



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

March 19, 1997

BUREAU CIRCULAR
No. 05 s. 1997

TO : ALL DRUG ESTABLISHMENTS AND PARTIES CONCERNED

**SUBJECT : REVISED CHECKLIST OF REQUIREMENTS AND THE 1997
GUIDELINES FOR THE REGISTRATION OF
PHARMACEUTICAL PRODUCTS**

The BFAD has adopted the 1997 Guidelines for the Registration of Pharmaceutical Products and has revised the checklist of requirements according to the said guidelines. Copies of the 1997 Guidelines etc. and the Revised Checklist of Requirements are attached as Annex "A" and "B" respectively.

Hence, effective April 1, 1997, all applications for products registration shall be contained in the PSD application form (PSD Form No. 8) and together with the submitted requirements as listed in the checklist, shall be pre-assessed and submitted at the Public Assistance, Information and Compliance Section in accordance with the 1997 Guidelines for Registration of Pharmaceutical Products.

Any application that will not comp pharmaceutically with the said guidelines shall be returned to the applicant and may be re-submitted only after the completion of the requirements.

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ANNEX B

1997 GUIDELINES FOR THE REGISTRATION OF PHARMACEUTICAL PRODUCTS

I. INTRODUCTION

These guidelines are formulated to guide the pharmaceutical companies in the preparation and submission of drug registration applications and as an aid for the Bureau of Food and Drugs - Product Services Division (BFAD-PSD) evaluators in assessing the acceptability of such applications as well as the approval of registration of the product applied for.

A correctly accomplished application form and well-arranged with complete documentation facilitate the work of the evaluators and can contribute to shorten the time required for the evaluation of applications for registration. All pertinent documents and information regarding the product shall be fully disclosed as these shall be used as bases in evaluating the acceptability of the drug product for registration.

1.1. DRUG REGISTRATION

The main function of the regulatory agency on pharmaceuticals is to ensure that all drug products being made available to the general public are safe, efficacious and of good quality.

Registration of drug products as required by RA 3720 as amended enables the BFAD to assess the benefits of a product complying with the criteria of safety, efficacy and good quality and to control or regulate its distribution.

All products which fall under the definition of drugs are required to be registered following the procedure and requirements stated in this guidelines.

If all the criteria and requirements for registration have been met all applications undergoing final evaluation are issued an approval of registration whose validity period is as follows:

1. Initial registration of drugs for general use shall be issued either 2 years or 5 years validity based on the application of the company.
2. Drugs which fall under the new drug monitored release category shall be given 3 years registration validity.
3. Renewal registrations are valid for 5 years.

If any of the requirements are not met, a letter shall be sent to the company denying the application. An application for reconsideration shall no longer be allowed but the application may submit an application for initial registration for the same product correcting all deficiencies.

1.2. DRUG EVALUATION

The evaluation of drug product is primarily a process to determine its safety, efficacy and quality.

Safety means that the drug product will not cause unfavorable reactions when used according to its declared indication and that it does not have unexpected toxic properties.

Efficacy pertains to a drug product's ability to deliver the desired effect. It may be expressed in terms of the extent of prevention or treatment of disease in man or the manner in which it affects the structure or any function of the body of man or animals.

Quality as applied to a drug product requires that the product contains the quantity of active ingredient(s) claimed on its label within the applicable limits of its specification. It also means that the drug product can maintain its appearance, potency and therapeutic availability until its claimed shelf-life/expiration.

All applications shall undergo a detailed evaluation of documents at the PSD and this includes:

- a. Complete formulation, facilities and methods of manufacture
- b. Technical specifications, methods and results of quality control tests and analysis conducted on all starting materials as well as on the in-process and finished product
- c. Complete data on stability testing and predicted shelf-life, container description/specifications and recommended storage conditions
- d. Labels or specimens of the proposed labels and other labeling materials such as inserts, brochures, etc.

The application shall be accompanied by samples which shall be forwarded to the Laboratory Services Division (LSD) for analysis which includes potency, identification and other test requirements. The results of analysis on the samples shall be forwarded to the PSD for final evaluation.

At any stage in the evaluation process an abeyance letter may be issued containing questions and deficiencies regarding the product application.

2. **FILING OF APPLICATION FOR REGISTRATION**

Only duly licensed pharmaceutical manufacturer, trader or distributor-importer/exporter may file an application for registration of a drug product. A distributor-wholesaler cannot file an application for registration.

The application submitted shall include a covering letter, a duly accomplished application form (PSD Form No. 8) and complete requirements as listed in the checklist of requirements for registration of pharmaceutical products. It is essential that the application shall be in accordance with this guidelines.

Applications for registration of pharmaceutical products are accepted according to the following schedule:

Company names starting with the letters A - E	Tuesday	- a.m.
F - M		- p.m.
N - Q	Wednesday	- a.m.
R - Z		- p.m.

A pre-assessment of the application shall be conducted by a PSD evaluator at the PAICS (Public Assistance Information and Compliance Section). Only applications complying with all registration requirements shall be accepted and processed.

3. **REQUIREMENTS FOR INITIAL REGISTRATION**

3.1 **ESTABLISHED DRUG**

3.1.1 ***Application Letter***

The Application/covering letter shall provide the following information

1. Name of the product
2. Dosage strength and dosage form
3. Name of the manufacturer, trader and distributor-importer/exporter, if applicable

3.1.2 Certificate of Brand Name Clearance

Every brand name of a drug or pharmaceutical specialty shall be submitted for name clearance prior to filing of application for registration. This will prevent similarity in brand names with other previously registered drug products or with the International Non-Proprietary Names (INN)

No imported drug or pharmaceutical specialty even if it is patented and/or registered in other countries, shall be registered if there exists an identical or similar brand name already registered with BFAD.

Application, processing and approval of brand names shall be in accordance with the provisions of the following regulations:

1. Administrative Order No. 76 s. 1984
2. BFAD Regulation No. 2 s. 1986
3. Memorandum Circular No. 16-A s. 1994

3.1.3 Agreement between Manufacturer and Trader or Distributor-Importer/Exporter

The licensed trader or distributor shall submit a copy of valid agreement with a BFAD-licensed manufacturer or a foreign manufacturer containing the following:

- the specific activity(ies) that each shall undertake relating to the manufacture
- a stipulation that both the manufacturer and trader/distributor-importer/exporter are jointly responsible for the quality of the product.

3.1.4 General Information

A detailed information regarding the product shall include the following:

- product's proprietary or brand name
- official chemical name(s) and generic name(s) of active ingredient(s)
- molecular or chemical formula and structure
- amount of active ingredient per unit dose
- pharmaceutical form of the drug
- indication
- recommended dosage
- frequency of administration
- route and mode of administration
- contraindication
- warnings and precautions

3.1.5 Unit dose and batch formulation

A complete list of names and quantities of all active and non-active ingredients shall be stated per unit dose (ex. per tablet) and per regular batch production size (ex. per 100,000 tablets). The names and quantities of all active ingredients shall be listed first followed by the non-active ingredients. Ingredients which are incorporated in the formulation but which may disappear during the production process (ex. alcohol, water) shall be included in the list.

Overages must be indicated in quantitative terms and the reasons for them are to be tested. Overages will usually not be acceptable unless it is proved that they are necessary to achieve a reasonable shelf-life, or to compensate for production losses.

3.1.6 Technical/Quality Specification of all Raw Material(s)

A complete technical/quality specifications and methods of analysis of all starting materials shall be submitted. The quality specifications claimed shall be those which are applied by the manufacturer in his own control procedures. These shall include all requirements and test methods applied as a routine to every batch. The description of the test methods shall be detailed enough to enable the test to be carried out in an independent laboratory

The technical/quality specifications of each raw material must be presented in separate lists comprising all test applied with the corresponding requirements or test limits. These specifications shall be dated and signed by a person in charge.

3.1.6.1 Ingredients (Active or Non-Active) described in a pharmacopoeia

The current edition of the United States Pharmacopoeia/National Formulary (USP/NF) is the official reference book adopted by the BFAD for substances and articles used in the preparation of pharmaceutical products. Reference to other national pharmacopoeia such as the British Pharmacopoeia (B.P.), European Pharmacopoeia (E.P) and the Japanese Pharmacopoeia (J.P) shall be considered if the product has been sourced from countries where such pharmacopoeia are official.

For substances which are subject of an official monograph, a concise presentation of all tests applied with the corresponding requirements or test limits shall be acceptable. The name and edition of the pharmacopoeia being referred may be cited in lieu of stating the detailed analytical producers.

In cases where different procedures are used in place of that described in an official monograph, the technical/quality specifications provided by the alternative procedure may be used but shall not be any less stringent than that of the official monograph.

3.1.6.2 Ingredients (Active or Non-Active) not described in a pharmacopoeia

The technical/quality specifications of ingredients not described in any pharmacopoeia shall be presented in the form of a monograph as follows:

1. The name of the substance supplemented by any trade or scientific synonyms
2. Data relevant to the proof or evidence of molecular structure. Detailed information on physical and chemical properties (e.g. Isomerism). Emphasis should be placed on solubility, crystalline form, particle size and state of hydration of state of other crystal solvents. Other physical properties to be described are polymorphism, hygroscopicity, melting point, boiling point, density, viscosity, pKa., oil/water partition coefficient, etc.
3. Methods of identification may be described in the form of complete techniques as used for production of the substance, and in the form of tests which ought to be carried out as a routine matter;
4. Purity tests shall be described in relation to the sum total of predictable impurities, especially those which may have a harmful effect and if necessary; those which, having regard to the combination of substances to which the application refers, might

adversely affect the stability of the medicinal product or distort analytical results.

3.1.6.3 Packaging Materials

Information shall be provided on the construction of the container, with a list of the different components, the type of materials used in the different parts, and the nature of the polymers. If the official standards/pharmacopoeia include requirements concerning the type of material used, it must be documented that these requirements will be complied with (e.g. Glass bottles for parenteral solution). This also applies to materials for accessories (infusion sets, syringes, measuring devices).

