Republic of the Philippines
Department of Health
BUREAU OF FOOD AND DRUGS
Filinvest Corporate City
Alabang, Muntinlupa City

June 19, 2001

ADMINISTRATIVE ORDER
No. 27 series of 2001

SUBJECT: RULES AND REGULATIONS FOR LICENSING LOCAL MANUFACTURERS OF VACCINES AND BIOLOGIC PRODUCTS

Pursuant to the provisions of the Republic Act No. 3720, otherwise known as Food, Drugs and Devices, and Cosmetic Act, as amended by the Executive Order No. 175, the following rules and regulations on licensing of local manufacturers of vaccines and biological products are hereby adopted and promulgated for information, guidance, and compliance of all concerned.

Section 1. Definition of Terms

The following terms are defined and adopted:

1.1. "***Good Laboratory Practice*** (GLP)" – Good Laboratory Practice are standards and procedures whereby the laboratory achieves a defined, consistent and reliable standard in performing laboratory tests and activities.

1.2. "***Good Manufacturing Practice*** (GMP) – Good Manufacturing Practice is that part of quality assurance which ensures that products, including vaccines and biologics, are consistently produced and controlled to the quality standards appropriate for their intended use, including all phases of vaccine clinical trials, and as required by registration and marketing authorization. For supplementary guidelines for the manufacture of investigational pharmaceutical products for human studies, refer to WHO/PHARM/94.571.

1.3. "***Developmental or Investigational Vaccine or Biologic***" shall refer to a vaccine or biologic product that needs or is undergoing pre-clinical and clinical studies to determine its safety, potency, efficacy, and therapeutic/prophylactic value. It refers to a vaccine or biologic product which has never been registered or licensed by any national regulatory authorities.

1.4. "***New Vaccine or Biologic***" refers to a vaccine or biologic product which has undergone adequate Phases I, II, and III clinical studies, but which requires a Phase IV clinical studies. It refers to a vaccine or biologic product which has never been registered or licensed by any national regulatory authorities for general use.

1.5. "***Established Vaccine or Biologic***" refers to a vaccine or biologic product which has undergone adequate Phase I, II, III and IV clinical studies. In addition, it has been reviewed by the WHO Expert Committee on Biological Standardization and has recommended sets of general and specific guidelines and requirements for the manufacture, control, and product evaluation for registration or licensing by a national regulatory authority.

Section 2. General Standards and Policies

The following are the general standards and policies in licensing a manufacturer to ensure that products are consistently produced and controlled to the quality standards appropriate to their intended use, and as required before a product is registered and allowed for general use:

2.1. All manufacturers of new, established and developmental biologic products shall apply for the BFAD License to Operate as manufacturer before going into production.

2.1. All manufacturers shall comply with the standards and requirements of the Code of current Good Manufacturing Practice and Good Laboratory Practice.

2.2. All manufacturers of developmental biologic products shall ensure that the specification and the composition of the product for clinical trials must be the same as the product to be registered for general use.

Section 3. Pre-Licensing Procedure and Requirements.

All manufacturers intending to produce new, established and developmental vaccines and biologic products shall consult the BFAD in the construction of a manufacturing laboratory. The following are the pre-licensing procedures and requirements:

3.1. The establishment shall inform in writing the Director of the BFAD of its intention to produce vaccines and biologic products. The following shall be submitted together with the letter:

3.1.1. The name of the company pharmacist who shall be responsible for coordinating with the BFAD on matters pertaining to pre-licensing and licensing requirements and activities,

3.1.2. The project plan, including location, building designs, equipment, facilities, and organizational structure,

3.1.3. The product or list of products to be produced, and

3.1.4. Other information deemed important by the establishment.

3.2. The BFAD shall schedule a meeting to discuss BFAD rules and regulations pertaining to vaccine and biologic products, such as current GMP, registration, lot release, laboratory testing, surveillance, and clinical trial.

3.3. After the meeting, the establishment shall submit a detailed plan and schedule of implementation from the start of the construction up to the application for a License to Operate.

3.4. The BFAD Director shall assign a team of BFAD personnel who shall coordinate with the manufacturer's pharmacist to ensure the existence of quality assurance systems and adequate provisions, among others, according to the Code of current Good Manufacturing Practice as shown in Annex 1.

