microbial contamination in products before sterilization.

Item There must be no possibility of mixing between sterilized and unsterilized products.
18 may use physical barriers. or an electronic system that has already been verified

Article Sterilization records must be verified for compliance by a qualified system.
19: At least two systems are independent from each other. Such a system may consist of two people. or computer systems that
Verified for accuracy with another person.

Article 20 The following additional items must be verified before each batch of product is released.

20.1 Inspection of planned maintenance and all routine inspections of the machine ensure
Completely sterile to use.

20.2 All repairs and modifications must be approved by an insurance engineer.
Sterile and microbiologist

20.3 All equipment is complete. and calibration as scheduled.

20.4 Sterilizers must undergo up-to-date verification procedures.
Arrange products

Article 21 Immediately upon approval of the parametric release. The decision to release or not release the production version
Must be based on approved specifications. If the results do not meet the requirements for clearance
parametric The production batch cannot be released even if the sterility test passes.

Definition of words

Parametric Release means a release system that
Guaranteed product quality as expected On the basis of information collected during production and in accordance with
Specific requirements of the principles and methods for pharmaceutical production regarding parametric release.

Sterility Assurance System means the sum of the management
All that is done to ensure sterility of the product in the case of final sterilization of the product.
It will include the following steps:

(1) Product design

(2) Knowledge and control of microbiological conditions of starting materials. and process aids such as gas and lubricant

(3) Controlling contamination in the production process to prevent microorganisms from entering. and increase the number in the product by cleaning and disinfecting product contact surfaces to prevent air contamination.
By managing in a clean room Limiting time in the production process and filtering steps

(4) Preventing mixing between There are different types of sterile and non-sterile products.

(5) maintaining the integrity of talisman
the fruit (6) sterilization process

(7) Coverage of the quality system that includes a sterility assurance system, such as control
Training changes Written instructions Emission verification Maintenance
Planned prevention, analysis of failure patterns Preventing human error, ensuring
Correct, B level examination and others.

Appendix 16

Reference examples and general examples

scope

clause 1 The requirements in this appendix are used for storage. and storage of reference samples of the starting material. Packing material or ready-made medicine and samples of the finished drug. Item 2.

Specific requirements for investigational drug products are in Appendix 12, Production of Investigational Drug Products. Principles and methods for producing drugs According to this announcement of the Ministry of Public Health

General principles

Item 3: Collection of samples has two purposes: first, to prepare samples for Analysis and secondly In order to prepare a full sample of the finished drug, therefore might Drug samples can be divided into two types:

Reference example means an example of the default object model. Packing material or finished products which is stored For purposes of on-demand analysis over the life of the model. In the case that it is in good condition, it must be measured Store reference important steps during production, such as cases that need to be Analyzed, tested and released samples from or products during production that are transported beyond the control of the

manufacturer. **Retention Sample** means a sample of each batch of finished product that is completely packaged and stored for identification purposes such as Sales format Packaging, labeling, leaflet, lot number, expiration date throughout the life of the lot. There may be exceptions that do not require collection of samples. Twice the amount used for complete investigation, for example. Production models that are packaged in small quantities for Different market needs or in the production of expensive pharmaceutical products

In many cases, reference samples and samples are collected together for finished products. May be used interchangeably, that is, is In the form of finished products that are completely packaged in the same way.

Section 4: The producer, importer, or person who releases the next generation of produce. No need to store reference samples Samples are collected for each production model. Finished products For manufacturers, reference samples must be collected from the batch of the starting material. (subject to certain exceptions according to Section 8) and/or products in process of production Each packaging facility must collect a reference sample of packaging materials. Printed primary and packaging materials for all models There is no need to store it. If the packaging material has printed text It is part of the reference sample and/or sample sample.

The date of the finished product. Item 5. The sample is a reference sample of the production batch of the finished product. or starting object Can be used to evaluate Various events such as complaints about drug quality Doubts about the accuracy of drug registration, labeling, and packaging or pharmaceutical surveillance reports (Pharmacovigilance report)

Item 6: Records used for traceability of samples. Must be kept and displayed for the officials of
The Food and Drug Administration can review it.