For plastics, the name of material, name of the manufacturer, chemical structure, and physico-chemical properties shall be presented. For polymers intended for containers of liquid and semi-liquid medicines, appropriate detailed information must be provided. Complete composition, including possible polymerization residues, stabilizers, plasticizers, colouring agents etc., shall be stated. The maximum permitted content shall be indicated. A report on toxicity may be required. Technical properties of the material relevant to the proposed use shall be stated (sterilizability, permeability, transparency, resistance etc.)

Detailed information is required about the technical construction of non-standardized containers, e.g. aerosol containers, spray packs, syringes etc.

3.1.7 Certificate of Analysis of Active Ingredient(s)

Validated and certified copies of the Certificate of Analysis from the supplier of the active ingredient(s) shall be included in any submission.

The certificate(s) shall:

- a. Be in English
- b. Be on a letterhead or other paper that adequately identifies the company manufacturing the materials.
- c. Name of the material to which it refers and identify it by a batch number. The batch number shall refer to the active material used in the manufacture of the sample submitted for analyses
- d. Be dated with the date of analyses and signed by a company officer over his/her typewritten name
- e. State the specifications (e.g. USP XXIII, BP 1993) and methods against which and by which the tests are performed. These shall include all the requirements stated in the technical/quality specifications document.
- f. Give the test results (all tests and analyses that involve measurement shall be reported as the actual numerical results, not description like "complies" or "pass").

Signed photocopies of such documents are acceptable as is a computer generated document meeting the above requirements.

There is no objection to indicating besides any test result (or as a footnote) that the test is equivalent to or more stringent than a corresponding compendial test of specification, when this is scientifically accurate.

3.1.8 Technical/Quality Specifications of Finished Product

The technical/quality specifications shall include all requirements and test methods routinely applied to every batch. Requirements shall apply throughout the shelf-life of the product. Information on requirements and test not routinely applied to every batch shall be provided if they are of importance to uniformity of quality as determined by the applicant company or by the BFAD-PSD.

Information shall be furnished about the following:

- a. The appearance of the product (colour, shape dimensions, odour, distinguishing features, etc.)
 - b. Identification of the active ingredient(s) (must include the specific identity test for the active moiety)
 - c. Quantitative determination of active ingredient(s) (i.e. Assay)
 - d. Test of impurities
 - e. The appropriate tests concerning the pharmaceutical properties of the dosage form (e.g. pH, content uniformity, dissolution rate, disintegration, etc)
 - f. Tests for safety, sterility, pyrogens, histamine, abnormal toxicity, etc. where applicable.
 - g. Technical properties of containers
- For drug preparations which are subject of an official monograph, the technical/quality specifications of the finished product as stated in the monograph shall be complied with.

3.1.9 Certificate of Analysis of the Finished Product

The Certificate of Analysis of the Finished Product shall include the results of all the requirements and test methods stated in the technical/quality specification of the product.

The Certificate, validated and certified, shall:

1. Refer to the same batch/lot number of the sample submitted for analyses
2. Be in English
3. Be on a letterhead or other copy that adequately identifies the manufacturer of the product.
4. Be dated with the date of analyses and signed by a company officer over his/her typed name
5. State the specifications and methods against which and by which the tests are performed.
6. Give the test results (all tests and analyses that involve measurement shall be reported as the actual numerical results, not descriptions like "complies" or "pass"). In addition, for products requiring dissolution testing, raw data shall be submitted for those described in a pharmacopoeia and for those not described, the calculations shall also be included.
7. Certificate of Analysis for finished products imported in bulk

Signed photocopies of such documents are acceptable as is a computer generated document meeting the above requirements.

3.1.10 Full description of the methods used, the facilities and controls in the manufacture, processing and packaging of the finished product.

A complete and detailed description of the manufacturing procedure including all the facilities and equipment used in each stage of the manufacturing process shall be given so that an assessment can be made of whatever the processes employed in producing the pharmaceutical form might have produced an adverse drug change in the constituents.

In case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity of the finished product shall be given. The actual manufacturing formulation, with the quantitative particulars of all the substances used shall be indicated. Mention shall also be made of any substance that may be removed in the course of manufacture and any overage shall be indicated and justified. Justification shall be submitted to evaluation and may either be accepted or denied.

Stages of manufacture at which sampling for in-process controls such as weight checks of tablets, homogeneity of suspensions, pH of solutions during mixing and filling shall be indicated. Where a non-standard method of manufacture is used or where it is critical for the product. Experimental studies validating the manufacturing process shall be given. The experimental studies shall likewise be subject to review or confirmation upon evaluation of BFAD-PSD.

For drugs which must be aseptically prepared and sterile a detailed description of the production process is required. This shall include data on how sterilization is carried out and controlled. In some cases, e.g. for aseptically prepared drugs, data must be provided on the microbiological quantity or raw material specification and the property of the filter aid. (Refer to M.C. _ s. 1996 for the Requirements for the Registration of Sterile Products)

For products imported in bulk and repacked locally by a manufacturer, identification and assay of active ingredient(s) shall be conducted prior to repacking.

3.1.11 *Details of the assay and other test procedures of finished product including data analysis*

Certain tests of the general characteristics of a product shall always be including among the tests on the finished product. These tests shall, wherever applicable, related to the control of average masses and maximum deviations, to mechanical, physical or microbiological tests, organoleptic characteristics, physical characteristics such as density, pH, refractive index, etc. For each of these characteristics, standards and tolerance limits shall be specified.

Identification and assay of the active ingredient(s) shall be carried out either in a representative sample from the production batch or in a number of dosage-unites analyzed individually.

Assay conducted at intermediate stages in the production process of multicomponent drug products shall be acceptable on any one of the following conditions:

- a. Assay of the active components in the finished product will require an intricate procedure.
- b. Active ingredients are present in very low amounts.

Whenever necessary or whenever reports on its use shall pose danger to the general public, the excipient(s) shall be subject at least to identification test.

Identification tests and assay of preservatives and antioxidants must also be included.

3.1.12 Detailed report of stability studies to justify claimed shelf-life

The manufacturer shall provide evidence to the effect that the product retains acceptable strength and pharmaceutical quality throughout its shelf life. In view of the fact that sufficiently long experience of storage of new products has often not accumulated when an application is made, the results of accelerated tests may be accepted for a preliminary shelf life, together with previous experience of similar products. The manufacturer must, however, outline his programme for further stability tests and will be required to report results for several batches, covering the entire shelf-life. Stability of the product must be followed up at a suitable frequency in relation to its shelf life, a suitable number of regularly produced batches being tested. Changes in composition, or the manufacturing process, or container and packaging material may necessitate renewed investigations and a revised shelf life.

Conceivable changes in the chemical, pharmaceutical and biological properties of the product during storage must be described. Changes in concentrations of preservative(s) or antioxidant(s) and changes due to interaction with the container must also be considered.

Information on the stability programme must include details of the number of batches included, their composition, containers, the parameters studied (e.g. content of active ingredient(s), degradation product(s), preservatives, antioxidants, disintegration and/or dissolution, suspension stability, particle size, etc), storage conditions testing intervals, etc. analytical methods must be stated, supplemented with documentation of their ability to detect possible changes. Special attention shall be given too the possibility of potentially harmful or otherwise biologically active products forming.

Results shall be presented in an illustrative form, tables and graphs. In addition, reports must specify the initial values, storage conditions, type of container and batch number. Based on this, the manufacturer shall propose a 'period of validity' (shelf life) and if necessary any storage directions applicable to distributors and consumers. (Refer to Annex GUIDELINES ON THE STABILITY TESTING OF PHARMACEUTICALS)

3.1.13 Labels or specimens of the proposed label and other labeling materials such as inserts, brochures, etc.

Requirements for the labeling of pharmaceutical products shall be in accordance with the provisions of the following regulations:

Administrative Order No. 55 s. 1988 (as amended)

Administrative Order No. 85 s. 1990

Administrative Order No. 99 s. 1990

Memorandum Circular No. 6 s. 1991

Drug products shall be granted an exemption from generic labeling requirements under any of the following categories:

1. Service Item
These shall include products which shall be available only on a limited basis upon physician's request
2. Specially packed
These shall include products with special containers that cannot be made and packed locally
3. Low volume of importation
These shall include products whose volume of importation shall not exceed 500 units/month or 6,000 units/year

4. The drug product applied for requires special handling.
(e.g. biologicals which must always be refrigerated)

The company applying for generic labeling exemption shall submit together with his application the following:

1. A copy of the subject product's valid CPR. In case the product is still undergoing registration process, the application may submit photocopies of the application letter of registration and Official Receipt duly stamped as received by BFAD-PAICS.
2. A representative sample including box and package insert of the product requested for an exemption reflecting pertinent information such as complete name and address of manufacturer and distributor/trader, batch/lot number, manufacturing and expiry dates, Rx symbol, caution and DR number.
3. A facsimile of the proposed generic labelling materials (immediate label, box, package insert, etc.) for BFAD file.

3.1.14 Samples in market of commercial presentation

Samples of laboratory analysis shall be taken at random from an actual production batch and packaged in the same container-closure system that will be used for commercial purpose.

Samples shall be sufficient for use in assessing the product's conformity with the given test specifications plus sufficient retention sample for future reference.

3.1.15 Duly authenticated Certificate of Free Sale from the country of origin

The Free Sale Certificate shall be issued by the regulatory agency on pharmaceuticals from the drug product's country of origin. It shall contain, among others, the following information: The proprietary name or brand name of the drug product, the generic name of International Non-Proprietary Name (INN) of the active ingredient(s); the dosage strength & dosage form; the complete name and address of the manufacturer and any other agency which claims responsibility for the product. The Certificate shall also contain a statement that the product is freely sold to the public.

In case the drug product is not freely sold in the country where it is manufactured, an Export Certificate issued by the regulatory agency on pharmaceuticals from the drug product's manufacturer and a Free Sale Certificate from a country with a reliable drug regulatory authority shall suffice as determine by BFAD.

