Standards for the Establishment of Pharmaceutical Factories

(2005.04)

Part 1  General Principles

Article 1.  This set of Standards is formulated in accordance with regulations of Paragraph 5, Article 57 of the Pharmaceutical Affairs Act (hereafter referred to as the Act).

Article 2.  Facilities and sanitary conditions of pharmaceutical factories or sites shall comply with the regulations of this set of Standards; matters not provided for herein shall be governed by other relevant laws and regulations.

Article 3.  When pharmaceutical manufacturers of domestic medicines establish new factories, relocate, expand, reopen for business, or add raw medicinal materials, dosage forms, items of processing or products, and are in compliance with Chapter 2 of this set of Standards and also regulations of the Factory Management Guidance Act, the competent industry authorites of municipalities or counties (cities) shall issue them acting on their application factory registration certificates, or approve their alterations of registration; the competent health authorites of municipalities or counties (cities) shall issue them acting on their application permit licenses for pharmaceuticals in manufacturing, or approve their alterations of registration.

Pharmaceutical manufacturers of domestic medicines holding by regulations of the preceding Paragraph factory registration certificates and permit licenses for pharmaceuticals in manufacturing, when are found through inspections to be in compliance with regulations of Part 3 or Part 4, said manufacturers shall be issued certificates of pharmaceutical GMP compliance or medical device GMP compliance for the items qualified by inspections by the central competent health authority.

Where foreign pharmaceutical manufacturers are found by inspections to be in compliance with regulations of this set of Standards, said manufacturers shall be issued certificates of pharmaceutical GMP compliance or medical device GMP compliance for the items qualified by inspections by the central competent health authority.
Part 2 Basic Requirements for the Establishment of Factories

Article 4. Pharmaceutical factories shall possess the following basic requirements and common facilities:

(1) Factory sites shall be situated in sanitary locations with fresh air; factory production, processing and packaging areas shall be constructed in accordance with relevant building codes, and located at a sufficient distance from factory boundaries to prevent pollution and fires; safety measures against pathogens implemented at factories and facilities that manufacture biopharmaceuticals or biotechnology products may not interfere with public health or safety; factory sewers shall be covered to prevent the entry and exit of animals to spread pathogens.

(2) Factory buildings shall be solid and safe, and designed to prevent rodents, insects and dust; interior ceilings, walls and floors shall be smooth and free of cracks and crevices, easy to clean, and non-conducive to the collection of dust; where necessary, materials that are easily cleaned and disinfected may be used; all operation areas shall be well illuminated and ventilated; where necessary, equipment for the regulation of temperature, humidity and air purity may be installed.

(3) Operation areas shall be clearly delineated (e.g. powder manufacturing room, liquid manufacturing room); in factories that environmental sanitation medicines are also manufactured, the operation areas shall be separated by an appropriate distance from manufacturing factories of other medicines; when necessary, separation walls may be installed.

(4) Warehouses for the storage of raw materials, supplies, semi-finished products and end products shall be established.

(5) There shall be facilities for the treatment of dust and powder, wastewater, hazardous wastes, toxic containers, hazardous gases, biological components and other hazardous components or materials.

(6) There shall be weighing facilities that comply with regulations, and they shall be rectified regularly.

(7) There shall be container washing facilities. Where container washing facilities are used in factories manufacturing eye drops, injectables and biopharmaceuticals or biotechnology products, special care shall be taken to prevent contamination, and said facilities shall be installed separately.
(8) There shall be hand-washing facilities for employers, and facilities for the washing or sterilization of work clothes, caps, face masks, gloves and shoes. Employee lounges and shower rooms shall be established, as needed, outside of the operation areas; appropriate lavatory facilities shall be established in manufacturing and processing areas, separated from operation areas.

(9) There shall be testing departments (laboratory and instrument room), and appropriate testing equipment. However, if tests are conducted on a contract basis by an organization approved by the competent authority, in accordance with the Contract Drug Manufacturing and Testing Operating Principles, and clear document is provided, establishment of said facilities may be waived.

(10) For operation areas involving flammable or hazardous raw materials, solvents, semi-finished or intermediate products and finished products, appropriate protective, first-aid and segregation facilities shall be installed.

Boilers, water pumps, vacuum pumps, compressors, general use water processing systems, purified water processing systems (ion exchange resin, etc.), water distillation systems, dust removal/exhaust systems, or air processing systems shall be installed as needed at pharmaceutical factories.

The various types of facilities mentioned in Subparagraph 6 through Subparagraph 10 of Paragraph 1 may be installed at medical device factories in accordance with actual needs.

Article 5. Facilities used to manufacture pharmaceuticals for internal use and intense toxic drugs for external use shall be kept strictly separate, and may not be used interchangeably.

Sites and facilities for the manufacturing of pharmaceuticals for human and animal use shall be kept separate; they may not be operated in the same building without separation. However, pharmaceuticals for animal use that comply with the standards governing drugs for human use are not subject to this restriction.

Article 6. Factories that manufacture pharmaceutical powders shall, as needed, install the following facilities:
(1) Pulverizing facilities;
(2) Screening facilities;
(3) Mixing facilities;
(4) Drying facilities;
(5) Dust collection facilities;
(6) Other relevant facilities.

Article 7. Factories that manufacture hard/soft capsule pharmaceuticals shall, as needed, install the following facilities:

(1) Pulverizing facilities;
(2) Screening facilities;
(3) Mixing facilities;
(4) Drying facilities;
(5) Gelatin blending facilities;
(6) Soft gelatin processing facilities;
(7) Soft capsule filling and pressing facilities;
(8) Automatic or semi-automatic capsule filling facilities;
(9) Dust collection facilities.

Facilities mentioned in Subparagraph 5 through Subparagraph 8 of the preceding Paragraph are commonly used in factories that produce soft capsules; areas where the facilities mentioned in Subparagraph 5 and Subparagraph 6 are installed shall be separate from other areas; areas where the facilities mentioned in Subparagraph 6 and Subparagraph 7 are installed must have equipment for the regulation of air temperature and humidity.

Article 8. Factories that manufacture pharmaceutical granules, tablets (including
tablets for eye use), coated tablets, or pills shall, as needed, install the following facilities:

1. Pulverizing facilities;
2. Screening facilities;
3. Mixing or annealing facilities;
4. Drying facilities;
5. Granulating facilities;
6. Milling facilities;
7. Tablet pressing or pill making facilities;
8. Gelatin or coating syrup blending, atomizing, coating, ventilation, drying, polishing facilities;
9. Molding machines, buffing machines;
10. Dust collection facilities.

Areas where the facilities mentioned in Subparagraph 8 of the preceding Paragraph shall be installed separately from other areas.

For factories manufacturing tablets for eye use, there shall be additionally as needed, sterilization, air purification, aseptic filling (packaging) and sterility test facilities.

Article 9. Factories that manufacture pharmaceutical emulsions shall, as needed, install the following facilities:

1. Emulsion stirring facilities;
2. Emulsion blending facilities;
3. Emulsion filling (packaging) facilities.
Article 10. Factories that manufacture pharmaceutical suspensions, tinctures, extracts, fluid extracts or liquid preparations (including eye drops, hemodialysis solutions and lavage solutions) shall, as needed, install the following facilities:

1. Facilities for the manufacturing of distilled water distillation or purified water;
2. Liquid blending containers, settling tanks or ceramic vats;
3. Percolation facilities;
4. Soaking facilities;
5. Filtration facilities;
6. Stirring facilities;
7. Quantitative filling (packaging) and container sealing facilities;
8. Heat compression (pressure-reduction) facilities;

For factories manufacturing liquid preparations for eye use, there shall be additionally as needed, sterilization, air purification, aseptic filling (packaging) and sterility test facilities.

Article 11. Factories that manufacture pharmaceutical aerosols shall, as needed, install the following facilities:

1. Stirring facilities;
2. Filling facilities.

Article 12. Factories that manufacture pharmaceutical ointments (including eye ointments) or suppositories shall, as needed, install the following facilities:

1. Powder grinding facilities;
2. Screening facilities;
(3) Heating vat;
(4) Blending facilities;
(5) Filling (packaging) facilities;
(6) Ointment tube sealing facilities;
(7) Suppository molding facilities;
(8) Sterilization, air purification, aseptic filling (packaging) and sterility test facilities;
(9) Dust collection facilities.

For factories that do not make use of ointment tubes, the installation of facilities mentioned in Subparagraph 5 and Subparagraph 6 of the preceding Paragraph may be waived.

Article 13. Factories that manufacture pharmaceutical sticks shall, as needed, install the following facilities:

(1) Mixing facilities;
(2) Filling facilities.

Article 14. Factories that manufacture pharmaceutical patches shall, as needed, install the following facilities:

(1) Heating facilities;
(2) Stirring and kneading facilities;
(3) Coating facilities;
(4) Cutting facilities.

Article 15. Factories that manufacture pharmaceutical implants shall, as needed,
install the following facilities:

(1) Pressing or molding facilities;
(2) Sterilization facilities.

Article 16. Factories that manufacture injectables (including dialysates) shall, as needed, install the following facilities:

(1) Facilities for the production of water for injectables;
(2) Ampoule cutting facilities;
(3) Container drying, sterilization, cooling and storage facilities; must effectively sterilize containers and prevent contamination;
(4) Injectable solution filtering facilities; must include cooling element and pathogen filter; for injectables in powder form, this requirement may be waived;
(5) Filling facilities with precise measuring capabilities;
(6) Injectables container sealing facilities;
(7) Sterilization facilities;
(8) Injectables container seal and leak testing facilities;
(9) Injectables foreign matter testing facilities;
(10) Distillation room (for employees’ washing and distillation);
(11) Changing room (for employees to changed into sterilized work clothes, caps, face masks, gloves and shoes);
(12) Drug solution preparation room;
(13) Drug solution filling and container sealing room;
(14) Animal experiment area, facilities and equipment, equipped with necessary animals and breeding and observation areas;
(15) Area, facilities and equipment necessary for conducting plate count, sterility tests and other tests;
(16) Freeze-drying facilities.
The rooms mentioned in Subparagraph 12 and Subparagraph 13 of the preceding Paragraph shall be strictly separated from other operation areas; they shall be equipped with double doors that seal tightly, air purification and sterilization facilities, and facilities for the regulation of temperature and humidity.