Section 4. Licensing Procedure and Requirements

The following are the procedures and requirements for applying for a BFAD License to Operate as vaccine manufacturer:

4.1. The applicant shall apply in writing to the BFAD Director for a License to Operate as vaccine manufacturer. Together with the letter, the applicant shall submit all the general and specific requirements, as appropriate, as listed in Annex 2.

4.2. The Regulation Division II of the BFAD shall evaluate the completeness of the documents based on the checklist of requirement. Depending on the products to be manufactured and the manufacturing process, additional documents may be required.

4.3. When all the documents and requirements have been completed, the Regulation Division II shall schedule specific dates for cGMP inspection by a team of BFAD personnel.

4.4. After the complete and thorough inspection, a final report containing all the findings and recommendations, among others, shall be prepared by the BFAD.

4.5. The final report of the inspection shall be the basis for the action of the BFAD on the application.

Section 5. Action of the BFAD on the Application

The BFAD action on the application shall consist of any one of the following:

5.1. Approval. Issuance of a BFAD LTO and a Certificate of cGMP Compliance

5.2. Abeyance. A copy of the final report containing the findings, deficiencies and recommendations, among others, shall be given to the applicant. The applicant shall be given a year to comply with all the deficiencies and recommendations. Beyond one year, the applicant shall reapply.

Section 6. Post-Licensing Obligation of the Manufacturer

The following are the obligations, among others, of the manufacturer after the issuance of the License to Operate and certificate as GMP compliant:

6.1. The manufacturer shall seek the approval of the BFAD before instituting any changes in any of the items listed in Annex 2. Evidence of validation and documentation for major changes shall be required from the applicant.

6.2. The manufacturer shall apply for a BFAD Batch or Lot Release Certificate before releasing any lot or batch of bulk or finished products for use or sale.

6.3. The manufacturer shall renew the BFAD License to Operate as vaccine manufacturer every 2 years.

Section 7. Schedule of Fees

For the schedule of fees, the applicant shall be guided by the latest Bureau Circular on the schedule of fees.

Section 8. Separability Clause

In case any provision of this administrative order is declared contrary to law or unconstitutional, other provisions, which are not affected thereby, shall continue to be in force and in effect.

Section 9. Effectivity

This regulation shall take effect thirty (30) days after its publication in a newspaper of general circulation.

(Sgd.) MANUEL M. DAYRIT, M.D., MSc.
Secretary of Health

Published on : _____
Name of Newspaper: _____

BFAD Director Initial and Date	**HPDPB Director** Initial and Date	**Head – HRC** Initial and Date	**HEA-OSEC** Initial and Date
William D. Torres Ph.D	**Dr. Mario C. Villaverde Director IV**	**Dr. Ma. Margarita M. Galon**	

Annex 1

LIST OF QUALITY ASSURANCE SYSTEM AND ADEQUATE PROVISIONS FOR A BIOLOGIC PRODUCT MANUFACTURER

1. Segregation of Operations
2. Handling of Biological Materials and Waste Disposal
3. List of Major Equipment
4. Validation of Facilities
5. Air, Water, Steam System, and Power Supply
6. Drainage and Effluent System
7. Personnel and Organization
8. Location and Construction of the building used for manufacture and control
9. Flow/Traffic of Materials, Personnel, and Manufactured Product
10. Testing Laboratory and Animal Facilities
11. Preventive maintenance schedules for equipment and building services
12. Cleaning Procedures and Schedules
13. Storage and Quarantine Facilities
14. Validation Procedures (Master Validation Plan)
15. Documentation, Standard Operating Procedures, Work Instructions, In-Process Forms, Protocols and Record Keeping Systems
16. Labeling and Packaging Facilities and Procedures
17. Recall and Retrieval Procedures
18. Quality Assurance and Quality Control Procedures for raw materials, packaging materials, in-process and bulk materials, and final product
19. Cold-chain compliance facilities up to distribution chain