3.1.16 Duly authenticated government certificate attesting to the registration status of the manufacturer

This Certificate shall be issued by the regulatory agency on pharmaceuticals from the drug product's country of origin. It shall contain a statement that the manufacturer is duly registered with the regulatory agency, and that the manufacturing facilities are regularly inspected and are found to conform with current Good Manufacturing Practices (GMP)

(Note: Certifications issued by the competent authority of the exporting country in accordance with the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce are highly acceptable.)

3.1.17 Bioavailability/Bioequivalence Studies for products under List B' (As per Bureau Circular No. 01 s. 1997)

Bioavailability studies are conducted to determine the rate and extent to which the active drug ingredient is absorbed from a drug product and becomes available at the site(s) of action. It is a crucial determinant in the rational formulation of dosage forms and influences the manner and route of drug administration.

Bioequivalence utilizes the concept of bioavailability in assessing the comparability of drug products containing the same amount of active ingredients but produced at different time or by different manufacturers.

Bioavailability and bioequivalence studies are an important component of drug regulation and control to ensure that only products of good quality are allowed in the market for consumption. (Refer to Annex REQUIREMENTS FOR THE SUBMISSION OF BIOAVAILABILITY/BIOEQUIVALENCE STUDIES)

3.2 NEWLY INTRODUCED DRUG

3.2.1 Application for Initial Registration shall comply with all the requirements under Established Drugs as follows:

1. Application Letter
2. Certificate of Brand Name Clearance
3. Certificate of Agreement between Manufacturer and Trader or Distributor-Importer/Exporter
4. Unit dose and batch formulation
5. Technical/Quality specifications of all raw materials
6. Certificate of Analysis of active ingredient
7. Technical/ Quality specifications of finished product
8. Certificate of Analysis of finished product
9. Full description of the methods used, the facilities and controls in the manufacture, processing and packaging of the finished product
10. Details of the assay and other test procedures for the finished product including data analysis
11. Detailed report of stability studies to justify claimed shelf-life
12. Labels or specimen of the proposed label and other labeling materials such as inserts, brochures, etc.
13. Samples in market or commercial presentation
14. Duly authenticated Certificate of Free Sale from the country of origin
15. Duly authenticated government certificate attesting to the registration status of the manufacturer

3.2.2 Certificate of the Medical Director registered with BFAD

To facilitate the objective evaluation of drugs, to provide adequate information to the consuming public, and to ensure safety and efficacy of drugs, all establishments engaged in the manufacture and distribution of drugs must have a Medical Director who is a registered physician with knowledge and training in basic and clinical pharmacology.

All communications with the BFAD regarding New Drugs and Investigational New Drugs and matters arising from clinical investigation shall be coursed through the Medical Director.

All labeling materials including inserts, brochures and other labeling/promotion materials must be approved by the Medical Director.

3.2.3 Reference Standard and its corresponding Certificate of Analysis

A sufficient amount of reference standard shall be submitted to enable the BFAD to test the purity or potency of the drug product.

Reference Standards are specifically required in many Pharmacopoeial assays and tests where results are determined on the basis of comparisons of the specimen under test with a Reference Standard that has been freed from or corrected for volatile residues or water content.

An analytical report providing the results of the test carried out to establish the identity, purity and potency of the reference standard shall also be submitted.

3.2.4 Pre-clinical Data

Before initial human studies are permitted, the full spectrum of pharmacologic properties of the new drug must be extensively investigated in animals. Animal researches, are done to provide evidence that the drug has sufficient efficacy and safety to warrant testing in man.

Pre-clinical studies shall include pharmacodynamics, pharmacokinetics, and toxicity studies of the drug.

1. Pharmacodynamics

Pharmacodynamic studies are done for the following purposes:

1. to identify the primary action of the drug as distinguished from the description of its resultant effects.
2. to delineate the details of the chemical interaction between drug and cell or specific receptor site(s), and
3. to characterize the full sequence of drug action and effects.
 - a. Pharmacologic effects - properties relevant to the proposed indication and other effects.

Pharmacodynamic data shall demonstrate the primary pharmacologic effect of the drug leading to its development for the intended use(s) or indication(s). It shall also show the particular tissue(s)/organ(s) affected by the drug and any other effect it produces on the various systems of the body.

- b. Mechanism of action including structure-activity relationship (SAR)

Pharmacodynamic data shall also demonstrate the correlation of the actions and effects of drugs with their chemical structures. Structure-activity relationship is an integral link in the analysis of drug actions since it is well known that the affinity of a drug for a specific macromolecular component of the cell and its intrinsic activity are intimately related to its chemical structure.

2. **Pharmacokinetics**

Pharmacokinetic data form the basis for prediction of therapeutic doses and suitable dosage regimen.

These data shall demonstrate the following:

1. the rate and extent of absorption of the drug using the intended route of administration;
2. the distribution pattern including a determination of the tissues or organs where the drug and its metabolites are concentrated immediately after administration and the time course of their loss from these sites;
3. the metabolic pathway of the drug or its biotransformation and the biological activity of the metabolites;
4. the route of excretion of the drug and its principal metabolites and the amount of unchanged substance and metabolites for each route of excretion;
5. the drug's half-life or the rate at which it is eliminated from the blood, plasma or serum.

3. **Toxicity data**

Toxicity data shall include results of acute toxicity, subchronic and chronic studies done on different species of animals.

1. **Acute Toxicity**

Acute toxicity data shall show the median lethal dose of a drug. Ideally, the study shall be carried out in at least two (2) species of animals, one (1) rodent and the other non-rodent, using 5 dose levels with the appropriate number of test animals. Example: 10 rodents per dose level with the drug given as a single dose and the animal observed for seven (7) days or more (preferably 14 days). The route of administration should be that anticipated for use in man, i.e., oral (by gavage) if to be administered orally.

Acute toxicity data should be able to:

1. define the intrinsic toxicity of the drug
2. assess susceptible animal species
3. identify target organs
4. provide information on risk assessment after exposure to the drug
5. provide information for the design and selection of dose levels for future chronic studies

The following parameters should be established:

1. Lethal dose 50 (LD50)
2. Effective dose 50 (ED50)
3. Therapeutic index
4. No observable adverse effect level (NOEL)
5. Toxidrome

2. **Subchronic Toxicity**

Subchronic toxicity studies are carried out using repeated daily exposure to the drug over a period of 21-90 days with the purpose of studying the toxic effects on target organs, the reversibility of the

effects and the relationship of blood and tissue levels on the test animals.

The following should be contained in the subchronic toxicity data:

1. a determination of the adverse effects from repeated exposures to a chemical over a portion not exceeding 10% of the average life span.
2. A determination of the cumulative toxicity and the development of tolerance in target organ with continuous exposure.
3. A monitored hematologic, renal, hepatic and biochemical changes.
4. A determination of the maximum tolerated dose or the dose with no observed effects in animals.

The parameters used for objective evaluation of drug effects in animals are as follows:

1. Physiologic changes such as body weight, food and water consumption, grooming, bowel movement and urination, temperature, heart rate and respiratory rate.
2. Hematologic such as Hemoglobin (Hb), Hematocrit (ct), White Blood Clot (WBC), Differential count, platelet and reticulocyte count
3. Biochemical such as liver enzymes, alkaline phosphatase, total protein, albumin, globulin, BUN, creatinine, blood sugar, uric acid and cholesterol.
4. Urinalysis
5. Neurological
6. Behavioral
7. Post-mortem analysis (anatomical and histopathological)
8. No observable effect level

3. Chronic Toxicity

Chronic toxicity studies constitute important steps in the analysis of a chemical. The entire lifetime exposure of an individual or animal to the environment or chemical is an on-going process which neither acute nor subchronic toxicity study can provide. The effect on animals when small doses of the drug are given over a long period of time may not be the same as when large doses are given over a short period.

Chronic toxicity studies are done to determine the no observed adverse effect level (NOEL) and to set the acceptable daily intake (ADI) tolerance and threshold limits. The parameters to be observed are the same as in subchronic studies.

4. Special Toxicity Data

Special toxicity studies in animals are conducted to

1. determine the safety of the drug or its preparation through acute, sub-acute and allergenicity tests using appropriate species of animals.

2. Evaluate the effects of the drug on reproduction when given prenatally using fertility and gestation rate as parameters and the effects on the fetuses when given to the lactating dams
3. Determine the morphological and functional effects on the fetus when the drug is administered to the pregnant animal during the period of organ development (organogenesis)
4. Evaluate the mutagenicity potential of the drug
5. Determine the potential of the drug to induce tumor or cancer formation with prolonged administration.

Reproduction tests are designed to evaluate the effect of the drug on the general reproductive performance of animals starting at implantation and continuing through the weaning period in doses significantly greater than those intended for man or in doses that give significantly higher blood and/or other tissue concentrations than those achieved in man.

Since test substances may adversely affect reproductive processes in several ways, at least three (3) tests are required for most new drugs:

1. Multigeneration reproduction study provides information on the fertility and pregnancy in parent animals and subsequent generations. The effects of a potentially toxic substance could be determined by the reproductive performance through successive generations such as adverse effects on the formation of gametes and on fertilization and to detect gross genetic mutations which may lead to fetal death, fetal abnormalities or inadequate development or abnormal reproductive capacity in the F1 generation. This study can also reveal, adverse drug effects that occur during pregnancy or during lactation.
2. Teratologic study determines the effect of a chemical on the embryonic and fetal viability and development when administered to the pregnant female rodent (rat) or non-rodent (beagle dog or monkey) during the period of organogenesis. The specific objectives include: (a) characterization of the type and incidence of malformations in comparison with negative and positive controls through detailed skeletal and visceral organ examination (Wilson Cutting Technique) (b) calculation of pregnancy rate, implantation efficiency, and fetal viability, and (c) evaluation of the effect of treatment of chemical on maternal weight, mortality, behavior, and fetal weight, including male/female ratio.
3. Peri-natal and post-natal study determines the effects of drugs or chemical given to the pregnant animal in the final one-third of gestation and continued throughout lactation to weaning of pups. The study should give data on the following:
 - (a) Labor, as to presence of dystocia, duration of labor, onset of labor.
 - (b) Gestation as to duration and weight gain of dams during pregnancy

- (c) Litter as to number of pups (litter size), weight of pups, nursing behavior of pups, physiologic and anatomic parameters (food and water consumption, length, etc.) and effect of crossover nursing of pups.