Storage period

Item 7: Reference samples and samples collected for each batch of finished products. must be stored at least ÿ year
After the expiration date, reference samples that are finished products must be packed in primary packaging materials or in a single material.
with the primary packaging of the product for sale

Item 8. Samples of starting materials (not including solvents, gases, and water as starting materials) if they are in good condition.
Must be stored for at least 2 years after releasing the finished product. If the stability results as specified in
Shorter terms The storage period may be shorter than two years. Packaging materials must be stored for the entire life of the product.
ready made

Number of reference samples and storage samples

Item 9: Reference samples must be in sufficient quantity to at least be fully inspected according to the drug registration.
Twice. If analysis is required, samples must be taken from unopened containers. If this is not the case
above There must be reasonable grounds and approval from the Food and Drug Administration.

Items 10 The granting official may determine the number of reference samples. and samples were collected according to the number
deemed appropriate

clause 11 The reference sample must be representative of the original model. Products in process or products
Ready-made images that were randomly drawn Additional samples may be collected to monitor important steps of the process.
For example, at the beginning or end of the production process. If the production model is packed in a different way
clearly, such as being packed in blister packs or in bottles or packed in glass bottles and plastic bottles or
Packed in different packaging lines At least one sample must be collected from each method of packaging. If
Not as mentioned above There must be a reasonable cause. and has been approved by the Food and Drug Administration.

Item 12: You must ensure that you have or are ready to find the chemicals and tools necessary for analysis in order to test everything.
Topics as specified in the drug registration until 1 year after the expiration date of the last batch of production.

Storage conditions

clause ÿÿ Storage conditions must be as specified in the drug registration, such as keeping in the refrigerator and
If there is a change in storage conditions, approval must be obtained from the granting official.

written agreement

Article 14 In the case where the owner of the drug registration is not the same juristic person as the place responsible for the release.
Product responsibility for sampling and storing reference and storage samples. Must be specified in writing
written in the agreement between the employer and the contractor As specified in Chapter 7, production and analysis of
Principles and methods for the production of drugs, part and shall apply to production or release activities which are carried out
At a location other than the location fully responsible for the production model. and agreements between the various responsible locations
Sampling or storing reference samples/collection samples This must be specified in the written agreement.

Article 15 The designated person who certifies the production model for sale must ensure that Reference example
and all relevant archived samples can be accessed in a timely manner. In case of necessity Providing access
This must be set out in a written agreement.

Article 16 In the case where the production of finished products takes place in more than one location, a written agreement must be arranged.
It is the key to controlling sampling and the storage of both reference and sample samples.

Reference Examples - General Points

Clause 17 Reference samples are used for analytical purposes and must be readily available for use.
Laboratories with validated analytical methods

Sample collection - general issues

Article 18 The samples collected must be representative of the production batch of the finished product that is sold. and may require
In checking to confirm non-technical properties such as physical properties, labels and accompanying documents that
It is accurate according to the drug registration. Samples must be stored at the location where the batch is kept.
Ready-made items that the person assigned to certify

Item 19: Samples collected must be kept at the production site and available to officials of the Food Administration.
and medicine check

Article 20 In the case where more than one production source is involved in the production Import/Packaging/Testing/Batch Release
Responsibility for sampling and maintaining samples must be defined in the
A written agreement between the parties involved.

Reference samples and samples were collected in case the manufacturer closed its business.

Clause 21 In the case where the drug production licensee closes down the business. or had their drug production license revoked If there are still medicinal products
which has not yet expired in the market The manufacturer must provide details regarding the transfer of the reference sample. Samples are kept together and

Related documents to a storage location approved by the Food and Drug Administration. Drug manufacturers must
Arrange for satisfactory storage of samples. and can access samples for analysis

Article 22 If the manufacturer is not in a position to make the necessary arrangements, it may be assigned to another manufacturer to do it instead.

The owner of the drug registration has the duty to make such an assignment. and provide all necessary information to the office.
Food and Drug Administration In addition, with respect to the suitability of the management proposal for

Maintain reference samples and storage samples together. The owner of the drug registration must consult with the Commission Office.

Food and Drugs in the case where the products on sale have not yet expired