

Guidelines of Good Manufacture Practice (GMP) for Veterinary Drugs Manufacturers

法規沿革(Legislative):

1. Total of 45 Articles were promulgated and taken into force on June 2, 2006 by Council of Agriculture, Executive Yuan: Nong-Fun-Tzi 0951472454
2. Article 45-1 was added and promulgated on February 21, 2008 by Council of Agriculture, Executive Yuan: Nong-Fun-Tzi 0971472046.
3. Article 23 was amended and promulgated on October 22, 2014 by Council of Agriculture, Executive Yuan: Nong-Fun-Tzi 1031472991 .

法規內文(Content):

Article 1

The Guidelines are instituted pursuant to Paragraph 3 of Article 12 of the Veterinary Drugs Control Act.

Article 2

There shall be premises, facilities and equipments in accordance with the Establishment Standards of Veterinary Drugs Manufacturers and the veterinary drugs manufacturer (hereinafter the Manufacturer) shall conform to the circumstances prescribed as follows:

1. There shall be the respective clearly written operating procedures for all operations;
2. There shall be operators with adequate training able to accurately perform the duties;
3. Raw material, product containers, seals, labeling material and packaging material conforming to the existing specifications and storage conditions shall be used;
4. All manufacture processes shall meet to the existing operating procedures along with the records of the product manufacture, processing, packaging, storage and distribution recorded and reserved in a clear and easy-to-evaluate manner sufficient to trace the aforesaid matters of each batch to ensure the product quantity and quality to conform to the existing

standards;

5. There shall be a proper system of product storage and distribution and the establishment of the rapid recall system of sold products.

Article 3

The terms prescribed in the Guidelines are defined as follows:

1. Drug: denotes the veterinary drugs prescribed in Article 3 of the Veterinary Drugs Control Act;
2. Raw material: denotes any substance used in the manufacture process of products, including those not included in the final product;
3. In process material or intermediate product: denotes any product obtained during the manufacture process able to become the product via the post manufacture process;
4. Product: denotes that after manufacture process, the active pharmaceutical ingredient, or finish product with effective ingredients, and they always has in-active ingredients in finish product;
5. Labeling: denotes all labels, instructions, package material and all of the word and picture with the finish product.
6. Packaging material: denotes the material used to package the product excluding the container and seal;
7. Finished product: denotes the veterinary drug with the finished packaging operation and the appearance tells the relevant information about the contents inside the package;
8. Batch: denotes that follow the same manufacture indications, obtained specific quantified drugs or other substances with the identical property and quality; as for the consecutive process, it denotes the specific quantity produced within a certain period or the consistent quality within a certain limit;
9. Batch number: the clear words, numbers, symbols or their combination attached sufficient to trace the complete information of the products or relative substances;
10. Contents: denotes one of the following circumstances:
 - (1) The unit quantity of the active ingredient contained in the finish product;
 - (2) The potency of the finish product, i.e. the therapeutic effect confirmed by the proper experiments or sufficient clinic data;
11. Fiber: denotes the substance with a length 3 times larger than the width;
12. Non-fiber liberation filter: denotes the filter that

- prevents the fiber from entering any filtered solution, bulk or product by the proper pretreatments such as rinsing or flushing;
13. Validation: denotes the action certified by documents which can prove that any procedure, manufacture process, machinery, bulk, action or system can definitely lead to the expected effect;
 14. active pharmaceutical ingredient: denotes the pharmacological active component or ingredient obtained via the physical or chemical treatment or the biotechnical process which may be employed to manufacture drugs, biomedicines or biotechnical products;
 15. Biotechnical product: denotes the product manufactured by biotechnological methods such as genetic recombination, cell fusion or microbes through cell culture and fermentation technology or tissue extract or the active material proliferation of embryos or animals. The biotechnical products are managed respectively by the reagents of veterinary drugs, veterinary biomedicines or veterinary diagnosis pursuant to the sources, ingredients and purposes;
 16. Biopharmaceutical: denotes the serum, antitoxin, vaccine, toxoid, and strain solution manufactured in accordance with microbiologic and immunologic theories.

Article 4

The quality control and manufacture departments shall be independent.