A concurrent negative control of animal must be run together with the treated groups (at least 3 dose levels).

2. **Carcinogenicity**

Carcinogenicity tests in animals are required when the drug is likely to be given to humans continuously or in frequent short course periods to determine whether chronic administration can cause tumors in animals. Mice and rats are the rodents of choice while dogs or monkeys are preferred non-rodents. These tests may be designed to be incorporated in the protocol for chronic toxicity studies wherein the animals are exposed to the drug after weaning and continued for a minimum of two years. At least 3 dose levels are used with the highest dose approximating the maximal tolerated dose and the route should be similar to that anticipated in man. Repeated expert observation, palpation and thorough examinations of animals for any lumps or masses are essential. All animals must be thoroughly autopsied and histological examination of all organs should be carried out.

For drugs which are related to known carcinogens, *in vivo* bioassay may be used such as skin neoplasm induction in mice, pulmonary neoplasm induction in mice, breast cancer induction in female Sprague-Dawley rats and altered foci induction in rodent liver.

The use of negative and positive controls allow for a statistical comparison of the incidence of tumors in the test groups.

3. **Mutagenicity**

Mutagenicity tests have the primary objective of determining whether a chemical has the potential to cause genetic damage in humans. Animal model systems, both mammalian and non-mammalian together with microbial systems which may approximate human susceptibility, are used in these tests. In most recommended tests, three categories of genetic damages are investigated: Chromosome mutations, point mutations and primary DNA damage by *in vivo* and *in vitro* assay.

3.2.5 Clinical Data

Data from clinical trials are the basis in designing the most appropriate treatment of future patients with a given medical condition.

The following documents shall be included in the submission of clinical data:

1. Certification of an independent institution review board of approval of clinical protocol and monitoring of clinical trial.

An independent Institutional Review Board (IRB) shall be responsible for the initial and continuing review and approval of the clinical investigation. An approval of the clinical protocol by the IRB shall be obtained before any stage of the clinical trial is started. All changes in the research activity and all unanticipated problems involving risks to human subjects should be promptly reported by the clinical investigation(s) to the IRB.

2. Clinical Investigation Data

1. Phase I Clinical Drug Trial

Phase I Clinical Drug Trial consists of initial testing of the study drug in humans, usually in normal volunteers but occasionally in actual patients. The number of subjects is small (N= 15 to 3). SAFETY evaluations are the primary objectives and attempt is made to establish the approximate levels of patient tolerance for acute and multiple dosing. Basic data on rates of absorption, degree of toxicity to organs (heart, kidney, liver, hamatopoietic, muscular, nervous, vascular) and other tissue, metabolism data, drug concentrations in serum or blood and excretion patterns are also obtained. Subjects shall be carefully screened. Careful monitoring for adverse or untoward effects and intensive clinical laboratory tests are required. This study shall be conducted by an approved or accredited Clinical Pharmacologist. A written informed consent of subject is necessary.

2. Phase II Clinical Drug Trial

Phase I Clinical Drug Trials are initial studies designed to evaluate EFFICACY of the study drug in a small number of selected populations or patient for whom the drug is intended which may be open label or single or double blind. Blood levels at various intervals, adverse experiences, and additional Phase I data may be obtained. Small doses are gradually increased until the minimal effective dose is found. All reactions of the subjects are carefully recorded. Preliminary estimates of the dosage, efficacy and safety in man are made.

The second part of Phase II consists of pivotal well controlled studied that usually represent the most rigorous demonstrations of a drug efficacy. Relative safety information is also determined in Phase II studies. A larger number of patients are enrolled into the second part (N= 60 to 200 subjects).

Phase II studies are conducted by accredited Clinical Pharmacologists. Phase II second part studies may be conducted by well qualified practitioners or clinicians who are familiar with the conditions to be treated, the drug used in these conditions to be treated, the drug used in these conditions and the methods of their evaluation. A written informed consent of patients-participants is needed.

Phase II clinical Trial is usually carried out in a hospital for more careful supervision and control.

3. Phase III Clinical Drug Trial

Phase III clinical drug trials are studies conducted in patient populations for which the drug is eventually intended.

These studies generate data on both safety and efficacy in relatively large numbers of patients under normal use conditions in both controlled and uncontrolled studies. The number of patients required vary (1,000 to 10,000). These studies provide much of the information that is needed for the package insert and labelling of the drug.

This phase may be conducted as a multicentric trial among accredited clinicians. The informed consent of participating subject is preferably in written form.

4. Bioavailability

Bioavailability studies are conducted to determine the rate and extent to which the active substance or therapeutic moiety is absorbed from a pharmaceutical form and becomes available at the site of action.

3. Name(s) of investigator(s) and their curriculum vitae

The name(s) and address(es) of the investigator(s) and subinvestigation(s) (e.g. research fellows, resident physicians) who will be assisting the investigator(s) in the conduct of the investigation should be submitted.

A curriculum vitae or other statement of qualifications of the investigator(s) showing the education, training and experience that qualifies the investigator as an expert in the clinical investigation of a drug should also be submitted.

The investigator shall be well qualified by scientific training and experience to conduct investigational studies of the subject drug and he is affiliated with a recognized medical school or with an independent institution recognized for its excellence or is otherwise appropriately qualified.

The training and experience needed will vary, depending upon the kind of drug and the nature of the investigation. In Phase I, the investigator must be able to evaluate human toxicology and pharmacology. In Phase II, the clinicians should be familiar with the conditions to be treated the drugs used in these conditions and the methods of their evaluation. In Phase III, in addition to experienced clinical investigators, physicians not regarded as specialists in any particular field of medicine may serve as investigators, properly guided by a competent clinical investigator who will collate all the data and be responsible for the final result of the body. At this stage a large number of patients may be treated by different physicians so that a broad background of experience may be secured.

4. Name(s) of center/institution wherein the clinical investigation was undertaken

The institution/center must be accredited by the regulatory agency and must have an independent ethical and technical review boards. The facilities and laboratories must meet the requirements for the phase of clinical trial that will be undertaken in such institution/center.

Phase I clinical trials require facilities and human resource capabilities of the highest degree. These requirements are usually met only by institutions/center in well developed countries. Phase II and III may be undertaken in academic institutions and tertiary hospitals with trained clinical pharmacologists, specialists and paramedical personnel.

The capabilities and standard of these institutions/centers must have been certified by the appropriate government agency as meeting the high standard of Good Laboratory Practice (GLP) and Good Clinical Practice (GCP)

The Medical Director of such institution/center or hospital must certify that such clinical trial is being allowed to be conducted in such institution or hospital.

5. Protocol for Local Clinical Trial

Local clinical trials are conducted to determine the safety, efficacy and suitability of the recommended dosage and therapeutic dose regimen to the local patient population. These trials can only be conducted after the protocol for a local clinical trial is approved by an accredited independent institutional review board and a temporary permit to market the drug locally is granted.

The protocol for the local trial shall include the following:

1. Study Title
2. Names of Investigator(s) including supervising investigator, principal investigator, co-investigator(s).
3. Funding/Sponsoring Agency
4. Summary of the Proposed Study
5. Introduction including an identification of what is being studied, an explanation of why the study is valid or the scientific rationale.
6. Objective(s) of the study indicating the general objective and specific objective(s).
7. Study Design e.g. descriptive study, case control, cohort, randomized concurrent trial.
8. Methods including a description of the study subjects, sample size, description of the study procedure, and a description of outcome measurements.
9. Data analysis including the criteria for substantive and statistical success, definition of drop-outs, withdrawals, treatment failure, details of statistical strategy to be used, and a specification of data handling, collation and computer use.
10. Ethical Consideration including
 - a. Good outweighing harm
 - b. Free informed consent
 - c. Freedom to withdraw from the study at any time
 - d. Confidentiality
11. Indemnification Policy which is compensation statement indicating availability payment for treatment or free treatment hospitalization in case of an adverse drug experience.
12. Time schedule or duration of clinical trial.
13. Duties and responsibilities of research personnel.
 - a. The investigator must conduct the studies in conformance with the "Declaration of Helsinki" or the laws and regulations of the country in which the research is conducted, whichever represent the greater protection of the individual.
 - b. The investigator must keep careful records of his study and retain them for at least two years after the new drug application is approved. The records must be available promptly to the drug sponsor (usually the drug manufacturer) and to the drug regulatory agency. Progress reports must be sent to the sponsor at intervals not exceeding one year.
 - c. The investigator must send emergency reports to the sponsor and the regulatory agency when dangerous adverse effects are observed.

- d. The investigators must observe the regulations regarding consent of human subjects being given an investigational drug.

14. Bibliography
15. List of Hospital Resources/Personnel Required.
16. List of Basic Sciences Resources
17. Appendices including informed consent form, patient/case report form, flowchart of activities, questionnaire, dummy tables and graphs.
18. A statement that the protocol was reviewed and approved by the Research Committee and the Director (and Dean, if applicable) of the institution/hospital.

3.3 PRODUCTS WITH NEW INDICATION(S) OR NEW ROUTE OF ADMINISTRATION

- 3.3.1 Application for Initial Registration shall comply with the following requirements under Established Drug

1. Application letter
2. Unit dose and batch formulation
3. Technical specifications of all raw materials
4. Certificate of Analysis of active raw material
5. Technical specification of finished product
6. Certificate of Analyses of finished product
7. Full description of the methods used, the facilities and controls in the manufacture, processing and packaging of the product
8. Details of the assay and other test procedures for finished product including data analysis.
9. Detailed report of stability studies to justify claimed shelf-life
10. Sufficient samples in market or commercial presentation for laboratory analysis and representative sample for PSD.

