Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY
M a n i l a

March 15, 1989

ADMINISTRATIVE ORDER
No. 67 s. 1989

SUBJECT: Revised Rules and Regulations on Registration of Pharmaceutical Products

Summary: This A.O. gives a comprehensive guidelines on the registration of pharmaceutical products and to be consistent with R.A. 6675 known as the "Generic Act of 1988".

Pursuant to Section 26(a) in relation to Section 21(b) and 11 (j) of R.A. 372 as amended by Executive Order No. 175 known as the "Food, Drugs and Devices and, Cosmetic Act" and consistent with R.A. 6675 known as the "Generics Act of 1988" the following rules and regulations for the registration of pharmaceutical products are hereby promulgated for the information, guidance and compliance of all concerned.

SECTION 1 DEFINITION OF TERMS

For purposes of these Rules and Regulations, the following definitions are adopted:

1.1. ***"Registration"*** means the process of approval for the manufacture, importation, exportation, sale, offer for sale, distribution or transfer of pharmaceutical products containing active ingredients) of known chemical structure and properties determined to be safe, efficacious and of good quality according to standards of BFAD.

1.2. ***"Pharmaceutical Product"*** means any pharmaceutical or biological product containing active ingredients responsible for its desired effect intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure or function of the body of man or animal.

1.3. ***"Drug for General Use"*** is a drug approved for sale to the general public without restriction other than the usual.

1.4. ***"Drug for Restricted use"*** is a drug approved for sale to the general public under certain conditions.

SECTION 2 GENERAL STANDARDS

2.1. Establishments applying to register a drug product are required to fully disclose all pertinent documentation and information regarding the product. Failure to fully disclose material information about the drug product is a ground for disapproval of registration application and a basis for withdrawal of the establishment's license to operate.

2.2. Action on registration application shall be based on the complete set of specifications of the drug product proposed to appear in the label, i.e. formulation, dosage form, strength, therapeutic indication and manufacturer. Any change in any of the above specifications will require a new registration.

ANNOTATIONS: BFAD Circular #12 s. 1991 was issued to clarify the requirements for a new registration when there is a change of manufacturer without any change in

other specifications covered by Section 2.2 or A.O. 67 s. 1989. A conditional certificate of product registration may be granted to establishments which changes manufacturers for its product to one that has better technical capabilities.

2.3. Action on registration application shall include the classification of the drug product among each of six classification categories defined in Section 3 below. Any change in classification shall require a new registration.

2.4. The standards of product registration as well as the method of evaluating application are subject to revisions. Revised standard and evaluation methods shall be made applicable to all covered drug products as appropriate.

2.5. Only establishments with a valid license to operate required under A.O. 56 s. 1988 can apply to register a drug product.

SECTION 3 CLASSIFICATION

All pharmaceutical products shall be evaluated and registered on the basis of specific requirements and standards pertinent to such classification of such products. All registered drug products shall be classified in terms of each of the following six categorizations:

3.1. Number of Active Ingredients

3.1.1. Single Ingredient

3.1.2. Fixed-dose combination of two or more ingredients

3.2. Available scientific evidence and experience on the drug's use

3.2.1. *"Investigational Drug"* refers to a new chemical or structural modification of a Tried and Tested or Established Drug proposed to be used for a specific therapeutic indication. An investigational drug needs further clinical pharmacology studies (Phase I, II or III) to determine its safety and efficacy, and meets the requirements of a new drug.

3.2.2. "*New Drug"* refers to a new chemical or structural modification of a Tried and Tested or Established Drug proposed to be used for a specific therapeutic indication, which has undergone adequate clinical pharmacology Phase I, II and III studies but which needs further Phase IV Clinical Pharmacology studies before it can be given regular registration.

3.2.3. *"Tried and Tested Drug"* is a drug which has been used for at least five (5) years and involving at least 5,000 patients.

3.2.4. "*Established Drug"* is a drug the safety and efficacy of which has been demonstrated through long years of general use and can be found in current official USP-NF, and other internationally-recognized pharmacopoeia.