Article 5

There shall be the respective responsible personnel in all departments of the Manufacturer along with adequate personnel to execute and supervise the manufacture, processing, packaging or storage of each product.

Article 6

The responsible persons, supervisors and employees in all departments of the Manufacturer shall have the adequate knowledge and experience, and accept, participate in and execute the practical training prescribed in the Guidelines. The staff in aseptic workplaces shall accept the relevant professional training.

Article 7

The Manufacturer shall order the written personnel operational

hygiene regulations and include the circumstances as follows:

1. A periodical health examination in compliance with the work properties;
2. Set up prevent impact procedure of employees affected by an infectious disease or suspected to be affected by an infectious disease or with open wounds from affecting the safety or quality of drugs;
3. Regulations that demand sufficient washing or sterilization prior to entering the workplaces, and prohibit the actions like wearing accessories, eating and drinking, smoking or other hindrances to sanitation in the manufacture areas;
4. Standards of the uniforms, caps, masks, gloves, sleeves and shoes covers that the employees shall wear in compliance with the nature of the workplaces.

Article 8

The Manufacturer shall order the written detailed operating procedures concerning the quality standards of raw materials, product containers or seals and the check on delivery, labeling, storage, treatment, sampling, inspection and examination concerned.

The containers packaging starting materials and product containers or seals shall be marked batch by batch with clear codes and the statuses of under test, acceptance, rejection or quarantine required along with the treatment records of the batches of objects.

Article 9

The representative sample shall be sampled batch by batch along with the notation upon the original containers for the stock of the raw materials and product containers or seals.

The adequate label shall be attached to the container of the preceding sample to trace the name, batch number, sampling basis and original container of the sample and the name of the sampler.

Article 10

The sample prescribed in the preceding Article shall be tested in compliance with the principles prescribed below:

1. Each raw material shall be tested to ensure the essence, purity and strength / contents to conform to meet the specifications. However, except for the identification test, the test may be exempted by assessing the reliability of the test report offered by the supplier;
2. The product containers and seals shall be tested to ensure

- the conformity to the existing specifications;
3. As for raw materials and product containers or seals vulnerable to the pollutants, insects, foreign matters or microbes leading to the impact on the expected purposes, there shall be tested items and methods in the quality specifications for the batch-by-batch test.

Article 11

The raw materials and product containers or seals which conform to meet the specifications through the test shall be release, whereas those which fail to meet the specifications shall be rejection.

The raw materials and product containers or seals with the acceptance shall be used under the principle “the first release first use”. Those under the long-term storage, or exposed to the air, high temperature or other unfavorable conditions shall be retested.

The raw materials and product containers or seals with the rejection shall be marked and be quarantined and controlled prior to proper treatment.

Article 12

The Manufacturer shall assign qualified personnel to set up the manufacture batch record of each product for the consistent quality of each batch along with other personnel to verify independently. The manufacture batch record in the preceding Paragraph shall include the following terms:

1. The product name, contents, active contend or dosage form;
2. The name, weight or volume of each effective ingredient contained in the product unit weight, volume or dosage form, and the total weight or volume per unit dosage form;
3. The name and specifications of all raw materials along with the code sufficient to indicate the property;
4. The batch size for each product;
5. The weight or volume required for each raw material. There shall be the rational excess and biased range of raw materials for manufacturing the preparation. There shall be an interpretation in the manufacture batch record;
6. The theoretic weight or volume in the proper stage in the manufacture process;
7. The theoretic yield, including the upper and lower limits of the theoretic yield percentage;
8. The specification of the product containers, seals and packaging materials shall be attached with the label of the

approver's name and the date and the sample or copy of other markings;

9. The complete instructions of the manufacture and control and the procedures, specifications and precautions of sampling and testing.

Article 13

The Manufacturer shall set up the written operating procedures of the process control which shall be approved by the Quality Control Department to insure the product property, contents, quality and purity. The bias between the actual control operation and the written procedures shall be recorded along with the rational judgment and illustration.

Article 14

For each manufacture operation, the container used to manufacture or storage, production line and key equipment shall be labeled for manufacture status, time, and date. And record in the manufacture batch record.

Article 15

The raw material quantity used for manufacturing operation shall enable the effective ingredient to remain not less than the label claim.