ANNEX 2

CHECKLIST OF REQUIREMENTS
FOR MANUFACTURERS OF VACCINES AND BIOLOGIC PRODUCTS

REQUIREMENTS	No. of Copies	BFAD Use Only
I. General		
1. Information regarding the activities of the establishment		
2. Notarized Accomplished Petition Form/Joint Affidavit of Undertaking		
3. ID (5 x 5 cm) Pictures of the Owner/General Manager and Pharmacist		
4. Photocopy of the Pharmacist's Registration Board Certificate and Professional Tax Receipt (PTR)		
5. Floor Plan, with complete dimension (scale) and proper identification and description of each area		
6. Distribution Record Book duly registered with the BFAD		
7. References, as appropriate: 7.1. Relevant World Health Organization Technical Report Series on Biological Standardization 7.2. Republic Act 3720, Republic Act 6675, Republic Act 5921 7.3. DOH Administrative Orders on Vaccine and Biological Products 7.4. British Pharmacopoeia (latest edition) 7.5. USP/NF (latest edition) 7.6. Philippine National Drug Formulary (latest edition) 7.7. Remington's Pharmaceutical Sciences (latest edition) 7.8. Goodman's & Gilman Pharmaceutical Basis of Therapeutics (latest edition)		
8. Location Plan/Site (size, location, immediate environment and type of building, among others)		
9. Certification that the Pharmacist and Owner/General Manager has attended a sponsored/accredited seminar on Licensing of Establishment		
10. Organizational Structure, including number of personnel (all, technical and support staff), academic qualification, relevant training and experience of each personnel		
11. Duties and responsibilities of the Pharmacist, Head/Chief of Departments/Division and other technical and non-technical personnel		
12. Information regarding the manufacturer and the products to be manufactured (see No.5 of specific requirements)		

II. Specific		
1. If private and non-government entity, Photocopy of Business Name Registration with BDT/SEC		
2. If importing raw materials and/or finished products (including bulk vaccines, among others), 6.4. Foreign Agency Agreement, duly authenticated by the Philippine consulate in the country of origin 6.5. Latest cGMP Certificate of the supplier/exporter issued by the appropriate Government Health Agency, duly authenticated by the Philippine consulate in the country of origin		
7. If the applicant does not own the space/building, notarized and valid Contract of Lease of the space/building occupied. 4. If a corporation/partnership, Articles of Incorporation		

5. If applicable, Notarized Financial Statement		
6. The following information and documents shall be organized and submitted (per product to be manufactured) #		
6.1. **Validation Protocols**. The following is a comprehensive listing of equipment, systems, processes and procedures which should be validated. Not all will be required in all facilities. It will depending on the manufacturing procedures required or the product to be manufactured. 6.1.1. **Waste Systems** 6.1.1.1. Domestic sanitary sewer systems 6.1.1.2. Process drain systems 6.1.1.3. Hazardous/Toxic waste systems 6.1.1.4. Solid Waste disposal systems 6.1.1.5. Hazardous emissions systems 6.1.2. **Air Handling Systems (IQ, OQ, PQ)** 6.1.2.1. Heating system 6.1.2.2.Ventilation system 6.1.2.3.Air conditioning system 6.1.2.4.Air filter system 6.1.2.5.Biological safety cabinets 6.1.2.6.Laminar flow hoods 6.1.2.7.Fume hoods 6.1.3. **Water System (IQ/OQ/PQ)** 6.1.3.1.Purified Water 6.1.3.2.Water for Injection (WFI) 6.1.3.3.Source of Potable Water 6.1.4. **Steam Systems (IQ/OQ/PQ)** 6.1.4.1.Plant system (raw steam) 6.1.4.2.Clean steam 6.1.5. **Cooling Systems (IQ/OQ/PQ)** 6.1.5.1. Chillers 6.1.5.2.Cooling towers 6.1.6. **Gas Systems (IQ/OQ/PQ)** 6.1.6.1.Compressed Air 6.1.6.1.1. Sterile 6.1.6.1.2. Non-sterile 6.1.6.1.3. Instrumental air 6.1.6.1.4. Industrial air 6.1.6.1.5. Purified air (used for fermentation) 6.1.6.2. Nitrogen systems 6.1.6.2.1. Sterile 6.1.6.2.2. Non-sterile 6.1.6.3. Other gases 6.1.6.3.1. Oxygen 6.1.6.3.2. Carbon dioxide 6.1.7. **Electrical System (IQ/OQ/PQ)** 6.1.7.1. Electrical standard 6.1.7.2.Electrical emergency power		