Article 17. Factories that manufacture antibiotics shall, as needed, install the following facilities:

1. For injectable antibiotics

   (1) For liquid form antibiotics, the facilities mentioned in Article 16 shall be installed; for powder form antibiotics, relevant facilities in Article 16 shall be installed in accordance with actual needs, and aseptic filling (packaging) facilities with appropriate temperature and humidity control capabilities, and automatic or semi-automatic precision scales shall also be installed additionally.

   (2) Doors/windows that open to the exterior shall be double doors/windows that seal tightly.

   (3) There shall be potency and safety testing facilities for antibiotic raw materials and products.

   (4) Preparation rooms (for drying, sterilization and storage of packaging materials and containers, and other preparatory tasks related to packaging) and packaging rooms (with appropriate temperature and humidity control capabilities, and automatic or semi-automatic precision scales) shall be installed in processing and packaging areas.

2. For non-injectable antibiotics (including capsules, tablets, liquids, ointments, etc.): The various types of facilities described in the rules governing each dosage form shall be installed; in processing and packaging areas, air purification and sterilization equipment, and equipment for the regulation of temperature and humidity, shall be installed in accordance with actual needs; furthermore, the facilities mentioned in Item 2 and Item 3 of the preceding Subparagraph shall also be installed.

3. Manufacturing, processing, re-packaging, packaging and other operation areas used in the manufacturing of penicillin products shall be located in a completely separate building; the air processing system for this building shall be independent from the systems of other drug production areas.
Article 18. Factories that manufacture biopharmaceuticals or biotechnology products shall have operation areas with interior ceilings, walls, doors, floors and other structural components that are easily cleaned and disinfected; and shall also, as needed, install the following facilities:

1. Facilities for the breeding and segregation of animals used in manufacturing and testing, and animals that have been inoculated with microorganisms;

2. Areas, facilities and equipment for safety testing and bioassaying;

3. Factories that collect animal blood or use other animal products in the manufacturing of vaccines shall possess water sources and facilities sufficient for required rinsing.

4. Waste water removal and disinfection facilities shall be installed in the operation areas.

5. Microorganism culturing facilities;

6. Microorganism filtering facilities;

7. Microorganism inoculation and collection facilities;

8. Freeze-drying facilities;

9. Dilution facilities;

10. Filling (packaging) and container sealing facilities;

11. Microorganism storage facilities;

12. Intermediate and end product storage facilities; said facilities should be kept at temperatures appropriate to each type of product stored.

13. Blending solution and culture medium production facilities;

14. Pre-use and post-use sterilization and disinfection facilities for containers, solutions and culture mediums used in manufacturing and testing;

15. Thermostats, sterilization facilities, refrigeration and freezing facilities, automatic regulators, thermometers and necessary recording instruments;

16. Facilities for the incineration or destruction of animal remains and other waste materials;
(17) Employees’ changing and bathing facilities;
(18) Animal dissection and organ grinding facilities;
(19) Other relevant facilities.

Areas where spores, bacteria or viruses are handled shall be completely separated from other areas.

Areas with the facilities mentioned in Subparagraph 7 through Subparagraph 10 of Paragraph 1 shall be aseptic facilities, and shall be equipped with necessary aseptic air conditioners. Areas with the facilities mentioned in Subparagraph 10 of Paragraph 1 shall be aseptic air conditioners with dehumidifying capabilities.

Article 19. Factories that grind Chinese herbal medicines shall, as needed, install the following facilities:

(1) Pulverizing facilities;
(2) Screening facilities;
(3) Drying facilities;
(4) Dust collection facilities;
(5) Re-packaging and packaging facilities.

Article 20. Factories that concoct sliced Chinese herbal medicines shall, as needed, install the following facilities:

(1) Sorting and processing facilities;
(2) Slice processing facilities;
(3) Slicing facilities;
(4) Drying facilities;
(5) Concocting facilities;
(6) Re-packaging and packaging facilities;
(7) Other relevant facilities.

Article 21. Factories that manufacture Chinese herbal plasters/poultices and adhesive pads shall, as needed, install the following facilities:

(1) Pulverizing facilities;
(2) Mixing facilities;
(3) Paste boiling vat and stirring facilities;
(4) Plaster coating facilities;
(5) Cutting facilities.

Article 22. Factories that manufacture flaked Chinese herbal medicines shall, as needed, install the following facilities:

(1) Slicing (mincing) facilities;
(2) Screening facilities;
(3) Mixing facilities;
(4) Drying facilities.

Article 23. Factories that manufacture Chinese herbal liquids, essences, liquors, syrups, or jellies shall, as needed, install the following facilities:

(1) Cutting (mincing) facilities;
(2) Soaking facilities;
(3) Filtering facilities;
(4) Boiling or concentration facilities;
(5) Distillation facilities;
(6) Stirring facilities;
(7) Liquid filling (packaging) facilities;
(8) ????

Article 24. Factories that manufacture Chinese herbal concentrates shall, as needed, install the following facilities:

(1) Cutting (mincing) facilities;
(2) Extracting facilities;
(3) Filtering facilities;
(4) Pressure-reducing and concentration facilities;
(5) Thermostatic or vacuum drying facilities.

Article 25. Factories that manufacture hard gelatin capsule shells shall, as needed, install the following facilities:

(1) Gelatin dissolving facilities;
(2) Molding facilities;
(3) Drying facilities;
(4) Capsule cutting and joining facilities;
(5) Sterilization and distillation facilities;
(6) Microorganism testing facilities;
(7) Operation areas shall be installed with air purification facilities, and facilities for the regulation of temperature and humidity.

Article 26. Factories that manufacture medicinal gases shall, as needed, install the following facilities:

(1) Storage facilities;
(2) Vaporizing facilities;
(3) Air compression facilities;
(4) Purifying facilities;
(5) Filling facilities.

Article 27. In factories that manufacture medical materials, operation areas shall be separated based on the type of material produced; they shall also, as needed, install the following facilities:

(1) Cotton fluffing, spreading or carding machines; where these procedures are contracted out to other factories, installation of said facilities may be waived.

(2) Pressure degreasing facilities;
(3) Rinsing facilities;
(4) Dehydration facilities;
(5) Drying facilities (drying room);
(6) Spinning machines, weaving machines and other textile facilities; where these procedures are contracted out to textile factories, installation of said facilities may be waived.

(7) Gauze cutting facilities;
(8) Bandage cutting facilities;
(9) Appropriate facilities to prevent recontamination of gauze and bandages after drying;
(10) Tape adhesive or medical material annealing facilities;
(11) Soaking and blending facilities; to be installed at factories using the solvent method;
(12) Coating facilities;
(13) Drying and sterilizing facilities;
(14) Ground fabric processing facilities;
(15) Fabric cutting and rolling facilities;
(16) Soaking and drying facilities for medicinal gauze;

(17) Aseptic testing facilities for semi-finished and end products shall be installed as needed.

The facilities mentioned in Subparagraph 1 through Subparagraph 5 of the preceding Paragraph are commonly used in the manufacturing of degreased cotton; the facilities mentioned in Subparagraph 2 through Subparagraph 8 are commonly used in the manufacturing of medicinal gauze and bandages; the facilities mentioned in Subparagraph 10 through Subparagraph 15 are commonly used in the manufacturing of adhesive tape; the facilities mentioned in Subparagraph 15 and Subparagraph 16 are commonly used in the manufacturing of first aid adhesive tape and medicinal gauze.

Article 28. Factories that manufacture syringes shall, as needed, install the following facilities:

(1) Gas processing facilities;

(2) Grinding processing facilities;

(3) Graduation mark facilities;

(4) Syringe joint inspection facilities;

(5) Glass alkalinity testing facilities;

(6) Crack detecting facilities;

(7) Heat impact testing facilities;

(8) Standard volume testing facilities;

(9) Airtight testing facilities.

Article 29. Factories that manufacture electric instruments for medical use shall, as needed, install the following facilities:

(1) Lathes;

(2) Drilling machines;
(3) Jacks;
(4) Grinding machines or grinding wheels;
(5) Electric facilities of 1/4 horsepower or greater;
(6) Punching machines;
(7) Power distribution panel for use in testing;
(8) Voltage detectors;
(9) Ohmmeters.

Article 30. Factories that manufacture blood collection and blood transfusion devices (that incorporate plastic tubes) shall, as needed, install the following facilities:

(1) High-speed stirring facilities;
(2) Stir cooling facilities;
(3) Plastic pellet facilities;
(4) High-pressure steam sterilization facilities;
(5) High-frequency welding facilities;
(6) Water sterilization facilities;
(7) Aseptic operation rooms.

Article 31. Factories that manufacture hypodermic needles shall, as needed, install the following facilities:

(1) Straight line facilities;
(2) Grinding facilities;
(3) Needle valve seat facilities;
(4) Tightening facilities;
(5) Bend testing facilities;
(6) Flexibility testing devices;
(7) Pull-out testing devices;
(8) Pinch meters;
(9) Microcalipers;
(10) Micrometers.

Article 32. Re-packaging, packaging and labeling areas shall, as needed, install the following facilities:

(1) Weighing instruments and other necessary re-packaging facilities (counting devices, automated re-packaging facilities, etc.)
(2) Damp-proof packaging facilities;
(3) Bottle sealing/stopping machines;
(4) Semi-automatic or automatic ampoule labeling facilities;
(5) Batch number printing facilities;
(6) Revolving or regular operation tables.

Article 33. Facilities at medical device factories shall be installed based on actual manufacturing needs; facilities used in the inspection and testing of products to ensure product compliance shall be appropriately monitored, managed, rectified and maintained.

Part 3  Good Manufacturing Practices for Pharmaceuticals

Chapter 1  General Principles

Article 34. The manufacturing, processing, re-packaging and packaging of pharmaceutical products shall be governed by the provisions of Part 3. However,
for active pharmaceutical ingredients, medicinal gases and pharmaceutical adhesive pads, the categories to be implemented, as well as the implementation methods and schedule, shall be determined separately by the central competent health authority.

Article 35. Terms used in Part 3 are defined as follows:

(1) Pharmaceuticals: refer to pharmaceuticals mentioned in Article 6 of the Act

(2) Raw materials: any materials used in the manufacture of pharmaceuticals, including those that do not remain in the end product.