The operation of the raw material dispensing and separation shall be conducted in the specified segregated place with the proper supervision and control.

There shall be the detailed written test procedures for the representative sample of each batch of in process product or intermediate product.

The quality control department shall execute in process control test on in process products or intermediate products under the existing test procedures and determine the acceptance or rejection concerned in the process. The in process products or intermediate products with the rejection shall be marked and be quarantined and controlled.

Article 16

Where the workplace to dispensing, blending, crack, compress, filling and package the antibiotics powder is shared with the common workplaces, there shall be a complete confirmation plan to avoid cross-contamination.

There shall be adequate measures made for the products needless of sterilization in their written operating procedures to avoid

contamination from the hazardous microbes.

There shall be adequate measures made for the products in need of sterilization in their written operating procedures, including the steps to confirm the sterilization validation result to avoid the microbial contamination.

Article 17

The in process products or intermediate products should be store separately; if they are not store separately, there shall be measures to prevent the contamination and the impact on the quality.

Article 18

The storage places for raw materials, in process products, intermediate products and products and the workplaces for manufacturing, processing and packaging products shall remain at the proper temperature and humidity which prevent the quality reduction except for special workplaces.

Article 19

The surface of the equipment which contacts directly with raw materials, in process products, intermediate products or products shall be made of a material with no property of reaction, liberation or adsorption.

The objects required by the operations such as lubricant or coolant may not contact any of raw materials, product containers, seals, in process products or products.

Article 20

The equipment and tool used for manufacture, processing, packaging and storage shall be periodically cleaned and maintained, and there shall be written operating procedures to avoid any malfunction or contamination.

The materials of the equipment and tool in the aseptic workplaces shall be easy to wash, dry and sterilize, and there shall be periodical washing,sterilization and maintenance to avoid the impact on the aseptic operation.

Article 21

The Manufacturer may not employ a fluid filter with the possibility of fiber liberation without an additionally set fiber liberation filter as manufacturing, processing and filling injections.

Article 22

The automated machinery, electronic devices and computers used in the manufacture process or the related side software and equipment of drugs manufacture, manufacture, packaging or storage shall be periodically calibrated, checked and inspected under the existing plan and be filed for further maintenance.

The major production and the management records controlled by the computer system must be maintained and may not be altered without the authorization of competent personnel. The accuracy of any input and print of all data shall be checked and the validation period concerned shall be determined by the complexity and the reliability of the computer system.

Article 23

The manufacturer shall implement the following validation procedures for all drugs. These restrictions do not apply to those domestic factories and foreign manufacturing factories which completed the approval of registration before the date of December 31, 2014:

1. Sterilization Process;
2. Water Systems;
3. Cleaning Validation;
4. Analytical Method;
5. Manufacturing Process;
6. Final Sterilization;
7. Air Conditioning;
8. Computerized Systems;
9. Aseptic manipulation;

The manufacturer may apply for inspection by the competent authority after completing the validation procedures for all drugs of the provisions of the preceding paragraph, and then the competent authority may publish the qualified manufacturing factories.

Article 24

There shall be written control operating procedures for the check on delivery, labeling, storage, management, sampling and test of packaging and labeling materials which shall be complied with.

The representative sample shall be inspected through batch-by-batch sampling at the check on delivery of or prior to the employment of the labeling or packaging materials. The result shall be recorded and reserved. Those with the conformity to the existing specifications may be granted the acceptance whereas those with the inconformity may be granted the rejection.

Article 25

There shall be individual storage and proper marking for the labels and other package materials in accordance with the product categories, strength / contents or dosage forms. It is prohibited to enter the aforementioned storage area without the agreement of the competent personnel.

The packaging and labeling materials inapplicable to use or with the rejection shall be returned or destroyed. The issuance and utility and the returned quantity of the labeling materials shall be identical.

The labeling materials printed with the batch number shall be destroyed immediately if there is any residual; the labeling materials with no batch number shall be properly examined and stored to avoid mix-ups.

Article 26

The accuracy and applicability of the packaging or labeling materials shall be checked prior to the packaging and labeling operations. The result concerned shall be record in the manufacture batch record.