6.1.7.3Electrical back-up power		
6.1.8. **Equipment (IQ/OQ/PQ)** 6.1.8.1.Production 6.1.8.2.Quality Control Laboratory		
6.1.9. **Sterilization** 6.1.9.1.Steam sterilization (autoclaves) (IQ/OQ/PQ) 6.1.9.1.1.Component preparation sterilizer 6.1.9.1.2.Terminal sterilizer 6.1.9.1.3.Laboratory sterilizer 6.1.9.2.Dry Heat sterilization/depyrogenation (IQ/OQ/PQ) 6.1.9.2.1.Tunnels 6.1.9.2.2.Ovens 6.1.9.3.Terminal filtration process 6.1.9.4.Gas sterilization (IQ/OQ/PQ) Ethylene oxide 6.1.9.5.Radiation		
6.1.10. **Cleaning Process** 6.1.10.1.Clean-in-Place (CIP) process 6.1.10.1.1.Aseptic 6.1.10.1.2.Non-aseptic 6.1.10.2.Sterilize-in-Place (SIP) process 6.1.10.3.Facility cleaning processes 6.1.10.3.1.Equipment 6.1.10.3.2.Clean area 6.1.10.3.3.Aseptic area 6.1.10.3.4.Sanitization 6.1.10.3.5.Garment laundering 6.1.10.3.6.General facility cleaning (janitorial)		
6.1.11. **Component Preparation Equipment** 6.1.11.1.Container washing equipment (IQ/OQ/PQ) 6.1.11.1.1.Manual 6.1.11.1.2. Semi-automatic (programmable controllers) 6.1.11.1.3.Automatic (computer controlled) 6.1.11.2.Closure washing equipment (IQ/OQ/PQ) 6.1.11.2.1.Manual 6.1.11.2.2.Semi-automatic (programmable controlled) 6.1.11.2.3.Automatic (computer controlled)		
6.1.12. **Washing/depyrogenation/sterilization processes**		
6.1.13. **Aseptic Solution Preparation** 6.1.13.1.Solution manufacture process 6.1.13.2.Solution filtration process		
6.1.13. **Sterile Filing (Aseptic or Terminally Sterilized)** 6.1.13.1. Solution filling 6.1.13.1.1.Manual 6.1.13.1.2.Automatic 6.1.13.2. Lyophilization 6.1.13.3.Container sealing 6.1.13.3.1.Manual vial stoppering 6.1.13.3.2.Automatic vial stoppering 6.1.13.3.3.Ampoule sealing 6.1.13.4.Container capping		
6.1.14. **Finishing** 6.1.14.1.Labelling process 6.1.14.1.1.Manual 6.1.14.1.2.Semi-automatic (programmable controllers)		

6.1.14.1.3.Automatic (computer controlled) 6.1.14.2. Packaging (boxing) process 6.1.15.**Manufacturing Processes** 6.1.15.1.Fermentation 6.1.15.1.1.Seed fermentation 6.1.15.1.2.Fermentation 6.1.15.1.3.Cell separation 6.1.15.2.Cell growth 6.1.15.2.1.Reactor 6.1.15.2.2.Roller bottle 6.1.15.3.Buffer preparation 6.1.15.3.1.Buffer weight 6.1.15.3.2.Buffer preparation 6.1.15.3.2.1.sterile filtration 6.1.15.3.2.2.sterilization 6.1.15.4.Purification 6.1.15.4.1.Purification step 1 6.1.15.4.2.Purification step 2, 3, etc. 6.1.15.4.3.Purification final step 6.1.15.5.Bulk lyophilization 6.1.16. **Storage/Warehouse Operations (Storage, Holding, Handling and Distribution)** 6.1.16.1.Incoming/Receiving 6.1.16.2.Warehousing 6.1.16.3.In-process storage 6.1.16.4.Approved finished goods storage 6.1.16.5.Outgoing/distribution/shipping 6.1.17. **Analytical Methods** 6.1.17.1.Raw materials 6.1.17.2.In-process product 6.1.17.3.Intermediates 6.1.17.4.Final Product 6.1.18. **Others** 6.1.18.1.Contractor validation (external manufacture) 6.1.18.2.Vendor validation/supplier audit 6.1.18.3.Animals 6.1.18.3.1.Animal care and handling processes 6.1.18.3.2.Supplier validation (audit) 6.2. **Documentation.** The system of documentation (written) devised or adopted should have as its main objective to establish, monitor and record quality for all aspects of production and quality control. The list of documents required, among others, are as follows: 6.2.1. **Standard Operating Procedures, Specifications and Master Formulae** 6.2.1.1.Raw Materials 6.2.1.1.1.Specifications/Product Codes 6.2.1.1.2.Supplier approval 6.2.1.1.3.Receipt and storage 6.2.1.1.4.Sampling procedures 6.2.1.1.5.QC testing and inspection 6.2.1.1.6.Quarantine, release and approval 6.2.1.2.Biological Starting Materials (e.g. cells, eggs, animals, virus, bacteria) 6.2.1.2.1.Specifications 6.2.1.2.2.Source, name, characteristics, history		