(3) Semi-finished or intermediate products: any products that are obtained during the manufacturing process, and that, with further processing, can become finished products.

(4) Products: active pharmaceutical ingredients, or preparations that contain active pharmaceutical ingredients and may contain other non-active ingredients, for which all manufacturing processes have been completed.

(5) Labeling: refers to all text and graphics that appear on labels, instruction sheets or packages, or that come with products.

(6) Packaging materials: include product containers, caps, and any materials used in the outer packages of products.

(7) End products: refer to pharmaceutical products that have been packaged, and whose outer packaging clearly indicates the contents therein.

(8) Batch: refers to a specific amount of pharmaceutical or other substance produced under a single set of manufacturing instructions, and that is consistent in character and quality. However, under conditions of continuous production, a batch refers to a specific amount of pharmaceutical or other substance produced within a specific time period, or that, within specific parameters, is consistent in character and quality.

(9) Batch number: refers to any definite combination of letters, numbers or other symbols that can be used to look up comprehensive information on a batch of products or other substances.

(10) Content: refers one of the following:

1. The unit quantity of the components of a pharmaceutical;

2. The potency or efficacy of a pharmaceutical; that is, the treatment efficacy as determined through testing or sufficient clinical data.
(11) Fiber: a substance whose length is at least three times its width.

(12) Non-fiber releasing filter: a filter which after any appropriate pretreatment, such as washing or flushing, will not release fibers into the filtrate of the product that is being filtered.

(13) Validation: written documentation attesting that any procedure, manufacturing process, mechanical device, raw material, action or system is capable of achieving its anticipated effect.

(14) Active pharmaceutical ingredient: an active substance or ingredient that is produced through physical, chemical or biotechnological processes for use in the manufacture of a pharmaceutical, biopharmaceutical or biotechnological product.

(15) Tamper-proof packaging: packaging with an identifying mark or barrier that enables consumers to clearly identify the contained product.

(16) Biotechnology product: any product that has been produced by means of gene recombination or cell fusion, or microorganisms obtained through cell culturing, fermentation, tissue extraction, proliferation of embryos or active animal or plant substances, or any other biotechnology method.

(17) Biopharmaceuticals: substances such as blood serum, antitoxins, vaccines, or toxoids that are manufactured using microbiological and immunological methods.

(18) Clinical trial drug: a pharmaceutical or placebo that is undergoing clinical trials, and has not yet obtained approval.

Article 36. Pharmaceutical manufacturers shall implement validation procedures; the categories to be implemented, as well as the implementation methods and schedule, shall be determined by the central competent health authority.

Chapter 2 Environmental Sanitation

Article 37. Pharmaceutical factory sites shall be situated in sanitary locations with fresh air; factory production, processing and packaging areas shall be constructed in accordance with relevant building codes, and located at a sufficient distance from factory boundaries to prevent pollution and fires.
The safety measures against pathogens implemented at factories or facilities that manufacture biopharmaceuticals or biotechnology products may not interfere with public health or safety; factory sewers shall be covered to prevent the entry and exist of animals to spread pathogens.

Article 38. In treating hazardous waste materials, toxic containers, hazardous gases, dust, wastewater, biological components and other hazardous components or materials, pharmaceutical factories shall act not only in accordance with relevant laws, but also with the following principles:

(1) For hazardous waste materials and toxic containers, storage facilities shall be established, and these materials and containers shall be decomposed in accordance with their properties, and then appropriately incinerated or buried. If toxic containers are to be reused, they shall be washed and rigorously controlled, and may not be used to hold food products.

(2) For hazardous gases and dust, airtight facilities, local exhaust ventilation systems and negative pressure procedures shall be established; these substances shall, in accordance with their properties, be scrubbed, collected, oxidized, reduced, combusted, or otherwise appropriately treated. If exhaust gas contains dust, it shall first be subjected to centrifuging, filtering, scrubbing, or some other form of dust-removal processing; the emission of such gases must comply with air pollutant emission standards.

(3) For the processing of wastewater, impermeable storage pools shall be established, and acidification, alkalization, neutralization, active carbon adsorption, or other effective methods shall be used to break down or remove wastewater toxins; the release of wastewater must comply with water release standards.

Chapter 3  Factory Buildings and Facilities

Article 39. Factory buildings shall be well constructed and safe; manufacturing, processing and packaging areas shall be completely separated from offices, reception rooms, laboratories, restaurants and their associated lavatories; the use of asbestos shall be avoided.
The buildings described in the preceding Paragraph shall be designed to prevent the entry of rodents, insects and dust; interior ceilings, walls and floors shall be smooth and free of cracks and crevices, easy to clean, and non-conducive to the collection of dust; where necessary, materials that are easily cleaned and disinfected, such as epoxy resins shall be used. Interior ducts shall be constructed of materials that do not easily collect dust, and shall be hidden where possible; drainage facilities and drainage exits shall be equipped to prevent wastewater backflow.

Article 40. Areas at pharmaceutical factories used for the storage of raw materials, product containers, caps, and labeling and packaging materials, and for the manufacture, processing, re-packaging, packaging and storage of products, shall be appropriately sized and located. These areas shall be suitably arranged, with operation areas clearly delineated by production type. Moreover, appropriate work space and levels of insulation and cleanliness shall be established as needed.

Levels of cleanliness, as mentioned in the preceding Paragraph, shall be established in accordance with the type of product being manufactured. Operation areas requiring the same level of cleanliness shall be grouped together; buffer zones or entry rooms shall be established between areas with different levels of cleanliness, and different colors or types of work clothes may be used to indicate the cleanliness levels of the various operation areas.

No operation area may be used as a passageway by personnel from other operation areas; passageways for people and for the transport of goods shall be separate, and shall not cross.

Facilities for the storage of raw materials, product containers, caps, labeling and packaging materials, semi-finished or intermediate products, and products shall be given “pre-inspection,” “approved for use” and “not approved for use” designations; if items are present that need to be kept frozen or are toxic, appropriate storage facilities shall be established.

Semi-finished or intermediate products shall be stored separately; if they are not stored separately, special care shall be taken to prevent contamination and degradation of quality.
Where biopharmaceutical and pharmaceutical factories use biotechnological methods to manufacture pharmacologically active substances or active pharmaceutical ingredients, they shall establish independent or separate factory buildings for this purpose; the air processing system for these buildings shall be independent from the systems of other drug production areas. However, where said factories manufacture non-contaminating biotechnology products, independent factory buildings and air processing systems shall not be necessary.

Where pharmaceutical factories manufacture environmental sanitation agents, environmental sanitation agent manufacturing, processing and re-packaging areas, as well as raw material storage facilities, shall be separated from pharmaceutical manufacturing, processing and re-packaging areas by a distance of no less than eight meters.

Where pharmaceutical factories manufacture pharmaceutical feed additives, the pharmaceutical feed additive operation area shall be independent from other operation areas.

Where pharmaceutical factories use their pharmaceutical production facilities to manufacture food products, cosmetics or general goods, care shall be taken to prevent cross-contamination, and validation procedures shall be carried out.

Article 41. All operation areas in pharmaceutical factories shall be equipped with appropriate illumination and ventilation facilities; where necessary, said areas shall also be equipped with appropriate facilities for the regulation of temperature and humidity.

Each production and processing area shall, in accordance with its air purity requirements, be equipped with appropriate air filtration systems, including pre-filters and particulate filters.

In areas for the storage of raw materials, products, semi-finished or intermediate products, and areas where products are manufactured, processed, re-packaged or
packaged, conditions conducive to the prevention of quality degradation shall be maintained.

Article 42. Factories shall locate manufacturing, processing, re-packaging, packaging and other areas used in the production of penicillin products, as well as related facilities, in a completely separate building; the air processing system for this building shall be independent from the systems of other drug production areas.

Factories shall establish independent operation areas for highly sensitizing substances such as antibiotics (cephalosporins, etc.), hormone drugs, cytotoxic drugs (including anticancer drugs), and drug and non-drug products that are highly physiologically active. If a special need arises to use said production areas and facilities for the manufacture of other products, special measures shall be established to prevent cross-contamination, and validation procedures shall be carried out.

The implementation date for the requirements mentioned in the preceding Paragraph shall be determined by the central competent health authority.

Article 43. For pharmaceutical factory production areas involving hazardous or flammable raw materials, solvents, semi-finished or intermediate products, or products, appropriate protective, first-aid and segregation facilities shall be established.

Facilities used in the manufacturing, processing and re-packaging process shall be airtight from start to finish; where facilities are not airtight and dust or hazardous gases are produced, local exhaust ventilation systems and negative pressure procedures shall be established.

Lighting, switches, sockets, motors and other electric devices for operation areas that produce dust, where organic solvents are used, or where hazardous substances are present, shall, as needed, be explosion-proof, airtight, or isolated from operation area.
Boilers, pressure vessels, cranes and other types of dangerous equipment and facilities shall be inspected and approved in accordance with relevant regulations before use.

Article 44. Pharmaceutical factories shall, as needed, establish employee lounges and shower rooms outside of work areas.

Manufacturing and processing areas shall be installed with appropriate lavatory facilities, and wastewater, garbage and other waste materials produced in said areas shall be treated in a safe and sanitary manner. Lavatory facilities shall be separated from work areas.

Article 45. Pharmaceutical factories shall, as needed, install facilities for the processing of general use and wastewater, and facilities for the production of boiler water or distilled water. Water supply facilities shall be kept from contaminating products.

Article 46. Container washing facilities shall be installed; where container washing facilities are used to wash containers for eye drops, injectables, or biopharmaceutical or biotechnology products, special care shall be taken to prevent contamination, and said facilities shall be installed away from other container washing facilities.

Article 47. Pharmaceutical factories shall carry out the manufacturing, processing and re-packaging of sterile products in aseptic room areas.

The aseptic room areas mentioned in the preceding Paragraph shall, as needed, be installed with the following facilities:

(1) Floors, walls and ceilings that are easily cleaned and disinfected;

(2) Temperature and humidity control systems;

(3) High performance air filtration systems capable of maintaining positive
pressure;

(4) Work area surveillance systems;

(5) Cleaning, disinfection, and other systems for maintaining sterile conditions.

Operation areas for sterile products that cannot be sterilized during the final stage of production must not only comply with the preceding Paragraph, but must also be installed with high performance air filters and laminar flow facilities for the circulation of sterile air. Furthermore, excessive traffic (personnel and objects) into and out of said areas shall be avoided.