3.2.5. *"Pharmaceutical or therapeutic innovation of a Tried and Tested or Established Drugs"* includes any or all of the following:

3.2.5.1. An innovation involving use for new indication(s)

3.2.5.2. An innovation involving a new mode of administration

3.2.5.3. An innovation involving a new dosage form

3.2.5.4. An innovation involving a new fixed dose combination of two or more active ingredients.

3.3. Pharmacologic/therapeutic category as specified in the Philippine National Drug Formulary

3.4. Source or circumstances of drug production
- 3.4.1. Imported as finished
- 3.4.2. Locally manufactured from imported materials
- 3.4.3. Locally manufactured from local materials

3.5. Brand identification and patent protection of the drug
- 3.5.1. Branded and patented
- 3.5.2. Branded and off patent
- 3.5.3. Unbranded and off-patent (generic drug)

3.6. Prescribing and dispensing regulations applicable
- 3.6.1. Over-the-counter (OTC) Drug or Non-Prescription
- 3.6.2. Ethical or Prescription Drug
- 3.6.3. Dangerous Drugs (List-A Drugs)

ANNOTATION: A memorandum of Agreement (MOA) was executed between BFAD and DDB to closely coordinate and jointly process registration of dangerous drugs. The Agreement makes DDB responsible to evaluate certain registration data before BFAD will decide on the application for registration of a dangerous drug. (a copy of the MOA is appended to this chapter)

3.6.4. Drugs requiring strict precaution in prescribing and dispensing (List-B Drugs)

SECTION 4 INITIAL PRODUCT REGISTRATION

4.1. ***Application***

An establishment applying for the initial registration of a pharmaceutical product shall file an application under oath. The application shall be in a form promulgated by BFAD and supported by the documents and requirements listed in Annex I.

4.2. ***Evaluation by review of submitted data***

BFAD evaluates the submitted data. First, it determines if the data presented is complete. If not, applicant is requested to submit additional data or undertake needed animal or clinical studies. Second, it determines if on the basis of data submitted, drug product meets current BFAD standards for safety, efficacy or therapeutic value listed in Annex II.

4.3. ***Evaluation by Testing of Submitted Samples***

BFAD evaluates submitted samples of drug product. The evaluation shall cover tests for quality, purity and other physico-chemical qualities.

4.4 ***Assessment of Findings***

At any point during the evaluation, BFAD may conclude that the product does not meet the standards of safety efficacy and therapeutic value. In such case, the application shall be denied. At the end of the evaluation, BFAD shall arrive at a recommendation regarding action on registration application.

4.5. ***Action on Registration Application***

BFAD action on the registration application consist of the following possible courses:

4.5.1 Disapproval of application for failure to meet standards of safety, efficacy or therapeutic value.

4.5.2 Disapproval of application for lack of qualifications required from drug establishment.

4.5.3 Approval for investigational use over a period of variable duration depending on the protocol.

4.5.4 Approval for monitored release for a period of three years under condition of limited sale with specified monitoring procedures and subject to annual evaluation.

4.5.5 Approval for general use for a period of five years renewable every five years.

4.5.6 Approval for restricted use for a period of five years, renewable for five years.

4.6. ***Grounds for Disapproval***

The two types of disapproval action (4.5.1. and 4.5.2) shall be taken on the following grounds:

4.6.1 Review of submitted data or testing of submitted samples indicate that the product does not meet current, BFAD standards of identity, purity, strength, quality, safety, efficacy and therapeutic value.

4.6.2 The label of the drug product is false and misleading or does not conform with current labelling requirements

4.6.3 Applicant materially misrepresented or withheld significant data or information regarding the product.

4.6.4 Applicant failed to comply with the requirements for registration.

4.7. ***Grounds for Limited Approval***

4.7.1 An Investigational Drug Application shall be approved for Investigational use when the following are met:

4.7.1.1 The results of prior animal studies are found adequate to warrant further clinical pharmacology studies (Phase I, II and/or III)

4.7.1.2 The protocol submitted for the clinical pharmacology studies are found to be adequate and scientifically sound in experimental design.

4.7.1.3 The clinical investigator who shall undertake the study is determined by BFAD to be competent and reliable.

4.7.2 A New Drug Application shall be approved for monitored release when the following are met:

4.7.2.1 The results of prior animal studies are found adequate and the clinical pharmacology Phase I, II and III show that the

New Drug is safe and efficacious when used for its therapeutic indication.

4.7.2.2 The protocol submitted for the monitored release study is found adequate and scientifically sound in experimental design.

4.7.2.3 The clinicians and medical centers to be involved are determined by BFAD to be competent and reliable.

4.8. ***Ground for Approval***

The two types of approval actions (4.5.5 and 4.5.6) shall be taken on the following grounds:

4.8.1 Review of submitted data and testing of submitted samples indicate that the application is supported by substantial evidence showing the drug to be safe, efficacious and good quality.

4.8.2 Applicant demonstrated that the methods used in, as well as the facilities and controls used for, manufacture of the drug are adequate to assure its identity, strength, quality and purity.

4.8.3 The label of the drug is a correct representation of such drug and conforms with current labelling requirements.

SECTION 5 RENEWAL OF REGISTRATION

5.1 Only drug products registered for general and restricted use are eligible for renewal registration.

5.2. Application for renewal of registration shall be made on a form promulgated by BFAD.

5.3 Renewal application shall be reviewed and evaluated on the basis of the product and the applicant meeting the current BFAD standards of identity, purity, strength, quality, safety, efficacy and therapeutic value.