- 3.3.2 Pharmacokinetic data

Pharmacokinetic studies should be conducted to determine the most suitable dosage regimen for the new indication or the new route of administration.

It is important to conduct pharmacokinetic studies relating to the new route of administration since the metabolic pathways of a drug substance and the biological activity of its metabolites may vary depending on the route it is administered.

- 3.3.3 Phase III clinical trial for the new indication(s) or the new route of administration

Phase III clinical studies should be aimed at determining the safety and efficacy of the drug product for its new indication or new route of administration.

For studies on a new indication, Phase III clinical trial should be conducted in patient population for which the new indication is intended.

- 3.3.4 Local Clinical Trial (optional)

Local clinical trials are conducted to determine the safety, efficacy and the most appropriate dosage or dosage regimen for the new indication in local patient population.

3.4 PRODUCTS WITH ADDITIONAL DOSAGE OR DOSAGE STRENGTH

3.4.1 Application for Initial Registration shall comply with the following requirements under Established Drug

1. Application letter
2. Unit dose and batch formulation
3. Technical specifications of all raw materials
4. Certificate of Analysis of active raw material
5. Technical specifications of finished product
6. Certificate of Analyses of finished product
7. Full description of the methods used, the facilities and controls in the manufacture, processing and packaging of the finished product
8. Details of the assay and other test procedures for finished product including data analysis
9. Detailed report of stability studies to justify claimed shelf-life
10. Sufficient samples in market or commercial presentation for laboratory analysis and representative sample for PSD

3.4.2 Pre-clinical studies

1. Toxicology data for increased dosage to ensure that the addition in the amount of active ingredient will not diminish the desirable effects of the drug.

3.4.3 Phase III Clinical Drug Trial (optional)

3.4.4 Local Clinical Trial (optional)

3.5 PRODUCTS WITH NEW DOSAGE FORM

3.5.1 Application for Initial Registration shall comply with the following requirements under Established Drug

1. Application letter
2. Unit dose and batch formulation
3. Technical specifications of all raw materials
4. Certificate of Analysis of active raw material
5. Technical specifications of finished product
6. Certificate of Analysis of finished product
7. Full description of the methods used, the facilities and controls in the manufacture, processing and packaging of the finished product
8. Details of the assay and other test procedures for finished product including data analysis
9. Detailed report of stability studies to justify claimed shelf-life

10. Sufficient samples in market or commercial presentation for laboratory analysis and representative sample for PSD

11. Unattached generic labeling materials: label, box, insert, blister/foil strip

12. Requirements for sterile products

3.5.2 Bioavailability or Bioequivalence Data, as needed

Bioavailability is largely dependent in the ability of the drug product to release the active ingredient at the site where it is intended to be absorbed.

Problems on bioavailability are more especially defined in solid oral dosage forms of drugs. medically significant cases of bioinequivalence rest mainly on four causal factors: particle size of an active ingredient; magnesium stearate in excess as a lubricant-glidant; coatings especially shellac; inadequate disintegrant. Every one of the factors is reactive to dissolution testing.

3.6 PRODUCTS WITH CHANGE IN:

1. Application for Initial Registration shall comply with the following requirements under Established Drugs

- a) Application letter
- b) Copy of latest Certificate of Product Registration
- c) Unit dose and batch formulation
- d) Certificate of Analysis of active raw material
- e) Technical specifications of finished product
- f) Certificate of Analysis of finished product
- g) Details of the assay and other test procedures for finished product including data analysis
- h) Detailed report of stability studies to justify claimed shelf-life
- i) Sufficient samples in market or commercial presentation for laboratory analysis and representative sample for PSD
- j) Actual unattached generic labeling materials; label, box, insert, blister/foil strip
- k) Requirements for sterile products

2. Notification of the change in formulation including a justification for such change.

3. Bioavailability of Bioequivalence data, as needed.

3.7 PRODUCTS FOR MONITORED RELEASE PRIOR TO APPROVAL FOR GENERAL USE

Newly Introduced Drugs (NID) (with history of 5 years registered use 5000 patient exposure in other countries), will be required to complete clinical pharmacological studies and pass through a 3-year Initial Registration (Monitored Release) before becoming eligible for application and approval for General Use.

The model protocol for monitored release is as follows:

An Uncontrolled Clinical Study reported the therapeutic effects and adverse reaction for 1000 patients per year or 3000 patients over 3 years, provided however that if the drug product is for a very limited therapeutic indication the 1000 patients/year requirement will be waived and only 10% of total patients is given the drug will be required to be monitored and reported to BFAD by the Pharmaceutical Company.

3.8 PHASE IV CLINICAL TRIAL FOR PRODUCTS UNDER THE FOLLOWING CATEGORIES:

1. NEWLY INTRODUCED DRUG
2. ESTABLISHED DRUG WITH
 - a. NEW INDICATION OR NEW ROUTE OF ADMINISTRATION
 - b. ADDITIONAL DOSAGE OR DOSAGE STRENGTH

Phase IV clinical drug trials are conducted after the drug is marketed to provide additional details on the drug's efficacy and/or safety profile.

The first part is done through a monitored release of drug to selected medical centers and qualified physicians. Monitoring of drug's safety and efficacy is done and impact under limited marketing is obtained (See Sections 3.7 for details)

Further, Postmarketing surveillance (Part II of Phase IV) is the evaluation of the drug's efficacy and safety among patients under conditions of general drug use. These are primarily observational or non-experimental in nature. Patterns of drug utilization are studied. All physicians agreeing to participate in organized reporting may conduct this phase of the study.

Adverse drug experiences shall be monitored and an independent review board shall evaluate the reports to determine cause-effect relationship or to conclude whether an adverse drug reaction has occurred or not.

4. RENEWAL REGISTRATION

Renewal of registration of all drug products is necessary to enable the authorities to check the quality, safety and effective dose regimen of drug products currently available to the public. Problems of drug interaction *in vitro* and *in vivo* must be assessed during renewal of registration. Any change in precautions, cautions and warnings shall be implemented during renewal of registration, if not done earlier.

4.1 Application for Renewal Registration shall comply with the requirements under Established Drug as follows:

1. Application letter
2. Copy of latest Certificate of Product Registration
3. Unit dose and batch formulation
4. Certificate of Analysis of active raw material
5. Technical specifications of finished product
6. Certificate of Analysis of finished product
7. Details of the assay and other test procedures for finished product including data analysis
8. Detailed report of stability studies to justify claimed shelf-life (3 batches)
9. Sufficient samples in market/commercial presentation for laboratory analysis and representative sample for PSD
10. Actual unattached generic labeling materials; label, box, insert, blister/foil strip
11. Requirements for sterile products

4.2 Application for renewal registration of drug or pharmaceutical specialty shall be filed within three (3) months before the expiration date of the Certificate of Product Registration.

- 4.2.1 A surcharge of 50% or renewal registration fees shall be imposed upon application for renewal registration filed within three (3) months after expiration date of CPR.
- 4.2.2 Application for renewal registration filed three (3) months after CPR's expiration date shall be considered as initial registration.

4.3 Payment of surcharge shall not make the product under the renewal process eligible for conditional registration.

5. FIXED-DOSE COMBINATION DRUG PRODUCTS

Definition:

Fixed Dose Combination Drug Products (FDC's) are pharmaceutical preparations containing two or more pharmacologically-active ingredients in a single formulation or dosage form.

Scope of these Guidelines: (A.O. 96 series 1990)

All products classified as FDC's are covered by these guidelines. These are three categories of products included:

- 5.1 Currently registered products already recognized and identified by BFAD as FDC's.
- 5.2 Currently registered product which may later be classified as FDC's
- 5.3 Products with pending or for future initial registration under the category of FDC's.

All these categories of FDC's are covered but the specific applicability will be defined below.

Safety, Efficacy and Quality Criteria

The drug regulatory criteria of safety, efficacy and quality shall be applied to the specific class of FDC's using the following rules:

1. The FDC drug product must comply with the appropriate requirements of A.O. 67 s. 1989 on registration of drug products.
2. The drug establishment seeking to register the FDC drug products should comply with the appropriate requirements of A.O. 56 s. 1989 on the registrations of drug establishments.
3. In addition to the above, the FDC drug product in its final dosage form must be proven to adhere to all the following criteria:
 - (a) The active and inactive ingredients should be pharmaceutically (i.e. chemically, physically) and pharmacologically compatible in combination.
 - (b) The FDC taken as a whole should have clinical and therapeutic advantage over the individual active ingredients taken separately. In this respect, acceptable clinical and therapeutic advantage involves more than additive affect, convenience or better compliance. It should include each advantages as complementary or synergistic pharmacological action or therapeutic effect, or reduction in adverse drug reaction.
 - (c) It must not contain any ingredient whose proper administration or clinical use require special adjustments different from or in conflict with its other ingredients.
 - (d) It must not contain active ingredients with abuse potential (those identified in List A of A.O. 63 s. 1989), with a narrow margin of safety and/or requires special precautions in its use and/or with bioequivalence problems (those identified in List B of A.O. 63 s. 1989), and which are banned or not yet registered in the Philippines.

Currently registered FDC drug products are classified into use groups and order of priority for review. The classification is based on PNDF characterization of product's active ingredients and the manufacturer's claims of the nature of the drug action in its approved product.

PRIORITY I

1. Anti-infectives
2. Anti-asthmatics
3. Cough/Cold remedies

PRIORITY II

1. Anti-TB
2. Cardio-vascular preparations
3. Endocrine/metabolics
4. Drugs acting on central nervous System

PRIORITY III

1. Gastro-intestinal preparations
2. OB/Gyne preparations
3. Musculoskeletal preparations
4. Urinary tract preparations
5. Vitamins-minerals
6. Eye-Ear preparations
7. Dermatologicals
8. Dermatologicals
9. Others

5.4 Fixed Dose Combination Drug Products listed in the latest edition of the Philippine National Drug Formulary and complying with A.O. 67 s. 1989 shall be accepted for registration without satisfying the requirements stated in Section 4.2 of A.O. 96 s. 1990.