The packaging and labeling equipment shall be checked prior to the operation to insure the entire removal of the packaging and labeling materials of the previous drugs and inapplicable to this operation. The result shall berecord in the manufacture batch record.The products which go through the packaging and labeling operations shall be checked in the final operating process to ensure the accuracy of the labeling of each container or package.

Article 27

There shall be an expiration or storage limit confirmed by the existing stability test marked on the products except for those prescribed additionally in order to ensure the conformity of the product ingredients, contents, quality and purity to the existing standards during the use.

There shall be a clear indication of the formulation method and the expiration of the unformulated and formulated product if the product demands the formulation prior to the use.

Article 28

The Manufacturer shall set up the written product warehouse operating procedures and include the circumstances as follows:

1. The quarantine procedure before the finish product release ;

2. The storage conditions such as the proper temperature, humidity and illumination that prevent the product ingredients, strength / contents, quality and purity from any impact.

Article 29

The Manufacturer shall set up the written distribution operating procedures and include the circumstances as follows:

1. The principle shall be "first manufactured first sold"; there may be temporary and proper adjustment in response to the demands;
2. The distribution method that prevents the product ingredients, strength/ contents, quality and purity from the impact of the bad circumstantial factors;
3. The establishment of a rapid recall system of sold products.

Article 30

The Manufacture shall set up the written responsibility and operating procedures for the Quality Control Department and include the circumstances as follows:

1. In charge of the acceptance and the rejection of all raw materials, product containers, seals, in process products or intermediate products, packaging materials, labeling materials and products along with the examination of the manufacture records to ensure no occurrence of any errors or the thorough investigation of the errors;
2. In charge of the examination of any operating procedures or specifications sufficient to affect the product ingredients, strength /contents, quality and purity;
3. There shall be sufficient testing equipments to test and examine raw materials, product containers, seals, packaging materials, in process products, intermediate products or products;
4. The institution of the written operating procedures of the calibration of the instruments, devices, meters and recorders along with the clear prescription of the calibration methods, timetables and limits of precision, and the limited use and supplemented measures if inconformity to the precision occurs;
5. The institution of the written operating procedures of the sampling quantity, test interval, and test methods relating to the product stability meeting the storage conditions in the retail market to determine the proper expiration.

Article 31

Any of the specifications, standard operation procedure, sampling plans and test method ordered by the departments of the Manufacturer or the inspection control measures prescribed in the Guidelines and any alteration concerned shall be executed through the examination of the Quality Control Department. The Manufacturer shall comply with the operating regulations prescribed in the Guidelines and record the executive process. If there is any bias, there shall be a record and rational judgment and statements.

Article 32

The test shall be exercised on each batch of products to ensure conformity to the existing specifications.

The relevant batch-by-batch test shall be exercised on the products which shall not contain any microbe if necessary.

As for the batches of products or finished products, and the raw materials of the effective ingredients, there shall be a representative reserved sample; moreover, the reserved sample of the product or finished products shall be kept in conditions identical with the labels.

The reserved quantity shall be 2 times and more than the demanded quantity required for all prescribed inspections; however, the quantity for the aseptic test shall be prescribed in accordance with the demands. The reserved sample shall be kept at least one year after the expiry date of the product concerned.

Article 33

The animals used for the testing of raw materials, in process products, intermediate products or products shall be bred, maintained and treated in proper ways.

The animals for the experiments shall be marked. The reserved records shall be sufficient to trace and realize the use process.

Article 34

The testing shall be exercised on a non-penicillin product to ensure that there is no contamination of penicillin, hormone, or cephalosporin drugs.

Article 35

The records relating to the manufacture, control and distribution shall be kept for at least 2 years after the expiry date of the batch of the product or finished product.

The records or the copies concerned, prescribed in the Guidelines, shall be reserved in the proper place in the

reserved period for random audits exercised by the competent authority at any time; the auditor may copy or duplicate the record or the copy concerned in any manner.

The Manufacturer shall exercise the assessment of the product quality standards at least once annually to determine whether there is any improvement for the product standards and the manufacture or control operating procedures based on the records prescribed in Paragraph 1.

Article 36

There shall be a manufacture batch record of each batch of products, and the complete data of the manufacture and control concerned.

The Manufacturer shall make a precise copy of the manufacture batch record and check the precision along with the signature and date noted.