Chapter 4  Facilities

Article 48. Facilities at pharmaceutical factories used for the manufacture, processing, re-packaging, packaging and storage of products shall be appropriately designed, sized and located for ease of use, cleaning and maintenance.

Facilities needed for the production of different dosage forms shall be positioned according to manufacturing process sequence.

Article 49. The surfaces of facilities at pharmaceutical factories that come into direct contact with raw materials, semi-finished products, intermediate products or products shall be made of non-reactive, non-releasing and non-adsorptive materials; where any process requires the use of lubricants, coolants or other similar substance, said substances may not come into contact with raw materials, product containers, caps, semi-finished products, intermediate products or products.

Article 50. Facilities and appliances at pharmaceutical factories used for the manufacture, processing, re-packaging, packaging and storage of products shall be regularly cleaned and maintained, and operational procedures shall be established in writing.
Facilities and appliances in aseptic room areas shall be made of materials that are easily cleaned, dried and disinfected, and shall be regularly cleaned, disinfected and maintained.

Article 51. The production capacities of mechanical facilities used at pharmaceutical factories to produce a single product shall be carefully coordinated to ensure consistency of product quality.

Automated machinery and electronic facilities used in the manufacturing process, as well as software and equipment related to computers or to the manufacture, processing, re-packaging, packaging or storage of pharmaceuticals, shall be regularly recalibrated, inspected, examined and maintained.

Computer systems used to control production and production management records shall be properly maintained, and alterations may not be made to said systems without permission from the personnel in charge; all data that is input or printed shall be checked for accuracy, and its period of validity shall be determined based on the complexity and reliability of the computer system.

Air used by drying facilities during the manufacturing process shall first be treated with a purification filter.

Facilities used to manufacture pharmaceuticals for internal and external use shall be kept strictly separate, and may not be used interchangeably.

Pharmaceutical factories shall install weighing facilities that comply with regulations, and shall recalibrate said facilities regularly.

Article 52. Where a pharmaceutical factory manufactures, processes or packs injectables, and has not installed filtration facilities capable of filtering out fibers, said factory may not use liquid filtration facilities that can possibly release fibers.
Article 53. Pharmaceutical factories shall keep facilities and equipment for the production of pharmaceuticals for human and animal use separate, and these two types of production may not be carried out in the same structure unless the two areas are completely separated. However, pharmaceuticals for animal use that comply with the standards governing drugs for human use are not subject to this restriction.

Article 54. Pharmaceutical factories shall, in accordance with the requirements of the products being manufactured, install necessary manufacturing, processing, re-packaging and packaging facilities.

Article 55. Pharmaceutical factories shall, in accordance with their specification testing requirements for raw materials, semi-finished products, intermediate products and products, establish testing departments and appropriate testing facilities. However, if tests are conducted on a contract basis by an organization approved by the competent authority, in accordance with the Contract Drug Manufacturing and Testing Operating Principles, and clear documentation is provided, establishment of said facilities may be waived.

Testing departments shall include testing and instrument laboratories. Instrument laboratories shall be separate from testing laboratories, and shall be kept at an appropriate temperature and level of humidity and air purity; testing laboratories shall be installed with sufficient and easy to use test benches, test stands, drug cabinets, fume hoods, water supply and washing facilities, as well as electric heating, thermostatic and drying facilities, and shall also be stocked with utensils and containers, chemical reagents and solutions, standard solutions and other necessary items.

Where eye preparations, injectable drugs, biopharmaceutical or biotechnology products are produced, areas, facilities and equipment necessary for conducting plate count, sterility tests and other tests shall be installed as needed; said areas and facilities shall be equipped with necessary culture mediums and control strains.

Where injectable drugs and biopharmaceutical or biotechnology products are produced, areas, facilities and equipment necessary for conducting pyrogen tests shall be installed as needed; said areas and facilities shall be equipped with
Where antibiotics and biopharmaceutical or biotechnology products are produced, areas, facilities and equipment necessary for conducting safety tests shall be installed as needed; said areas and facilities shall be equipped with necessary animals and breeding and observation areas.

Where antibiotics, hormones and biopharmaceutical or biotechnology products are produced, areas, facilities and equipment necessary for conducting bioassays shall be installed as needed.

The specifications of aseptic rooms and dissection laboratories shall be determined in accordance with the requirements of the tasks to be performed; microorganism strains, culture mediums and animals necessary for conducting bioassays shall be adequately stocked and maintained.

Chapter 5  Organization and Personnel

Article 56. Quality control departments and manufacturing departments at pharmaceutical factories shall be established separately.

Article 57. A person shall be placed in charge of each pharmaceutical factory department, and sufficient personnel shall be assigned to carry out and supervise the manufacture, processing, re-packaging, packaging or storage of each product.

Article 58. The person in charge, supervisors and employees of each pharmaceutical factory department shall all possess suitable educational backgrounds, and shall all undergo practical training in implementing the rules prescribed in Part 3 of this set of Standards; employees who work in aseptic room areas shall undergo specialized training in aseptic room operations.

Article 59. Pharmaceutical factories shall establish in writing sanitary standards
for employees; said standards shall include the following items:

1. Regular health examinations in accordance with the nature of the employee’s job;

2. Measures to prevent employees with illnesses or open wounds from having a negative impact on pharmaceutical safety or quality;

3. Rules requiring employees to wash or disinfect their hands when entering work areas, refrain from wearing jewelry, eating, drinking, smoking, or engaging in any other behavior that may impact sanitation in manufacturing areas;

4. Standards for the types of work clothes, hoods, face masks, gloves, arm covers, and shoe covers for each job.

Chapter 6  Management of Raw Materials and Product Containers and Caps

Article 60. Pharmaceutical factories shall establish detailed quality specifications for raw materials and product containers and caps, as well as operational procedures for the acceptance, labeling, storage, handling, sampling, testing and inspection of these items.

Containers that hold raw materials, product containers or caps shall be clearly labeled with batch numbers and status, pending-inspection, approved for use, not approved for use, or to be isolated; this information shall be entered into the disposition record of each batch.

Container caps shall, as needed, be fitted with children safety devices to prevent accidental consumption.

Article 61. When pharmaceutical factories receive shipments of raw materials, product containers or caps, they shall collect representative samples from each batch for testing; a note of this action shall be made on the original container.
Containers holding the samples described in the preceding Paragraph shall be appropriately labeled to facilitate tracking of sample names, batch numbers, sampling basis, original container and name of sampler.

Article 62. The samples referred to in the preceding Article shall be tested in accordance with the following principles:

(1) Every raw material shall be tested to determine whether it is in compliance with documented specifications. However, aside from identification tests, other tests may be waived if the test reports provided by the supplier are evaluated and found to be reliable.

(2) Products containers and caps shall be tested to determine whether they are in compliance with established specifications.

(3) Where raw materials, product containers or caps are susceptible to contamination by filth, insects, foreign objects or microorganisms, thus affecting their intended uses, relevant test items and methods shall be included in the quality specifications for said items, and each batch shall be inspected for contamination.

Article 63. Where raw materials, product containers or caps are tested and found to be in compliance with documented specifications, pharmaceutical factories may approve them for use; where said items are not in compliance, they shall not be approved for use.

Raw materials, product containers or caps that are approved for use shall be used in the order of approval. However, where said items have been stored for long periods, exposed to the air or high temperatures, or subjected to other detrimental conditions, retesting shall be carried out.

Raw materials, product containers or caps that are not approved for use shall be labeled to this effect, and kept isolated prior to their proper disposal.

Chapter 7 Manufacturing Process Control
Article 64. To insure that each product batch is of consistent quality, pharmaceutical factories shall have designated personnel establish process control standards for every product, and have said standards independently reviewed by other personnel.

The process control standards mentioned in the preceding Paragraph shall include the following items:

1. Product name, content and dosage form;
2. Name and weight or volume of each active ingredient per product by unit weight, volume or dosage form, and total weight or volume of unit dosage form;
3. Names and specifications of all raw materials; if a code name or number is used to represent a raw material, said code shall be sufficient to determine the nature of the material;
4. Quantity of each product batch;
5. Weight or volume required by each raw material for each product batch. However, the quantities of raw materials used to produce a given dosage form may be increased or varied within a reasonable range; said range shall be explained in the manufacturing process control standards;
6. Appropriate theoretical weights or volumes for each stage of the manufacturing process;
7. Theoretical production quantity, including upper and lower production quantity limits expressed as percentage;
8. Product container, cap and packaging material specifications (along with label signed and dated by inspector and samples or copies of all other labeling);
9. Complete manufacturing and control manuals, sampling and test procedures, specifications and guidelines.

Article 65. Pharmaceutical factories shall establish in writing process control procedures; said procedures shall be approved by the quality control department. Where actual operations deviate from documented procedures, said deviation shall be recorded, a determination of how best to handle the deviation shall be made, and an explanation shall be given.
Article 66. To insure the each product batch is of consistent quality and integrity, pharmaceutical factories shall take steps to evaluate and validate the consistency of process control operations, including related equipment and facilities, for each product; documented procedures for the validation of each manufacturing process shall also be established, and shall be complied with and validated on a regular basis.

All original verification records and statistical analysis data related to evaluation and validation procedures shall be compiled and filed for future reference.

Article 67. Pharmaceutical factories shall clearly mark the contents and product batch manufacturing stage dates and times of mixing and storage containers, production lines and main manufacturing facilities used in the production and manufacture of each product batch, and enter said information into the batch manufacturing record.

Article 68. In regard to the quantities of raw materials used by pharmaceutical factories in the manufacture of products, the amounts of active ingredients in each product batch may not fall below the nominal quantity.

Weighing, dividing and other procedures carried out on raw materials shall be performed in designated segregation areas, and shall be appropriately supervised and controlled.

Documented operational procedures shall include detailed test and control procedures for representative samples from each batch of semi-finished or intermediate products.

During the manufacturing and production process, the quality control departments of pharmaceutical factories shall carry out tests on semi-finished or intermediate products in accordance with established test procedures, thereby determining whether to approve said products for use; semi-finished or intermediate products that are not approved for use shall be labeled to this effect and kept isolated.
Article 69. Where pharmaceutical factories weigh, mix, pulverize, form tablets from, fill, re-package or carry out other related procedures on antibiotic powder, and said procedures are carried out in areas also used for the production of general pharmaceutical products, steps shall be taken to prevent cross-contamination, and validation procedures shall be carried out.