6. PRODUCTS WITH CHANGE OF MANUFACTURER (M.C. No. 12 s 1991)

6.1 When a drug establishment changes manufacturer for its product(s) to one that has better technical capabilities as evidenced by a record showing no deficiencies or only minor deficiency (not substantively affecting product quality) in either GMP or its whole product lines, a conditional certificate of product registration (CPR) may be granted following the registration procedure defined under BFAD Circular No. 12 s. 1991.

6.2 Compliance with the following requirements under Established Drug as follows:

1. Application letter
2. Original Certificate of Product Registration
3. Unit dose and batch formulation
4. Certificate of Analysis of active raw material
5. Technical specifications of finished product
6. Certificate of Analysis of finished product
7. Details of the assay and other test procedures for finished product including data analysis
8. Sufficient samples in market/commercial presentation for laboratory analysis and representative sample for PSD
9. Actual unattached generic labeling materials; label, box, insert, blister/foil strip
10. Requirements for sterile products

6.3 The conditional CPR shall be effective for a period of one (1) year subject to the results of the BFD Laboratory tests and stability studies for the product conducted by the new manufacturer.

7. PRODUCTS WITH IMPROVEMENT OF IMMEDIATE CONTAINER OR PACKAGING (M.C. No. 16 s1991)

7.1 Encouraging technical improvement of validly registered drug products, a conditional initial registration may be granted to products whose only change is an improvement in the immediate container or packaging. For this purpose, the procedure under the Memorandum Circular No. 16 s. 1991 shall be observed.

7.2 Compliance with the following requirements under Established Drug

1. Application letter
2. Copy of latest Certificate of Product Registration
3. Unit dose and batch formulation
4. Certificate of Analysis of active raw material
5. Technical specifications of finished product
6. Certificate of Analysis of finished product

7. Details of the assay and other test procedures for finished product including data analysis
8. Sufficient samples in market/commercial presentation for laboratory analysis and representative sample for PSD
9. Actual unattached generic labeling materials; label, box, insert, blister/foil strip
10. Requirements for sterile products

7.3 If the establishment opts to retain the registered products with the old packaging specifications, a new registration number will be assigned to the same product with the new packaging specifications; however if the establishment applies to use the same DR number of the old product for the new, the product with the old packaging specifications shall be considered automatically phased out after the Conditional CPR for the new product is approved. In this case, the original CPR with the old packaging specification shall be submitted.

7.4 The Conditional CPR shall be valid for a period of one (1) year from the date of issue. It shall be subject to the satisfactory result of laboratory tests and of stability studies.

8. REGISTRATION OF BRANDED VERSION OF REGISTERED UNBRANDED GENERIC DRUG PRODUCT AND GENERIC VERSION OF REGISTERED BRANDED DRUG PRODUCT (AS PER M.C. No. 10-A S 1992)

8.1 Requirements for Branded version

A manufacturer, trader or distributor-Importer who has a registered unbranded generic drug product may apply for registration of the branded version of the said product provided that if the registration of that generic product was processed through the Special Lane (M.C. No. 5 s. 1990) under product category B, the registration of the branded version will become effective only one (1) year from the date of application for the branded version but not less than one (1) year after the date the generic version was approved. (Product category B under MC No. 5 s. 1990 is a special privilege for generic (unbranded) drug product, hence this rule).

The applicant shall submit together with his application the following:

- a) A copy of the Certificate of Brand Name Clearance
- b) If the company opts to retain the unbranded version, a copy of the Certificate of Product Registration of the generic drug product, if the company will no longer market the generic version, the current original Certificate of Product Registration.
- c) A prototype of the proposed complete commercial form and presentation of the branded version of the product including labels and inserts.
- d) Unit dose and Batch Formulation
- e) Technical/Quality Specification of the finished product

8.2 Requirements for Generic version

A manufacturer, trader or distributor-importer who has a registered branded drug product, may apply for registration of the unbranded generic version of the same.

The applicant shall submit together with his application the following:

- a) If the company opts to retain the branded version a copy of the Certificate of Product Registration of the branded version; if the company will no longer market the branded version, the current original Certificate of Product Registration.
- b) A prototype of the proposed complete commercial forms and presentation of the unbranded generic version of the product.
- c) Unit dose and batch formulation
- d) Technical/Quality specifications of finished product

9. The foregoing guidelines shall not preclude the BFAD form requiring any specific technical data whenever question of safety, efficacy and quality arises during the evaluation.

These 1997 Guidelines shall be amended or modified after consultation with the pharmaceutical sectors to update the same with technological advancement in pharmaceutical products.

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Director

Date approved:

January 30, 1997

Date of Effectivity

April 1, 1997

GUIDELINES ON THE STABILITY TESTING OF PHARMACEUTICALS

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Preamble

These notes provide guidance as to the design, conduct and reporting of stability studies. These guidelines primarily cover:

- products containing drugs which are prepared by chemical synthesis
- products containing drugs which are pure chemical entities isolated from a natural source, e.g. vincristine, digoxin
- radiopharmaceuticals (but see below)
- products containing drugs which are produced by microbial fermentation, principally antibiotics and some anticancer drugs.
- materials of biological origin (see below)

Materials of biological origin. The principles described in this document also generally apply to stability studies on materials of biological origin, such as hormones, allergens, modified animal tissues, vaccines and the products of genetic engineering or other newer biological techniques. However some specific guidelines may not be appropriate for biologicals, in particular:

- References to chemical assay techniques, such as the preference stated in 3.3 for chromatographic methods for decomposition products, may not always be appropriate for biologicals.
- It may not always be possible to establish degradation pathways and identify decomposition products formed in significant amounts (see 2.1 and 3.3)
- The degradation of biologicals is not usually amenable to kinetic analysis and extrapolation from 'accelerated' testing (see 5)

Stability data for biologicals will be evaluated on a case by case basis, having regard to the nature of the product and the methods of analysis (physical, chemical biological) which are appropriate for that product.

I. General Principles

The objectives of a stability study is to determine the period of time during which a pharmaceutical product meets appropriate standards when stored under defined conditions. As a minimum, the product must be shown to comply with relevant specifications for the whole of its shelf-life.

The following statement, which appears in the 1993 edition of the British Pharmacopoeia, reflects a principle which should be familiar to any pharmaceutical manufacturer:

"A manufacturer must recognize that a product or material may be challenged at any time during its claimed period of use by the methods of the Pharmacopoeia and that it must then comply with the pharmacopoeia requirements. These requirements allow for acceptable levels of change that may occur during storage and distribution and reject articles showing unacceptable levels of change. Frequently a manufacturer will need to apply more stringent test limits at the time of release of a batch of the product or material in order to ensure compliance.' (BP 1993, p xxii)

Thus the difference between release and expire specifications must take into account the results of stability testing.

The maximum permitted shelf life is normally five years.

2. Stability Trial Design

2.1 Active raw material. An assessment of the stability of the active raw material (see Glossary of Terms) is required for new drugs and is useful in support of shelf lives for new formulations of existing drugs. such information provides a useful guide to the problems which may be encountered during stability studies on finished products.

Studies should establish the inherent stability characteristics of the molecule, in particular the degradation pathways, the identity of degradation products formed in significant amounts and the suitability of proposed analytical procedures for quantitation of both the drug substance and degradation products. The nature of the studies will depend on the drug substance but is likely to include the effect of elevated temperature, susceptibility to moisture and oxidation, and the effect of light. The effect of pH may be important when the finished product is an aqueous solution or suspension, in the latter case by means of effects on the fraction of drug actually dissolved, however small.

The kinetics of degradation of the active raw material cannot be assumed to apply to reactions which occur in the finished product, and care should be exercised in extrapolating on the basis of such data.

2.2 Finished product

2.2.1 The formulation must be the same as that proposed for registration in the Philippines. Stability data on related formulations may be submitted as supporting evidence provided the differences between the formulation employed in the stability trial and that proposed for registration are clearly stated. A shelf life will not normally be allocated for the purposes of registration if there are no data on the formulation to be registered.

All manufacturing processes must have been carried out on the batches used in the stability trial, e.g. filtration, packaging, sterilization.

2.2.2. The product should be tested in the container/closure system in which it will be registered in the Philippines. If the product is to be registered in more than one container/closure system, stability data should normally be provided for each presentation (however see 6.2 below). Stability data in other types of pack are of limited value, unless comparative studies of the two types of pack are provided which clearly demonstrate the equivalence or superiority of the container/closure intended for registration over the system used on the stability trials.

2.2.3. Stability information should be generated on a minimum of three batches. Where this information has been obtained on pilot production batches. A full trial must be conducted using at least three production batches as soon as they become available.

Where the product is registered in several strengths, stability data should be generated on three batches of each strength, unless the different strengths are direct scales (see Glossary of terms) in which case at least one batch of each of the highest and lowest strengths should be tested. For multiple strengths where the highest and lowest strengths bracket the others in terms of proportions of excipients, only the highest and lowest strengths normally need to be tested (two batches of each)

2.2.4. Conditions of storage likely to be encountered in the Philippines should be considered in designing the stability trial. Storage conditions should be clearly defined, preferably in terms of the categories specified in Appendix 1. Lighting conditions should be specified.

The use of uncontrolled temperature conditions in stability trials is unacceptable. Terms such as 'room temperature' and "normal warehouse conditions" are discouraged as these allow the product to be exposed to a wide range of conditions and make shelf life assessment difficult. Where a shelf life is based upon uncontrolled storage conditions, it will usually be shorter than the duration of the submitted study.