The Manufacturer shall record in detail the key steps of the processes of manufacture, processing, packaging or storage and include the circumstances as follows:

1. The date and product batch number;
2. The labeling of raw materials, in process products or intermediate products;
3. The identification between the major equipment and production lines;
4. The weight and volume of materials used in the processing process;
5. The result of the manufacture process and testing result;
6. The pre-use and post-use check of labeling and packaging workplaces;
7. The percentage of actual yield and the theoretic yield in the proper stage in the manufacture process;
8. The complete labeling control records, including samples or copies of all labeling;
9. The labeling and consumption of the product containers and seals;
10. The sampling records;
11. The operating date, time, operator and the supervisor's or auditor's signature and date of the key steps of the operating processes.

Article 37

The test record made by the Manufacturer shall note that whether the obtained data conforms to the existing specifications, and include the circumstances prescribed below:

1. The sampling place, quantity, batch number or any other clear code, sampling date and the date of checking the sample on delivery;
2. The basis of all test methods;
3. The weight or volume of the sample used in the test;
4. The complete records of the data produced in the test process, including the graphs and spectra output by instruments, with the definite labeling of test raw materials, product containers, seals, in process products, intermediate products or products and the batch number concerned;
5. All calculate records of the testing operation;
6. The record of the testing result and the judgment via comparing it with the existing specification;
7. The testing date and the operator's name;
8. The verification signed by the auditor of the precision and actuality of the original record and the conformity to the existing specifications.

Article 38

The manufacture and quality control records of all products including the packaging and labeling control records shall be tested by the Quality Control Department to ensure the conformity of the products to the existing written operating procedures prior to the release or distribution.

A thorough investigation shall be exercised on the batch of product whether it is sold or not if the percentage of the theoretic yield exceeds the maximal or minimal percentage prescribed by the manufacture control standard manual or there is any unexplained difference, or there is any inconformity of products or materials.

The investigation shall extend to the identical products of other batches or other products relating to the difference concerned.

The investigation in the preceding Paragraph shall be recorded in written form and shall include the conclusion and treatments.

Article 39

The distribution record shall include the product name, strength /contents, dosage form, batch number, the receiver's name and address, shipped date and quantity.

Article 40

The written record of each complaint shall be reserved in the product complaint file which shall be kept in proper places or

other facilities available to the audit at any time.

A written record shall be kept for 2 years after the expiry date of the complained product or 2 years after receiving the complaint; the longer period shall be the standard.

Article 41

The record of the returned product shall include the name, strength /contents, batch number, reason, quantity, treatment date and the final treatment method. The record shall be kept in compliance with the provision prescribed in Article 35.

Article 42

The Manufacturer shall order the written treatment operating procedures for written or oral complaints from customers. The Quality Control Department shall exercise the examination and confirmation of all written or oral claims.

Any apparently severe and unexpected product defect shall be reported to the respective relevant competent authorities and treated in compliance with the related provisions in the Veterinary Drugs Control Act.

There shall be written records of the treatment of all complaints along with collation and filing as the references to the quality assessment of the product concerned.

Article 43

The returned product shall be examined and stored separately. The Manufacturer shall destroy the product if there is any doubt of the product safety, ingredients, strength / contents, quality or purity due to storage and transport conditions prior to the return or in the return process or the product, container, packaging, labeling or other situations where the safety, ingredients, strength / contents, quality or purity fails to conform to the existing specifications through inspection or investigation.

The reprocessing may be conducted if the product can conform to the existing specifications through the reprocessing.

Article 44

The veterinary raw materials manufacturer shall manufacture the veterinary starting materials pursuant to the Guidelines. The enforced items, methods, schedule, standards and other compliances concerned shall be ordered by the central competent authority.

Article 45

The competent authority may exercise the check and assessment on the Manufacturer. The operating methods of the check, assessment and severe defects shall be ordered by the central competent authority.

Article 45-1

The central competent authority is in charge of the veterinary drugs inspection registration or the imported veterinary drugs license extension. Where it is necessary to check the foreign veterinary manufacturers, the fees follow the precedent of the foreign errands travel fee which the applicant bears.

Article 46

The Guidelines shall come into force on the date of the promulgation.