Pharmaceutical factories shall include appropriate measures to prevent contamination by harmful microorganisms in the documented operational procedures for products that do not require sterilization; steps or other appropriate measures to ensure sterilization results shall be established for products that require sterilization.

Chapter 8  Management of Packaging and Labeling

Article 70. Pharmaceutical factories shall establish in writing management procedures for the acceptance, labeling, storage, handling, sampling and testing of packaging and labeling materials.

Where over-the-counter drug products for human use are produced, packaging for said products shall be tamper-proof, and shall be kept intact during the manufacturing, shipping and retail display process; moreover, said packaging shall be designed in such a manner that tampering is easily detectable by consumers.

Prior to the acceptance or use of labeling and packaging materials, representative samples shall be taken from each batch for testing; testing results shall be recorded and samples preserved. Where test results comply with established specifications, said materials may be approved for use; where said materials are not in compliance, they shall not be approved for use.

Article 71. Pharmaceutical factories shall, in accordance with product type, content and dosage form, separately store and appropriately mark labels and other labeling materials; storage areas for said materials may not be entered without the consent of the personnel in charge.
Packaging or labeling materials that have expired or are not approved for use shall be returned or destroyed. The amounts of labeling materials received, used and returned shall be kept track of, and no discrepancies shall be allowed.

Unused portions of labeling materials printed with batch numbers shall be destroyed; unused labeling materials that are not printed with batch numbers shall be appropriately identified and stored.

Article 72. Prior to packaging and labeling products, pharmaceutical factories shall first inspect packaging and labeling materials to ensure that they are correct and suitable for use; said inspection results shall be entered into the batch manufacturing record.

Packaging and labeling facilities shall be inspected prior to use to ensure that all pharmaceuticals from the previous run and packaging and labeling materials not suited to the present run have been completely removed; said inspection results shall be entered into the batch manufacturing record.

During the final stage of production, products that have already been packaged and labeled shall be inspected to ensure that every container or package is correctly labeled.

Article 73. To ensure that the ingredients, contents, quality and purity of products ready for use are in compliance with established specifications, pharmaceutical factories shall, unless other regulations apply, label said products with a usage period or expiration date as determined through stability testing; products that must be prepared before use shall be clearly labeled with the method of preparation and usage period following preparation.

Chapter 9  Storage, Shipping and Sales

Article 74. Pharmaceutical factories shall establish in writing product storage
procedures; said procedures shall include the following items:

(1) Segregation measures for products awaiting approval for use;

(2) Appropriate temperature, humidity and light exposure standards to ensure that product ingredients, contents, quality and purity are not adversely affected by storage.

Article 75. Pharmaceutical factories shall establish in writing shipping and sales procedures; said procedures shall include the following items:

(1) Measures to ensure that products are sold in the order of manufacture;

(2) Shipping and sales methods that ensure product ingredients, contents, quality and purity are not adversely affected by environmental factors;

(3) Systems to ensure prompt recycling.

Chapter 10 Quality Control

Article 76. Pharmaceutical factories shall establish in writing quality department duties and operational procedures; said duties and procedures shall include the following items:

(1) Examination of approval, non-approval and manufacturing records for all raw materials, product containers, caps, semi-finished or intermediate products, packaging materials, labeling materials and products;

(2) Examination of operational procedures specifications that affect product ingredients, contents, quality and purity;

(3) Inspection of facilities used in the testing of raw materials, product containers, caps, semi-finished or intermediate products, packaging materials, labeling materials and products;

(4) Establishment in writing of operational procedures governing the calibration of instruments, devices, meters and recording apparatuses; said procedures shall clearly prescribe calibration methods, schedules, accuracy limits, as well as usage restrictions and remedial measures for items that do not comply with accuracy limits;
(5) Establishment in writing of operational procedures governing sample quantities, test intervals and test methods for product stability testing.

Article 77. Specifications, standards, sampling plans, test procedures, and test control measures established for the various departments of a pharmaceutical factory, and any alterations related to said items, shall be examined and approved by the quality control department of said factory prior to implementation.

Pharmaceutical factories shall faithfully follow the operational guidelines that they have established and keep records of the implementation process; where a deviation from said guidelines occurs, said deviation shall be recorded, a determination of how best to handle the deviation shall be made, and an explanation shall be given.

Pharmaceutical factories shall select senior specialist personnel from each department to establish a quality assurance system to regularly assess the status of factory operations; this process shall include establishment of self-assessment procedures for the implementation of regulations of Part 3 of this set of Standards, as well as the production of records and reports for future reference.

Article 78. Pharmaceutical factories shall test every batch of products to ensure that they are in compliance with established specifications; each batch of products that must not contain harmful microorganisms shall, where necessary, be subjected to appropriate tests.

Representative samples shall be removed from each batch of products or end products, and taken from the raw materials containing active ingredients used in making said products, and placed in reserve; said reserve samples shall be stored under indicated conditions, and shall be of at least twice the quantity needed for all required tests. However, the quantity of reserve samples for sterility and pyrogen tests shall be determined in accordance with requirements.

Reserve samples shall be retained until one year after the expiration date of the product from which it was taken; reserve samples of products that do not require
expiration dates shall be kept for at least three years after the date of dispatch of the last batch of said product.

Article 79. Pharmaceutical factories shall use appropriate methods to breed, maintain and dispose of animals required for the testing of raw materials, semi-finished or intermediate products, and products.

Laboratory animals shall be marked; records sufficient to trace their usage history shall be kept.

Article 80. Pharmaceutical factories shall, where necessary, test non-penicillin antibiotics to ensure that they have not been contaminated by penicillin, hormone or cephalosporin products.

Chapter 11 Records and Reports

Article 81. The manufacturing, control, shipping and sales records prescribed in Part 3 of this Part shall all be stored in suitable locations, made available for inspection, and used at least once a year in the assessment of product quality standards; said records shall be kept until one year after the expiration date of the batch of products or end products in question. However, records for products that do not require expiration dates shall be kept for three years after the date of dispatch of the batch of products or end products in question.

When relevant competent authorities make inspections, they may photocopy, or copy by other means, the records described in Paragraph 1 or copies of said records.

Article 82. Pharmaceutical factories shall keep batch manufacturing records for each batch of products produced; said records shall contain comprehensive manufacturing and quality control information on the product batch in question.
Pharmaceutical factories shall produce accurate copies of manufacturing management standards, verify the accuracy of said copies, and sign and date them.

Pharmaceutical factories shall make detailed records of the important steps in the manufacture, processing, re-packaging, packaging and storage of each batch of products; said records shall include the following items:

1. Date and product batch number;
2. Identification marks for each batch of raw materials and semi-finished or intermediate products;
3. Identity of major facilities and production lines;
4. Quantity and volume of raw materials used in product processing;
5. Manufacturing process, testing and control results;
6. Pre- and post-use inspection of labeling and packaging areas;
7. Ratio of actual production output to theoretical output at appropriate stages of manufacturing process;
8. Comprehensive labeling control records, including samples or copies of all labeling;
9. Product container and cap identification marks and usage quantity;
10. Sampling record;
11. Dates and times of each major step in the production process, as well as signatures and dates for operation personnel, direct supervisors or inspectors involved in each step.

Article 83. The test records produced by pharmaceutical factories shall include all test data used in determining compliance with established specifications and standards; said data shall include the following items:

1. Sampling location, quantity, batch number or other clear identifying code, sampling date, and date of test completion;
2. Basis of all test methods;
3. Weight or volume of all samples tested;
(4) Comprehensive records of all data generated during testing process, including charts, graphs and spectra produced by test instruments, and clearly listing all the raw materials, product containers, caps, semi-finished products, intermediate products or products tested, along with the batch numbers of said items;

(5) Record of all test-related calculations;

(6) Records of test results and comparison of said results with established specifications;

(7) Names and dates for all personnel involved in conducting tests;

(8) Signatures of inspectors testifying that the original records inspected are accurate, truthful and in compliance with established specifications.

Article 84. The manufacturing and quality control records (including packaging and labeling control records) for all products manufactured by pharmaceutical factories shall be examined by the quality control departments of said factories to ensure that all products are in compliance with all established documented operational procedures prior to release, shipment or sale.

Where the theoretical production quantity exceeds the upper or lower production quantity limits prescribed by manufacturing control standards, or if any other similar discrepancy occurs, or if any batch or raw material does not conform to specifications, a thorough investigation shall be conducted even if said batch of products has already been shipped or sold; such investigations shall be extended to other batches of the product in which said discrepancy occurred, and to any other products that may be affected by said discrepancy.

Written records shall be kept of the investigations described in the preceding Paragraph; said records shall include investigation conclusions and methods.

Article 85. Pharmaceutical factory’s shipping and sales records shall include products names, contents, dosage forms, recipient names and addresses, and shipping dates and quantities.
Article 86. Pharmaceutical factories shall make written records of product complaints, and keep said records in product complaint files; said files shall be stored in a suitable location, or in a facility where they can be easily accessed for inspection.

The written records referred to in the preceding Paragraph shall be kept until the expiration date of the product in question, or for one year after the complaint was received, whichever period is longer. However, for products that do not require expiration dates, said records shall be kept for at least three years after the date of dispatch of the product in question.

Article 87. Records of returned products kept by pharmaceutical factories shall include product names, contents, batch numbers, reasons for return, quantities, disposition dates, final disposition methods; said records shall be kept in accordance with the regulations prescribed in Article 81.

Chapter 12 Handling of Complaints and Returned Products

Article 88. Pharmaceutical factories shall establish in writing procedures for the handling of oral and written complaints from consumers; all oral and written complaints shall be investigated and assessed by the quality control departments of said factories.

Where pharmaceutical factories discover serious and unanticipated product defects, they shall report said defects to the relevant competent authorities, and handle said defects in accordance with the stipulations of the Act.

Written records shall be kept of the handling of all complaints; said records shall be properly collated and filed.