If storage in a refrigerator is proposed without the caution "Do not freeze", then stability, particularly physical stability (e.g. no formation of a precipitate, no denaturation of a protein) at about -5°C must be demonstrated.

Stability studies at elevated temperatures are useful in predicting longer term shelf life periods from short term data (see part 5 below) but these predictions should be verified by studies on production batches in the pack intended for registration at the maximum recommended storage temperature for the full term proposed, for example at 30°C , if the recommendation storage temperature statement is "Storage below 30°C "

2.2.5. The cycling effect of night and day temperatures and humidity can be important for example where the drug is present partly in suspension and partly in solution. Cycling conditions may be simulated in environmental cabinets. The data are useful in confirming the stability of the product under conditions of stress. However it is difficult to derive accurate predictions for the shelf life of a product from this information and it is not a formal requirement.

2.2.6. Where the product is to be registered in a moisture permeable material such as polyvinyl chloride (PVC) or some grades of polyethylene, or where the closure system allows moisture transfer, the stability of the product should be determined under conditions of high humidity at the recommended temperature (see 3.7 below).

Loss of moisture by transpiration can be important for some products, such as intravenous infusions in plastic packs and waterbased creams in PVC tubes. The extent of loss can be assessed by accurate weighing of marked individual packs over time. If severe it may also be apparent as an increase in drug concentration in the product.

Where a sponsor asserts that his container/closure system is moisture-impermeable, evidence to this effect can be provided by, for example, the technique described in the USPXXIII pages. 1575-1576 entitled 'Containers-Permeation.'

2.2.7. The possibility of leaching of substances from containers into the product should be considered for:

- injectables and ophthalmics supplied in non-glass containers or with plastic or with plastic or rubber stoppers,
- plastic components of metered dose aerosols, and
- any other product where this could occur and may be a hazard.

2.2.8 "In-use" stability data should be generated where relevant, for example:

- where the product must be reconstituted or diluted prior to use,
- where the product is claimed to be stable when mixed with other products,
- products which may be labile once the container is opened.

The stability of the in-use form of the product should be established for the period of time and under the conditions for which storage is recommended.

Published papers may be submitted as evidence of in-use stability provided (1) they can be shown to be relevant to the formulation proposed for registration, and (2) they include sufficient detail to allow independent evaluation.

Where it is claimed (on the label or in product information) that the product may be diluted with a range of solutions, the most common example being parenteral drugs diluted in large volume intravenous infusions. Stability data should establish compatibility with each recommended diluent at the extremes of the recommended dilution ratios for the permitted duration of storage.

Tests on reconstituted and/or diluted solutions should normally include pH, clarity/particulate matter, assay and, if assay sensitivity allows, degradation products. Note however that, regardless of chemical stability, the product information for reconstitutable and dilutable injectables should normally include the direction. 'To reduce microbiological hazard use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2-8°C for not more than 24 hours', or words to that effect. If there are valid reasons why the reconstituted and/or diluted solution may be kept for longer periods then data should be generated to establish the effectiveness of the preservative for the duration of the recommended storage period.

2.2.9 Where a precipitate may form during normal storage, for example in an intravenous injection where the drug may precipitate because of borderline solubility, directions for redissolution must be included in product information and should be supported by appropriate stability data.

2.2.10 Studies of container/closure interaction with the product should be considered where this is a risk, for example injectable liquids should be stored both upright and inverted to determine whether contact with the closure affects stability.

3. Appropriate Tests

3.1 General

3.1.1 Where test methods are identical to those in the routine quality control specifications, this should be explicitly stated and not left to the evaluator to assume.

Alternative test methods maybe used in stability studies, but they should be fully described and validated. Dissolution procedures other than those in finished product specifications are discouraged.

- 3.1.2 If changes are made to the assay or other test method during a stability study, it may be difficult to compare results before and after the change. On the other hand, if the change is being made because of a deficiency in the first method, it may be warranted. In such a case, data should be generated comparing the two methods in terms of accuracy, precision, specificity and other relevant characteristics. Both procedures should be conducted at several stations to find how the results compare.

Change to dissolution test methodology during stability studies are discouraged.

- 3.2 **Assay.** Details should be provided of all analytical methods used in the stability studies together with validation data including:

- accuracy and precision in the range of the concentrations to be measured
- shape of the calibration curve over the same range (linearity is preferred)
- specificity, i.e. freedom from interference by degradation products, other likely impurities and excipients.

It is not sufficient to determine that the drug content remains within the limits of the specifications; the study design and assay parameters should be such as to allow any trend over time to be observed.

As well as assay of drug, it may be necessary to assay other components, e.g. antimicrobial preservatives. In multidose parenterals, and in some cases the content of antioxidant.

It should be noted that loss of drug may be due to factors other than degradation, such as absorption on to or absorption into the container wall, volatilization, etc.

- 3.3 **Degradation products.** Determination of trends in formation of major degradation products provides, in conjunction with the assay for content of drug substance, a better basis for assigning a shelf life to a product than assay results for the drug substance alone. Therefore, as far as possible, degradation products should be quantified or, if this is not possible, semiquantified.

Results for content of degradation products should be provided even if the assay method is specific for the drug. Where results are below the limit of detection of the test method, these should be expressed as "below x%", where x% is the detection limit of the test(s) used. Results should be given for total and all individual impurities detected, even where the identity of the impurity is unknown. Where the identity of the impurity is unknown, results may have to be semiquantitative.

Chromatographic techniques are preferred for the separation and detection of degradation products, but validated alternative methods of quantification may be acceptable. The chromatographic system employed should be capable of separating and detecting compounds which are likely to be present as impurities or which may arise via established degradation pathways. It may be necessary to provide data from two or more systems to confirm the adequacy of resolution.

Information should be provided on the means by which the methods used in the stability study for estimating degradation products were selected.

Degradation products, present at 0.5% of the active content or greater should normally be identified.

- 3.4 **Physical properties.** In addition to assay for content of active ingredients and degradation products, it is also necessary to monitor the physical properties of the product during storage. The physical tests will vary with the formulation in question but important attributes of various dosage forms may include the following:

- 3.4.1 **Tablets and capsules.** Dissolution rate profiles or disintegration if dissolution is not relevant, appearance, odour, hardness, friability, moisture content, brittleness (hard gelatin capsules).

- 3.4.2 **Liquid formulations and injections.** Appearance, colour, odour, pH, clarity (solutions) and freedom from visible particulate contamination, size range of particulate contamination (large volume parenterals), particle size distribution

(suspensions), micelle size distribution (micellar solutions), resuspendibility (suspensions), viscosity, moisture content (powders for reconstitution), phase separation (emulsions).

- 3.4.3 **Ointments and creams.** Appearance, odour, viscosity, softening range, loss of water, physical and chemical homogeneity, particle size distribution, particle formation, pH.
- 3.4.4 **Freeze-dried material.** (including materials for reconstitution). Appearance of both freeze-dried and reconstituted material, pH, water content, rate of solution.
- 3.4.5 **Aerosols.** Leak tests, particulate contamination, valve function and appearance, weight loss. Metered dose aerosols, and some pump actuated aerosols, will also require measurements of drug mass aerodynamic particle size distribution on aging.
- 3.4.6 **Suppositories and pessaries.** Appearance, softening temperature (moulded products), dissolution rate (compressed products).
- 3.4.7 **Transdermal patches.** Appearance, in vitro release rate.
- 3.5 **Preservative efficacy.** Because chemical assays do not necessarily indicate antimicrobial efficacy, if a product is required to contain an antimicrobial preservative, for example eye drops or multidose injections, it will usually be necessary to conduct a microbial challenge test at the end of the shelf life in addition to chemical assay of the preservative during the study.
- 3.6 **Dissolution rate.** The behavior of dissolution rate over time should be examined for all solid oral dosage forms and other compressed products (suppositories, implants, etc.) even where the drug is water soluble. Dissolution data should normally be generated on at least six individual units at each test station (e.g. 1 month, 3 months, 6 months etc) and should be reported as both individual and mean data. Test conditions should normally be those used in routine quality control or, if dissolution is not a part of routine quality control, any reasonable, validated method.

It may be necessary to generate dissolution profiles (percent of nominal content dissolved at a number of time points at appropriate intervals to almost complete dissolution) for certain products, for example:

- modified release products.
- certain immediate release products, for example carbamazepine tablets where it has been shown that tablets which release the drug rapidly lead to a higher incidence of adverse effects,
- in cases where there are doubts as to the validity of the dissolution test method,
- in cases where single point data suggest there may be a problem with the dissolution rate of the product, especially with aging.

- 3.7 **High Humidity Studies.** The use of plastic containers for the packaging of pharmaceuticals raises questions concerning the stability of the contents when stored under conditions of high humidity. High relative humidity can affect chemical stability (for example some antibiotics are readily hydrolysed) and physical stability (for example, altered dissolution rate).

Data should be generated to establish the effect of high humidity on solid dosage forms packaged in containers which are likely to be permeable to moisture. This includes containers made from polyvinyl chloride or low density polyethylene but does not include those made from glass or high density polyethylene. If a sponsor believes that high humidity data are not needed for a product which is packed in a plastic material, this view should be supported by, for example, information on the composition, thickness, density and/or moisture transmissibility of the packaging materials.

Temperature and relative humidity data available from the Bureau of Meteorology have established that a number of centres in Philippines experience a combination of high humidity and high temperature during the summer months.

Satisfactory stability results when the product is stored at 25°C and 80% RH or 30°C and 75% RH for 3 months are normally sufficient to establish the adequacy of the packaging to protect the product from moisture for a period of up to 2 years. Data which show stability for a period of 6 months are normally sufficient to support shelf lives in excess of 2 years.

These short term high humidity data provide support for stability data accumulated at the maximum recommended storage temperature at lower relative humidity, but do not obviate the need for studies for the duration of the shelf life.

4. Presentation of Results

4.1 Results obtained at the commencement and at nominated time intervals throughout the trial (for example 0, 3, 6, 9, 12, 18, 24 months, or 0, 1, 2 and 3 months for high humidity studies) should be provided. This will allow any trends to be detected and will enhance the predictive value of the trial.