SECTION 6 SCHEDULE OF REGISTRATION

Upon application for registration of a drug product, the following non-refundable annual fees to be paid in full for the entire period of registration shall be charged.

6.1 ***Initial registration***

Investigational drug application	-	P1,000 per year or any fraction thereof
New drug application For provisional monitored release	-	P2,000 or P6,000 for 3 years + cost of laboratory analysis
New drug application for General or restricted use	-	P2,000 or P10,000 for years + cost of laboratory analysis
Tried and Tested or Established drug or their Pharmaceutical or therapeutic Innovations		

	Generic drug	-	P500 per year or P2,500 for 5 years + cost of laboratory analysis
	Branded drug	-	P1,000 per year or P5,000 For 5 years + cost of laboratory Analysis
6.2	***Renewal of registration***	-	P300 per year or P1,500 for 5 years + cost of laboratory analysis

ANNOTATION

THE COSTS OF LABORATORY ANALYSIS
As of Dec. 31, 1991 are as follows:

	Types of Laboratory Analysis			
1.	**Physico-chemical Analysis**	**( )**		
	Assay-Single Component	**( )**	**P**	**300.00**
	Multi Component	**( )**		**500.00**
	Disintegration Test	**( )**		**50.00**
	Dissolution Rate Test	**( )**		**300.00**
	Hardness Test	**( )**		**30.00**
	Identification Test	**( )**		**50.00**
	Purity Test	**( )**		**100.00**
	Vitamins (A, B1, B2, B6, B12)	**( )**		**200.00 each**
	Vitamin C	**( )**		**80.00**
	Vitamin E	**( )**		**150.00**
	Other Vitamins	**( )**		**150.00**
	Minerals (Ca, P, Pe, Zn, I, Mg, Na, K)	**( )**		**100.00 each**
	Heavy Metals (Pb, Cd, Hg, As, Sn)	**( )**		**300.00 each**
	Moisture Content	**( )**		**100.00**
2.	**Microbiological Test**	**( )**		
	Aerobic Plate Count	**( )**		**60.00**
	Coliform count	**( )**		**80.00**
	Yeast and Mold	**( )**		**80.00**
	Others (Salmonella, etc)	**( )**		**80.00 each**
3.	**Sterility Test**	**( )**		**300.00**
4.	**Pyrogen Test (Rabbits)**	**( )**		**2,000.00**
5.	**Safety Test**	**( )**		**750.00**
6.	**Depressor Substance test**	**( )**		**1,500.00**
7.	**Other Tests**	**( )**		
	Acute Toxicity Test (Mice)	**( )**		**4,000.00**
	Batch Certification (Antibiotics)	**( )**		**150.00**
	Alcohol Content (GC)	**( )**		**200.00**

SECTION 7 APPEAL

Disapproved application(s) may be appealed to the Secretary of Health for reconsideration.

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 REPEALING CLAUSE

All administrative orders, rules and regulations and other administrative issuance of parts thereof inconsistent with the provisions of this Regulation are hereby repealed or modified accordingly.

SECTION 10 EFFECTIVITY

This Regulation shall take effect fifteen (15) days after its publication in a newspapers of general circulation.

(Sgd) ALFREDO R.A. BENGZON
Secretary

ANNEX I

REQUIREMENTS FOR REGISTRATION

General Requirements

1. License to Operate of the drug manufacturer, trader, distributor/importer, distributor/exporter

2. Certificate of clearance from the Bureau of Patents and information on patent status.

3. Technical data which shall include:

   3.1 Physical description of the product

   3.2 Complete formulation and technical specifications for the raw materials and finished products.

   3.3 Process of manufacturing including facilities and control used in the manufacturing and packaging of the product.

   3.4. Description of all quality control tests performed including dissolution Test, if applicable, and results contained.

      3.4.1 For antibiotic products, results of batch analysis

   3.5. Assay procedure for active ingredient(s) and degradation product(s), if any.

   3.6. Complete stability data to justify expiry date.

4. Samples and corresponding reference standards.

5. Two copies of labels or specimens of the proposed label

6. Relevant literature and/or scientific evidence based on foreign or local studies to show safety, efficacy and therapeutic value of the drug.