Article 89. Pharmaceutical factories shall properly identify and separately store returned products. If there are any doubts regarding a product’s safety, ingredients, contents, quality or purity due to storage or shipping conditions, the condition of the product, container, packaging or labeling, or any other relevant circumstances
either before or after the product is returned, unless the product’s safety, ingredients, contents, quality and purity are confirmed to be in compliance with established specifications through testing or investigation, said product shall be destroyed. However, where said product can be brought into compliance with established specifications through remanufacturing, remanufacturing may be carried out.

Chapter 30  Pharmaceuticals for Use in Clinical Trials

Article 90. The production and manufacturing of pharmaceuticals for use in clinical trials by pharmaceutical factories shall, unless otherwise regulated by regulations of this Chapter, be governed by other relevant regulations prescribed in this Part.

Article 91. Where pharmaceutical factories have not yet established validated manufacturing processes for pharmaceuticals for use in clinical trials, or have not yet established comprehensive manufacturing control standards, said factories shall establish in writing operational procedures and keep detailed and accurate records for each batch of products manufactured and each batch of raw material used. Batch manufacturing records shall be kept until clinical trials are completed, or until at least two years after the product is completed, whichever period is longer.

Article 92. Where pharmaceutical factories produce biopharmaceuticals or biotechnology products for use in clinical trials, impurities caused by virus inactivation/removal or other organisms may not exceed the limits imposed on other similar products on the market. Where operational procedures for said products have not yet been validated, quality control tests shall be performed.

Article 93. Where pharmaceutical factories produce pharmaceuticals for use in clinical trials, said pharmaceuticals, in addition to complying with regulations governing labeling in the Act, must also be labeled “for use in clinical trials only,” and marked with the name of the party that commissioned the clinical trial and a trial code sufficient to identify the trial location and research personnel involved. However, where pharmaceuticals for use in clinical trials are tested in closed trials (double-blind trials), drug name, potency and efficacy may be replaced by product codes, serial numbers and packaging batch numbers.
Article 94. Pharmaceutical factories shall determine suitable expiration dates for pharmaceuticals for use in clinical trials based on the product properties, container characteristics and storage conditions; the expiration dates marked on said pharmaceuticals may not exceed the expiration dates marked on the original product packaging.

Where clinical trials do not provide stability testing information, the usage period of a repackaged product may not exceed 25% of the remaining portion of the usage period of the original bulk product, or the six-month period following repackaging, whichever period is shorter.

Article 95. Where a pharmaceutical factory has a pharmaceutical for use in clinical trials manufactured or tested on a contract basis, said contract shall clearly state that the product in question is for use in clinical trials only.

Article 96. Where pharmaceutical factories destroy pharmaceuticals for use in clinical trials, destruction of said pharmaceuticals may not take place until all clinical trials and the final report are completed; detailed records shall be kept of the destruction process, and said records shall be preserved by the manufacturer.

Part 4 Good Manufacturing Practices for Medical Devices

Chapter 1 General Principles

Article 97. Manufacturers of medical devices (hereafter referred to as the manufacturers) shall comply with regulations of this Part. However, where the Medical Device Management Measures or other relevant laws or regulations apply, compliance with this Part may be waived.

Article 98. Terms used in this Part are defined as follows:

(1) Active medical device: any medical device relying for its functioning on a
source of electrical energy or any source of power other than that directly generated by the human body or gravity;

(2) Active implantable medical device: any active medical device that is totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and that is intended to remain after the procedure;

(3) Implantable medical device: any medical device that is totally or partially introduced by surgical means into the human body or a natural orifice, or to replace an epithelial surface or the surface of the eye, that is intended to remain after the procedure for at least 30 days, and that can only be removed by medical or surgical intervention;

(4) In-vitro diagnostic device: any medical device that is a reagent, instrument, or system used for the collection, preparation and examination of specimens from the human body for use in the diagnosis of disease or other conditions (including determination of the state of health);

(5) Customer complaint: any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety or performance of a medical device that has been placed on the market;

(6) Advisory notice: supplementary information or advice issued by the manufacturer upon delivery of a medical device, regarding the use, modification, return or destruction of said device, for the purpose of taking corrective or preventive action or complying with regulatory requirements;

(7) Risk analysis: the investigation of available information to identify hazards and assess risks.

Article 99. Manufacturers of medical devices that fall under the Class 1 category as defined in Attachment 2 of the Medical Device Management Measures, unless said devices must be sterile, are not required to comply with regulations of this Part.

Where medical devices that must be sterile, as described in the preceding Paragraph, are Class 1 or Class 2 medical devices that have been granted a five-year grace period by the central competent health authority, the manufacturers of said products shall come into compliance with regulations of this Part by June 21, 2005.
Chapter 2  Management Responsibility

Article 100. Manufacturers shall clearly establish quality policies, including objectives for, and commitment to, quality.

The quality policies described in the preceding Paragraph shall be relevant to manufacturers’ organizational goals and the expectations and needs of their customers.

Manufacturers shall ensure that these quality policies are understood, implemented and maintained at all levels of the organization.

Article 101. Manufacturers shall clearly define and document the responsibility, authority and interrelation of personnel who manage, perform and verify work affecting quality, particularly personnel who need the organizational authorization to perform the following tasks:

(1) Initiate action to prevent the occurrence of any nonconformities relating to products, process or quality system;
(2) Identify and record any problems relating to products, process or quality system;
(3) Initiate, recommend or provide solutions through designated channels;
(4) Verify the implementation of solutions;
(5) Control further processing, delivery or installation of nonconforming product until the deficiency or unsatisfactory condition has been corrected.

Article 102. Manufacturers shall identify resource requirements and provide adequate resources, including the assignment of trained personnel for management, performance of work and verification activities including internal quality audits.

Article 103. Manufacturers shall appoint a member of their own management team who, irrespective of other responsibilities, shall define authority for the following tasks:

(1) Ensuring that a quality system is established, implemented and maintained in accordance with regulations of this Part;
(2) Reporting on the performance of the quality system to the management for review and as a basis for improvement of the quality system;

(3) Ensuring the safety and effectiveness of manufactured medical devices.

Article 104. Manufacturers shall review their quality systems at defined intervals sufficient to ensure its continuing suitability and effectiveness in satisfying the requirements of this Part and the manufacturer’s stated quality policies and objectives. Records of said reviews shall be kept and maintained.

Chapter 3 Quality Systems

Article 105. Manufacturers shall establish, document and maintain quality systems as a means of ensuring that products conform to specified requirements.

Manufacturers shall prepare a quality manual covering the requirements of this Part; said manual shall include or make reference to the quality system procedures and outline the structure of the documentation used.

Article 106. Manufacturers shall adhere to the following quality system procedures:

(1) Prepare documented procedures consistent with the quality policy and the requirements of this Part;

(2) Effectively implement the quality system and its documented procedures.

The quality system procedures described in the preceding Paragraph shall be dependent upon the complexity of the work, the methods used, and the training required by the personnel involved.

Article 107. Manufacturers shall establish in writing a quality plan detailing how quality requirements are to be met.

The quality plan described in the preceding Paragraph shall be consistent with the requirements of manufacturers’ quality systems, and shall be documented in a format to suit the supplier’s operation. Manufacturers shall give consideration to the following activities, as appropriate, in meeting specified requirements for
products, projects or contracts:

(1) Preparation of quality plans;

(2) The identification and acquisition of any controls, processes, facilities, (including inspection and test facilities), fixtures, resources and skills that may be needed to achieve the required quality;

(3) Ensuring the compatibility of the design, the production processes, installation, servicing, inspection and test procedures and the applicable documentation;

(4) The updating, as necessary, of quality control, inspection and testing techniques, including the development of new instruments;

(5) The identification of any measurement requirement involving capability that exceeds the known state of the art, in sufficient time for the needed capability to be developed;

(6) The identification of suitable verification at appropriate stages in the realization of products;

(7) The clarification of standards of acceptability for all features and requirements, including those that contain a subjective element;

(8) The identification and preparation of quality records.

Manufacturers shall establish and maintain medical device manufacturing procedure, installation and maintenance files, or a location where relevant information can be accessed. Said files or information shall include product specifications and quality system requirements (including process and quality assurance) for each product type or model.

Chapter 4 Contract Review

Article 108. Manufacturers shall establish in writing and maintain procedures for contract review and for the coordination of review activities.

Article 109. Before submitting a tender, or accepting a contract or order,
manufacturers shall review said tender, contract or order to ensure that the following conditions are met:

(1) Requirements are adequately defined and documented; where an order is placed orally and there is no accompanying documentation, steps shall be taken to ensure that requirements have been met before said order is accepted.

(2) Any discrepancies between items in contract/order and tender have been resolved.

(3) Contract/order requirements are capable of being fulfilled.

Manufacturers shall identify contract amendments and accurately communicate said amendments to relevant departments within the organization.

Records of the review procedures described in the preceding two Paragraphs shall be kept and maintained.

Chapter 5  Design Control

Article 110. Manufacturers shall control and verify product design, and establish in writing and maintain procedures to ensure that specified requirements are met. However, products for which the central competent health authority does not mandate the implementation of design control, are not required to comply with the provisions of this Chapter.

Manufacturers shall, in the course of the design process, assess the need for risk analysis and keep and maintain records of any risk analysis performed.

Article 111. Manufacturers shall draft plans for each design and development activity; said plans shall comply with the following conditions:

(1) Each plan shall document or refer related activities.

(2) Implementation responsibility shall be defined.
(3) Design and development tasks shall be assigned to qualified personnel equipped with adequate resources.

(4) Plans shall be updated as designs evolve.

Manufacturers shall define organizational and technical interfaces between the different groups involved in the design process; necessary information shall be documented, circulated and reviewed on a regular basis.

Article 112. Manufacturers shall identify, document and adequately review product design input requirements (including applicable statutory and regulatory requirements). Where said requirements are incomplete, ambiguous or conflicting, solutions shall be reached in consultation with those responsible for imposing said requirements.

Design input shall take into consideration contract review results.

Article 113. Manufacturers shall document design output; said output shall comply with the following conditions:

(1) Design output shall comply with design input requirements, and expressed in terms that can be verified and validated against design input requirements.

(2) Design output shall contain or make reference to acceptance criteria.

(3) Design input shall identify the design characteristics that are crucial to the safe and proper functioning of the product (e.g. operation, storage, shipping, maintenance and handling requirements).

(4) Design output documentation shall be reviewed before release.

Article 114. Manufacturers shall, in the course of the design process, plan and conduct formal written reviews of design results.