6.2.1.2.3.Seed lot system and storage 6.2.1.2.4.Test before use in production 6.2.1.2.5.Supplier (approval, ordering, among others) 6.2.1.2.6.Animal care 6.2.1.2.7.Animal protocol review 6.2.1.3.Facility 6.2.1.3.1.Systems operation, maintenance and calibration (e.g. HVAC, water, steam) 6.2.1.3.2.Cleaning of facility 6.2.1.3.3.Environmental monitoring 6.2.1.3.4.Entry and exit to clean rooms 6.2.1.3.5.Gowning 6.2.1.3.6.Product flow 6.2.1.3.7.Supply flow 6.2.1.3.8.Staff flow 6.2.1.3.9.Air flow 6.2.1.3.10.Waste flow and disposal 6.2.1.3.11.Garment cleaning and sterilization 6.2.1.3.12.Glassware cleaning and sterilization 6.2.1.3.13.Disinfectant/fumigation 6.2.1.3.14.Pest control 6.2.1.4.Equipment (Production and Quality Control) 6.2.1.4.1.Operation 6.2.1.4.2.Cleaning/sterilization (surface, CIP, SIP, clean-out-of-place {COP}) 6.2.1.4.3.Preparation of cleaning solutions 6.2.1.4.4.Residual product and cleaning agents 6.2.1.4.5.Preventive maintenance 6.2.1.4.6.Calibration 6.2.1.4.7.Monitoring 6.2.1.4.8.Calibration of certified NIST instruments 6.2.1.4.Production 6.2.1.4.1.Master formulae 6.2.1.4.2.In-process tests (production) 6.2.1.4.3.Preparation of process buffers and solutions 6.2.1.4.4.Environmental sampling 6.2.1.5.Labeling and Packaging 6.2.1.5.1.Label and package review and control 6.2.1.5.2.Specifications 6.2.1.5.3.Reconciliation of labels 6.2.1.5.4.Expiration dates 6.2.1.6. Quality Control 6.2.1.6.1.Testing and release of final product 6.2.1.6.2.Testing and release of intermediates/bulk product 6.2.1.6.3.Analytical assays 6.2.1.6.4.Samples: Test and retention 6.2.1.6.5.Summary protocols of QC results 6.2.1.6.6.Stability studies 6.2.1.6.6.Reference standard and control (Maintenance testing) 6.2.1.6.7.Recertfication/recalibration of QC equipment 6.2.1.6.8.Preparation of reagents and materials for QC tests 6.2.1.7.Quality Assurance 6.2.1.7.1.Batch Record Review 6.2.1.7.2.Inspection/Internal Audits		

6.2.1.7.3.Validation Protocol Approvals 6.2.1.7.4.Product Recall 6.2.1.7.5.Product Complaints 6.2.1.7.6.Contract Audit 6.2.1.7.7.Vendor Audit 6.2.1.7.8.Document control, revision and distribution 6.2.1.7.9.Change control 6.2.1.7.10.Employee Records, health records 6.2.1.7.11.Training (Technical and GMP) 6.2.1.7.12.SOP Writing and Approvals 6.2.1.7.13.Adverse Event Reports 6.2.1.7.14.Storage Temperature Monitoring 6.2.1.7.15.Product Distribution Procedures 6.2.1.7.15.Distribution Records 6.2.1.7.16.Quarantine, Release, Rejection and Storage 6.2.1.7.17.Master Validation Plan 6.2.2. **Forms for Recording Data** 6.2.3. **Identification Numbers** 6.2.4. **Labels** # Reference is made to the WHO Guide to Good Manufacturing Practice (GMP) Requirements (Part 1, 2 and 3), ASEAN GMP, Bayanihan GMP, and the WHO Technical Report Series on Biological Standardization.		