Specific Requirements

1. Investigational Drug

   1.1. Medical Director registered with BFAD per A.O. 34 s 1979

   1.2. Animal Studies

      1.2.1. Acute toxicity

      1.2.2. Sub-chronic toxicity

      1.2.3. Teratogenicity

      1.2.4. Other Studies

   1.3. Clinical Pharmacology Studies

      1.3.1. Phases I and II tolerance and efficacy studies

1.3.2. Phase III clinical trial

1.3.2.1. Foreign

1.3.2.2. Local

2. New Drug

2.1 Medical Director registered with BFAD per A.O. 34 s 1979

2.2 Results of animal and clinical studies as required in Section 1.2 and 1.3 of Annex 1

2.3 Phase IV Clinical Trial

2.3.1 Provisional monitored release study

2.3.2 Post-marketing surveillance

3. Tried and Tested Drug

3.1 Dissolution test for solid oral dosage forms, if applicable

3.2 Bioavailablity/bioequivalence study for certain drugs as determined by BFAD.

3.3 Clinical trial to determine effective therapeutic dose range in Filipinos, when applicable.

4. Established Drug

4.1 Dissolution test for solid oral dosage forms, if applicable

4.2 Bioavailablity/bioequivalence study for certain drugs as determined by BFAD.

5. Pharmaceutical Preparation of Tried and Tested or Established Drug

5.1 Dissolution test for solid oral dosage forms, if applicable

5.2 Bioavailablity/bioequivalence study for certain drugs as determined by BFAD.

6. Therapeutic Innovation

6.1 Local clinical trial to test efficacy of the therapeutic innovation.

C. Additional Requirements for Certain Categories

1. Dangerous Drugs

1.1 Certificate of clearance from the Dangerous Drug Board

2. Non-prescription or Over-the-counter (OTC) Drugs

2.1 Certificate of OTC status from the country of origin issued by a competent authority of the country.

2.2 Record of safety of the drug demonstrated for general use under local conditions.

3. Branded Drugs

3.1 Certificate of trademark from the Bureau of Patents

3.2 Certificate of brand name clearance issued by BFAD

4. Imported Finished Products

4.1 Certificate of Free Sale of product in country of origin authenticated by the territorial Philippine Consulate

4.2 Certificate from WHO International Certification Scheme for manufacturers or equivalent.

5. Locally manufactured Products from Imported Materials.

5.1 Certificate of quality of imported raw materials from the Drug Regulatory Authority of the country of origin or from the World Health Organization (WHO).

5.2 License to operate of manufacturer, if different from applicant.

5.3 Copy of contract between applicant and manufacturer, if applicable.

5.4 Certificate of Free Sale for registration of any product containing said ingredient or raw material in country of origin authenticated by the territorial Philippine Consulate.

6. Locally manufactured Products from local Materials

6.1 License to operate of the manufacturer of the local raw material(s)

6.2 License to operate the manufacturer of the finished product, if different from applicant

6.3 Copy of contract between applicant and manufacturer of the finished product, if different from applicant

ANNEX II

REQUIREMENTS AND STANDARDS FOR REGISTRATION OF PHARMACEUTICAL PRODUCTS

REQUIREMENTS	STANDARDS
I. Identity, Purity and Quality Tests by BFAD e.q. Dissolution Test	United States Pharmacopoeia/National Formulary British Pharmacopoeia European Pharmacopoeia International Pharmacopoeia BFAD-established standards
II. Safety and Efficacy A. Animal Studies 1. Toxicity Acute Subacute/Subchronic Chronic (b)	$\frac{LD_{50}}{ED_{50}}$ Margin Safety, ---------- > 4 No serious toxicity within proposed therapeutic range (ED_{50} + 1 SD)
2. Pharmacodynamics	Desirable pharmacologic effects
3. Pharmacokinetics	Satisfactory time-curve
4. Special toxicity including mutagenicity, teratogenicity (c)	No serious toxicity within proposed therapeutic range ($ED_{50} \pm 1$ SD)
B. Human Studies 1. Clinical pharmacology Phase I (tolerance and safety) Phase II (safety and efficacy)	$\frac{TD_{50}}{ED_{50}}$ Therapeutic index =-------- $\geq$ 2(a)
Phase III (controlled clinical trials)	Significantly better than placebo and/or at least as good as standard drug
Phase IV (provisional monitored release/post-marketing surveillance)	Acceptable benefit in relation to risk (d)
2. Bioavailability	Adequate concentration
3. Bioequivalence	Equivalent to or better than standard drug

Notes:

a. The margin of safety and therapeutic index are minimum requirements and should be set at higher levels depending upon the therapeutic indication and standard prototype drugs.
b. This requirement may be waived for drug the therapeutic use which is limited to one week.
c. Other special toxicity tests may be required depending upon nature of the drug and its therapeutic indications.
d. The acceptability will depend on the nature of the therapeutic indication and the availability of alternative safer drugs.