Participants in said reviews shall include representatives of all departments
involved in review of the design stage; where necessary, other specialist personnel shall be asked to participate.

Records of said reviews shall be kept and maintained.

Article 115. Manufacturers shall perform design verification at appropriate stages in the design process to ensure that design stage output complies with design stage input requirements.

Records of the design verification measures referred to in the preceding Paragraph shall be kept and maintained.

Article 116. Manufacturers shall perform design validation and clinical evaluations to ensure that products comply with established user needs and specified requirements; records of these activities shall be kept and maintained as part of the design validation process.

The clinical evaluations referred to in the preceding Paragraph shall include relevant scientific literature and established evidence proving that similar designs and materials are clinically safe, or use clinical studies or experiments to ensure that said equipment conforms to specified functions.

Article 117. All design alterations and modifications made by manufacturers shall be identified, documented and reviewed, as well as approved by authorized personnel, prior to implementation.

Chapter 6  Document and Data Control

Article 118. Manufacturers shall establish in writing and maintain procedures for the control of all documents and data governed by the provisions of this Part; where feasible, said procedures shall include original documents of external origin (such as standards and client drawings)
Document and data control by manufacturers shall comply with the following conditions:

(1) Documents and data shall be reviewed and approved for adequacy by authorized personnel prior to issue.

(2) A master list or equivalent document control procedure identifying the current revision status of documents shall be established and be readily available to prevent the use of obsolete or invalid documents.

(3) Valid versions of appropriate documents shall be made available at all locations where operations essential to the effective functioning of the quality system are performed.

(4) Obsolete or invalid documents shall be promptly removed from all points of issue or use, or other steps shall be taken to ensure that inadvertent use does not occur.

(5) Obsolete documents retained for legal or information purposes shall be appropriately identified.

(6) Manufacturers shall retain at least one copy of obsolete control documents, and shall determine the period of retention. Said period shall be sufficient to ensure that the specifications to which medical devices have been manufactured are available for at least the specified usage period of said products.

Article 119. Alterations to documents shall, unless otherwise designated, be reviewed and approved by the same functional units/organizations that performed the original review and approval. If other functional units/organizations are assigned to review said alterations, said units/organizations shall have access to background information used in the original review upon which to base their review and approval.

Where feasible, the nature of the alteration shall be indicated in the document or an appropriate attachment.

Chapter 7  Purchasing
Article 120. Manufacturers shall establish in writing and maintain purchasing procedures to ensure that all products purchased comply with specified requirements.

Purchasing documents shall clearly describe the products being purchased; where feasible, said documents shall include the following items:

1. Product type, class, grade or other precise identifying information;
2. Product name or other proper identification and applicable versions of specifications, graphics, process requirements, inspection instructions and other relevant technical data, including items required for product, procedure, process equipment and personnel approval or validation;
3. Name, serial number and version of the quality system standard used.

Where it is necessary to verify a purchased product on the subcontractor’s premises, verification arrangements and the method of product release shall be specified in the purchasing documents.

Manufacturers shall review and approve purchasing documents for adequacy of specified requirements prior to release.

In accordance with the provisions of Chapter 9, for medical devices with specified traceability requirements, manufacturers shall retain copies of relevant purchasing documents.

Article 121. Manufacturers shall adopt the following measures in regard to subcontractors:

1. Evaluate and select subcontractors based on their ability to meet subcontracting requirements, including quality system and specific quality assurance requirements.
2. Define the method and extent of control exercised over subcontractors
based on product type and impact of subcontracted product on quality of end product; where applicable, the subcontractor’s quality audit reports or quality records demonstrating the subcontractor’s capabilities and performance shall be consulted.

(3) Establish and maintain subcontractor quality records.

Manufacturers shall not take testimonials from clients regarding subcontractors as evidence for use in effective subcontractor quality control.

Chapter 8  Control of Customer-supplied Products

Article 122. Manufacturers shall establish in writing and maintain procedures for control of the verification, storage and maintenance of customer-supplied products.

Customer-supplied products, as referred to in the preceding Paragraph, are supplies provided by customers that are incorporated into products or used in related activities. Where customer-supplied products are lost, damaged or otherwise unsuitable for use, the manufacturer shall record the problem and report it to the customer.

Chapter 9  Product Identification and Traceability

Article 123. Where appropriate, manufacturers shall establish in writing and maintain procedures detailing suitable means for identifying their products at the various stages of receiving, production, delivery and installation.

The procedures described in the preceding Paragraph shall include instructions ensuring that where returned medical devices are reprocessed due to special requirements, said products are properly identified and differentiated at all times.
Article 124. For products where traceability is required, manufacturers shall establish in writing and maintain procedures to ensure unique identification of individual products or product batches. Records shall be kept of said identification.

Manufacturers shall establish and maintain traceability procedures; said procedures shall define the extent of traceability and facilitate corrective and preventive measures.

The extent of traceability for active implantable medical devices and implantable medical devices shall include records of all components, materials and environmental conditions that could possibly prevent said devices from complying with specified requirements.

Manufacturers shall require that their agents or distributors maintain and retain medical device sales records for inspection purposes.

Chapter 10  Production Process Control

Article 125. Manufacturers shall identify and plan the production, installation and service processes that directly affect quality, and shall ensure that these processes are implemented under controlled conditions.

The controlled conditions referred to in the preceding Paragraph shall include the following:

(1) Where the absence of certain production, installation or service procedures would adversely affect quality, said procedures shall be established in writing.

(2) Suitable production, installation and service facilities shall be used in a suitable work environment.

(3) Relevant laws, standards, and quality plans or documented procedures shall be complied with.

(4) Suitable process parameters and product characteristics shall be monitored
and controlled.

(5) Where necessary, processes and facilities shall be approved.

(6) Workmanship criteria (e.g. documented standards, representative samples or illustrations) shall be stipulated in a clear and practical manner.

(7) Facilities shall be suitably maintained to ensure continuing process capabilities.

Where process results cannot be fully verified through subsequent product inspection and testing (including manufacturing deficiencies that only become apparent with product use), said process shall be carried out by qualified operators, or the parameters of said process shall be continuously monitored and controlled, to ensure that specified requirements are met.

Conditions required for process operation, including relevant facilities and personnel, shall be stipulated.

Article 126. Where contact between personnel and products or the production environment could adversely affect product quality, manufacturers shall establish in writing and maintain regulations governing personnel health, cleanliness and attire.

Manufacturers shall ensure that all temporary personnel required to work under special conditions receive necessary training or work under the supervision of trained personnel.

Article 127. Where medical devices meet the following conditions, manufacturers shall establish in writing requirements for the environments to which said devices are exposed:

(1) Said devices are sterile at time of supply.

(2) Said devices are not sterile at time of supply, but require sterilization prior to use.
(3) Removal of microorganisms or dust, or other environmental conditions are critical to the use of said devices.

(4) Environmental conditions during the production process are critical to said devices.

Where necessary, environmental conditions shall be controlled or monitored.

Article 128. Where products meet the following conditions, manufacturers shall establish in writing product cleanliness requirements:

(1) Said products are cleaned by the manufacturer prior to sterilization or use.

(2) Said products are not sterile at time of supply, but require cleaning prior to sterilization or use.

(3) Said products need not be sterile at time of use, but their level of cleanliness is critical to usage results.

(4) Agents used in the manufacture of said products require removal.

Where necessary, products cleaned in accordance with regulations of Subparagraph 1 and Subparagraph 2 of the preceding Paragraph may be waived from the special requirements regarding control of personnel and production environment prescribed in the preceding two Articles.

Article 129. Manufacturers shall establish in writing and maintain requirements for maintenance and repair activities where said activities may affect product quality. Maintenance and repair records shall be kept and maintained.

Article 130. Where necessary, manufacturers shall establish operational guidance documents and acceptance criteria regarding the installation and inspection of medical devices.

Installation and inspection records made by manufacturers or their authorized
Where contracts do not require manufacturers or their authorized representatives to take responsibility for product installation, those who purchase said products shall be provided with documented installation and inspection instructions.

Article 131. Where computer software is applied in process control, manufacturers shall establish in writing and maintain procedures for the validation of said software application. Records shall be kept of validation results.

Article 132. Where medical devices require sterilization, manufacturers shall subject said devices to a validated sterilization process; records shall be kept of all control parameters involved in said sterilization process.

Chapter 11 Inspection and Testing

Article 133. Manufacturers shall establish in writing and maintain procedures for inspection and testing activities in order to verify that products meet specified requirements.

The inspection and testing referred to in the preceding Paragraph, as well as the records to be established of said activities, shall be detailed in the quality plan or in documented procedures.

Article 134. Manufacturers shall apply the following control measures to incoming products:

(1) Manufacturers shall ensure that incoming products are not used or processed until said products have been inspected or otherwise verified as complying with specified requirements. Verification of compliance with specified requirements shall be carried out in accordance with the quality plan or documented procedures.

(2) In determining the nature and amount of receiving inspection, consideration
shall be given to the amount of control implemented at the subcontractor’s premises and the records of conformance provided.

(3) Where incoming products are released for urgent production purposes prior to verification, said products shall be clearly identified and a record kept in order to facilitate immediate recall and replacement in the event of noncompliance with specified requirements.

Article 135. Manufacturers shall implement the following in-process inspection and testing measures:

(1) Inspect and test products in accordance with quality plan or documented procedural requirements.

(2) Hold products until required inspection and tests have been completed or necessary reports have been received and verified; however, this requirement does not apply to products that are released under positive-recall procedures.

Products released under positive-recall procedures must still be inspected and tested in accordance with Subparagraph 1 of the preceding Paragraph.

Article 136. Manufacturers shall carry out final inspection and testing, and create a record of said activities, in accordance with the quality plan or documented procedures, to ensure that end products are in compliance with specified requirements.

The quality plan or documented procedures for final inspection and testing shall require that all specified inspection and tests (including those specified either on receipt of product or in-process) have been carried out and that results meet specified requirements.

No product shall be dispatched until all the activities specified in the quality plan or documented procedures have been satisfactorily completed and the associated data and documentation is available and authorized.
Article 137. Manufacturers shall establish and maintain records that give evidence that products have been inspected and/or tested.

The records described in the preceding Paragraph shall meet the following conditions:

(1) Said records shall show clearly whether products have passed or failed the inspection or tests performed according to acceptance criteria; where products fail to pass any inspection or test, the procedures for control of nonconforming products shall apply.

(2) Records shall identify the inspection authority responsible for the release of products.

(3) Manufacturers shall record the identity of personnel performing any inspection or testing of active implantable medical devices or implantable medical devices.

Chapter 12 Control of Inspection, Measuring and Test Facilities

Article 138. Manufacturers shall establish in writing and maintain procedures to control, calibrate and maintain inspection, measuring and test facilities (including test software) used by the manufacturer to demonstrate the conformance of product to the specified requirements.

The inspection, measuring and test facilities referred to in the preceding Paragraph shall be used in a manner that ensures that the measurement uncertainty is known and is consistent with the required measurement capability.

Article 139. Where test software or comparative references (such as test hardware) are used as suitable forms of inspection, they shall be checked to prove that they are capable of verifying the acceptability of products, prior to release for production, installation or servicing, and shall be rechecked at prescribed intervals.
Manufacturers shall establish the extent and frequency of such checks and shall maintain records as evidence of control.

Where the availability of technical data pertaining to the inspection, measuring and test facilities is a specified requirement, such data shall be made available, when required by the customer or the customer’s representative, for verification that the inspection, measuring and test facilities is functionally adequate.

Article 140. Manufacturers shall apply the following control procedures to inspection, measuring and test facilities:

(1) Determine the measurements to be made and the accuracy required, and select the appropriate inspection, measuring and test facilities that are capable of the necessary accuracy and precision.

(2) Identify all inspection, measuring and test facilities that can affect product quality, and calibrate and adjust them at prescribed intervals or prior to use, against certified equipment having a known valid relationship to internationally or nationally recognized standards; where no such standards exist, the basis used for calibration shall be documented.

(3) Define the process employed for the calibration of inspection, measuring and test facilities including details of facility type, unique identification, location, frequency of checks, check method, acceptance criteria and action taken when results are unsatisfactory.

(4) Identify inspection, measuring and test facilities with a suitable indicator or approved identification record to show the calibration status.

(5) Produce and maintain calibration records for inspection, measuring and test facilities.

(6) Assess and document the validity of previous inspection and test results when inspection, measuring or test facilities are found to be out of calibration.

(7) Ensure that the environmental conditions are suitable for the calibrations, inspections, measurements and tests being carried out.

(8) Ensure that the handling, preservation and storage of inspection, measuring and test facilities are such that the accuracy and fitness for use are maintained.

(9) Safeguard inspection, measuring and test facilities, including both test hardware and test software, from adjustments that would invalidate the
Chapter 13 Identification of Inspection and Test Status

Article 141. Manufacturers shall identify the inspection and test status of products by suitable means to indicate the conformance or nonconformance of product with regard to inspection and tests performed.

The identification of inspection and test status shall be maintained, as defined in the quality plan or documented procedures, throughout production, installation and servicing of products to ensure that only products that have passed the required inspection and tests, or released under an authorized concession, is dispatched, used or installed.

Chapter 14 Control of Nonconforming Products

Article 142. Manufacturers shall establish in writing and maintain control procedures to ensure that products that do not conform to specified requirements are prevented from unintentional use or installation.

The control procedures referred to in the preceding Paragraph shall provide for identification, documentation, evaluation, segregation (when practical) and disposition of nonconforming products, and for notification of relevant authorities.

Article 143. Manufacturers shall define the responsibility for review and authority for disposition of nonconforming products. Nonconforming products shall be reviewed in accordance with documented procedures, and handled in one of the following manners:

1. Reworked to meet the specified requirements;
2. Accepted with or without repair by concession;
3. Re-graded for alternative applications;
(4) Rejected or scrapped.

Where required by contract, the proposed use or repair of products that do not conform to specified requirements shall be reported for concession to the customer or customer’s representative. The description of the nonconformity that has been accepted, and of repairs, shall be recorded to denote the actual condition.

Repaired or reworked products shall be re-inspected in accordance with the quality plan or documented procedures.

Article 144. Manufacturers shall ensure that nonconforming products are accepted by concession only if regulatory requirements are met. The identity of the person(s) authorizing the concession shall be recorded.

If products need to be reworked, manufacturers shall document the rework in a work instruction that has undergone the same authorization and approval procedure as the original work instruction. Prior to authorization and approval, a determination of any adverse effect of the rework upon the product shall be made and documented.

Chapter 15  Corrective and Preventive Action

Article 145. Manufacturers shall establish in writing and maintain procedures for implementing corrective and preventive actions.

Any corrective or preventive action taken to eliminate the causes of actual or potential nonconformities shall be to a degree appropriate to the magnitude of problems and commensurate with the risks encountered.

Manufacturers shall implement and record any changes to the documented procedures resulting from corrective and preventive actions.
Manufacturers shall establish in writing and maintain a feedback system to provide early warning of quality problems and for input into corrective and preventive action systems.

Manufacturers shall gain experience through monitoring of post-production phase feedback data; the review of this experience shall form part of the feedback system.

Manufacturers shall maintain records of all customer complaint investigations. When the investigation determines that the activities at remote premises contributed to the customer complaint, relevant information shall be communicated between the manufacturer and the remote premises.

If any customer complaint is not followed by corrective and preventive action, the reason shall be recorded.

Manufacturers shall establish reporting procedures governing notification of the central competent health authority when injuries involving medical devices occur.

Manufacturers shall establish, document and maintain procedures for the issue of advisory notices for medical devices. These procedures shall be capable of being implemented at any time.

Article 146. The procedures for corrective action shall include the following:

(1) The effective handling of customer complaints and reports of product nonconformities;

(2) Investigation of the causes of nonconformities relating to product, process and quality system, and recording the results of the investigation;

(3) Determination of the corrective action needed to eliminate the cause of nonconformities;

(4) Application of controls to ensure that corrective action is taken and that it is
Article 147. The procedures for preventive action shall include the following:

(1) The use of appropriate sources of information such as process and work operations which affect product quality, concessions, audit results, quality records, service reports and customer complaints to detect, analyze and eliminate potential causes of nonconformities;

(2) Determination of the steps needed to deal with any problems requiring preventive action;

(3) Initiation of preventive action and application of controls to ensure that it is effective;

(4) Ensuring that relevant information on actions taken is submitted for management review.

Chapter 16  Handling, Storage, Packaging, Preservation and Delivery

Manufacturers shall establish in writing and maintain procedures for handling, storage, packaging, preservation and delivery of products.

Manufacturers shall establish in writing and maintain procedures governing medical device shelf life or special storage conditions. Said conditions shall be controlled and recorded. If appropriate, special arrangements shall be established, documented and maintained for the control of used products in order to prevent contamination of other products, the manufacturing environment or personnel.

Article 149. Manufacturers shall carry out handling, storage, packaging, preservation, and delivery of products in accordance with the following rules:

(1) Handling: methods of handling products that prevent damage or deterioration shall be used.

(2) Storage: designated storage areas or stock rooms shall be used to prevent
damage or deterioration of product, pending use or delivery; appropriate methods for authorizing receipt to and dispatch from said areas shall be stipulated; the condition of products in stock shall be assessed at appropriate intervals in order to detect deterioration.

(3) Packaging: packing, packaging and marking processes (including materials used) shall be controlled to the extent necessary to ensure conformance to specified requirements; the identity of persons who perform the final labeling operation for active implantable medical devices and implantable medical devices shall be recorded.

(4) Preservation: appropriate methods for preservation and segregation of products when said products are under the manufacturer’s control.

(5) Delivery: arrangements shall be made to protect the quality of products after final inspection and test; where contractually specified, this protection shall extend to include delivery to destination; the name and address of the shipping package consignee shall be included in the quality records for active implantable medical devices and implantable medical devices.

Chapter 17  Control of Quality Records

Article 150. Manufacturers shall establish in writing and maintain procedures for identification, collection, indexing, access, filing, storage, maintenance and disposition of quality records.

Quality records and their control shall conform to the following rules:

(1) Quality records shall be maintained to demonstrate conformance to specified requirements and the effective operation of the quality system.

(2) Pertinent quality records from the subcontractor shall be an element of this data.

(3) Retention times of quality records shall be clearly defined, and shall be at least equivalent to the lifetime of the medical device, but not less than two years from the date of dispatch from the manufacturer.

(4) Quality records shall be legible and shall be stored and retained in such a way that they are readily retrievable in facilities that provide a suitable
environment to prevent damage, deterioration and loss.

(5) Where agreed contractually, quality records shall be made available for evaluation by the customer for an agreed period.

Article 151. Manufacturers shall establish and maintain a record for each batch of medical devices that provides traceability and identifies the quantity manufactured and quantity approved for distribution.

The batch record referred to in the preceding Paragraph shall be verified and authorized.

Chapter 18 Internal Quality Audits

Article 152. Manufacturers shall establish in writing and maintain procedures for planning and implementing internal quality audits to verify whether quality activities and related results comply with planned arrangements and to determine the effectiveness of the quality system.

Article 153. Internal quality audits shall be scheduled by manufacturers on the basis of the status and importance of the activity to be audited, and shall be carried out by personnel independent of those having direct responsibility for the activity being audited.

The results of the audits shall be recorded and brought to the attention of the personnel having responsibility in the area audited. The management personnel responsible for the area shall take timely corrective action on the deficiencies found during the audit.

Follow-up activities shall be carried out to verify and record the implementation and effectiveness of the corrective action taken.
Chapter 19  Training

Article 154. Manufacturers shall establish in writing and maintain procedures for identifying training needs and provide for the training of all personnel performing activities affecting quality; personnel performing specific assigned tasks shall be qualified on the basis of appropriate education, training or experience, as required.

Appropriate records of the training referred to in the preceding Paragraph shall be maintained.

Chapter 20  Servicing

Where servicing is a specified requirement, the manufacturer shall establish in writing and maintain procedures for performing, verifying and reporting that the servicing meets the specified requirements.

Chapter 21  Statistical Techniques

Article 156. Manufacturers shall identify the need for statistical techniques required for establishing, controlling and verifying process capability and product characteristics.

Manufacturer shall establish in writing and maintain procedures to implement and control the application of the statistical techniques referred to in the preceding Paragraph.

Part 5  Supplementary Provisions

Article 157. This set of Standards shall come into force from the date of announcement.