Data which do not include initial results (that is at the start of the trial) are of limited value.

4.2 If more than one assay result is available for any particular time interval, all results should be quoted rather than, or in addition to, an average figure. Where bioassays are employed to study antibiotics, the accompanying fiducial limits of error ($p=0.95$) of each assay should be provided.

4.3 Assay results obtained during the study should be recorded either as absolute values (such as number of mg of drug per capsule) or as a percentage of the nominal (labeled) content.

4.4 Care should be taken that individual dose unit variations, such as between individual tablets or between individual vials of freeze-dried powder, are allowed for in stability studies. For freeze-dried vials, this may be achieved by assaying the content of active per unit weight of powder. For tablets and capsules, an average content may be obtained by conducting the assay on pooled samples (normally 20 tablets or capsules), or by averaging individual dose unit results.

4.5 Wherever possible, quantitative results should be quoted rather than a statement that the product complies with a particular specification.

4.6 All results obtained should be discussed and explanation given where necessary, for example anomalous or unusual results, change in assay method, change in appearance.

4.7 A brief outline of the sampling procedure followed in the stability trial should be provided.

5. Prediction of Shelf-Life from Stability Data

One of the more difficult steps in a stability trial is to assign appropriate storage conditions and a shelf life from the accumulated data. The difficulty is reduced and the reliability of extrapolation enhanced if the data include frequent intermediate stations, are derived from several batches, consider a range of conditions, are high precision, include analysis for breakdown products and consider the physical properties of the formulation.

The accumulation of stability data is a lengthy procedure and it is sometimes necessary to predict a probable shelf life for a product stored at a defined temperature from stability data obtained at an elevated temperature. This "accelerated" stability testing is useful in providing information from which to assess the probable stability of a new product but it should be conducted in conjunction with long term stability studies at the maximum recommended storage temperature for the duration of the nominated shelf life.

In theory, the stability of the drug substance is directly related to the kinetics of the various degradation reactions. However the relevant physicochemical equations are strictly applicable only when a single reaction occurs by a single mechanism. Because pharmaceutical products are usually mixtures of substances and may be in the solid state (for example, powders and tablets), these theoretical models do not necessarily hold and cannot be relied upon as predictive tools. The issue of physical stability (for example dissolution rate and particle formation) adds a further complication. There is therefore no substitute for the shelf life being determined empirically ultimately over the full shelf life.

The following general rule-of-thumb is used by the evaluators when assessing data from elevated temperature studies:

If no trends are noted after storage for a period of (x) months at an elevated temperature (at least 10°C above the maximum storage temperature proposed for the product) then an interim shelf life of a maximum of 2(x) months may be permitted, where 2(x) does not exceed 3 years.

Shelf lives of longer than 3 years should be supported by data on production batches stored at the maximum recommended temperature for the duration of the proposed shelf life.

Stability trials involving at least three production batches stored at the maximum recommended temperature should in any case be continued for the full period to validate the predicted shelf life. Interim shelf lives may be extended through submission of additional data accumulated in the later stages of the trial. Manufacturers should not however that the shelf life may not be extended until the data have been evaluated by BFAD and a new shelf life agreed.

6. Product Modifications

Manufacturers may not implement changes to pharmaceutical data without prior approval by BFAD. Applications to make changes should provide details of the proposed change and relevant pharmaceutical data to the PSD. Whether or not stability data are required will be a matter of judgment in each case.

These are examples of changes which would normally require supporting stability data:

- a change to the pH specifications of a liquid product.
- change of tablet container from a glass bottle to a PVC blister.
- a change in the synthetic route for the active raw material together with changes in impurity levels.
- an increase in the radioactive concentration at which a radiopharmaceutical is provided.

The following are examples of changes which would not normally require justification in terms of additional stability data provided that adequate stability data are available for the existing product (note however that data other than stability data may be required):

- tightening of existing specifications for the drug product consistent with existing stability data, for example narrowing of assay limits for a drug,
- change of site of manufacture of the active raw material or finished products with no other change to pharmaceutical data,
- an additional pack size for tablets stored in a blister pack with no change of packaging materials.

The following general comments may assist sponsors in the accumulation of stability data in particular circumstances.

6.1 Change in Formulation. A proposed change to a completely new formulation would be regarded as an application to register a new product and would require

6.2 Change in Packaging. The major consideration in evaluating a proposal for a change in packaging is the relative protection afforded the product by the new and old packs. If the new pack is shown to be more protective, e.g. an amber screw-capped glass bottle compared with a clear PVC bottle, it is likely that no data would be required. Where the pack is less protective or where some interaction with the container is possible, additional stability data will be required.

For parenteral or ophthalmic solutions in new plastic packs, information on leaching is important. Appendix XIX of the BP 1993 and <661) of the USP XXIII (1995) provide an outline of some of the factors to be considered and test methods. Where the new pack has a greater permeability to moisture, the effects of high humidity on solid dosage forms or the extent of possible fluid loss from liquid preparations should be considered.

7. Prospective Extensions of Shelf-Life for Individual Batches

Under certain circumstances BFAD may approve a limited extension of shelf life for individual batches approaching their expiry date in the absence of the stability data that may normally be necessary. The prerequisites are as follows:

- 7.1 the existing shelf life should be at least 2 years
- 7.2 stability data should be available to BFAD which validate the existing shelf life and show no deterioration of the product during this product
- 7.3 a recent (less than 2 months old) dated certificate of analysis should be supplied for the batch showing compliance with specifications, together with the results obtained at batch release
- 7.4 the company should provide an assurance that it has commenced or intends to commence a stability study to validate a permanent extension of the shelf life

8. Shelf-life Extensions According to an Approved Protocol

Shelf lives may be extended in accordance with a stability test protocol which was approved explicitly for this purpose. Such protocols may be submitted with the application for registration or subsequent to registration. All of the following conditions apply:

- 8.1 BFAD must have explicitly approved the protocol for the purpose of self-assessable shelf life extensions.
- 8.2 All pharmaceutical aspects of the product, including its immediate container and closure and labeled storage conditions, are identical to those approved at the time a stability test protocol was approved, except for changed made in accordance with other parts of this document.
- 8.3 At least two production batches of the product have been tested in accordance with the approved stability test protocol.
- 8.4 The total shelf life is not longer than the time for which stability data meeting the approved protocol are available on two production batches, and in any case is not longer than 5 years.
- 8.5 If BFAD requests copies of the additional stability data, these will be supplied within one month of the request.
- 8.6 Any stability test protocol proposed for this purpose should include:
 - 8.6.1 A statement of the proposed tests and test methods.
 - 8.6.2 A matrix indicating the time stations at which each of the tests will be conducted.
 - 8.6.3 Acceptable limits for results for each test

Note that:

- BFAD may impose conditions on the implementation of an approved test protocol, such as a maximum total shelf life of less than 5 years and
- To provide a suitable safety margin, the acceptable limits for results should be somewhat tighter than expiry specifications. If results are outside these tighter limits but within expiry specifications, the sponsor has the option of submitting the data for evaluation with an argument as to why the shelf life should be extended.

Stability Guidelines Appendix I

Acceptable Temperature Storage Conditions Which may Appear on Labels

1. Store below - 18°C (Deep freeze)
2. Store below - 5°C (Freeze)
3. Store below - 8°C (Refrigerate)
4. Store below - 8°C (Deep freeze)
5. Store at 2 to 8°C (Refrigerate. Do not freeze)
6. Store below - 25°C

Stability Guidelines Appendix 2

Common Deficiencies in Stability Data and Trial Design

To assist sponsors in the design and reporting of stability studies, a list of deficiencies which are commonly encountered and which lead to question and delays in approval of a shelf life are given below.

1. Failure to specify the formulations used in the trial, and to state which batches are identical to the formulation that will be registered in the Philippines.
2. Failure to state whether the batches used in the trial were the pilot or production batches.
3. Failure to describe clearly the packaging used in the trial and to confirm whether it is identical to the pack which will be used in the Philippines.
4. Failure to accumulate stability data on more than one batch of the product.
5. Failure to define accurately the temperature, lighting and humidity conditions applied during the trial.
6. Failure to fully describe test methods and sample sizes.
7. Failure to provide validation of analytical methods
8. Expression of results as "passes test" or similar when a quantitative figure would be available.
9. Failure to include quantitative or semiquantitative determinations of the content of degradation products, or to provide only total content rather than values for individual impurities.
10. Use of an HPLC assay procedure to detect impurities without validation for the purpose. HPLC assay procedures as used for determination of the active ingredient are often unsuitable for separation and detection of impurities as they use too short a run time. Such a procedure would be acceptable if validated for impurity detection. (Note, however, that long run times do not in themselves ensure good separation.)
11. Failure to comment or conduct additional tests when there is a lack of mass balance between the formation of degradation products and the loss of the active substance. For example, are the assay procedures sufficiently specific? Is the drug volatile? Is it adsorbed on to the container wall?
12. Failure to conduct additional tests to investigate the significance of obvious alterations in the characteristics of the product. For example a distinct change in the colour of the product may necessitate additional investigation for degradation products.
13. Failure to include information on the physical characteristics of the product during storage, such as dissolution characteristics, homogeneity, particle size etc.
14. Failure to reconstitute radiopharmaceuticals at the activities and radioactive concentrations that would be used in a clinical situation.
15. Failure to include stability studies under conditions of high humidity for products which are to be registered in moisture permeable containers, and especially for those which are potentially labile to moisture such as antibiotics.
16. Failure to provide results from intermediate time stations to facilitate assessments of any trends in the parameters measured.
17. Failure to provide results for individual dosage units where these are available, for example dissolution profiles.
18. Attempting to extrapolate data obtained in the trial beyond reasonable limits.

Stability Guidelines Appendix 3

Glossary of Terms

Active Raw Material: The unformulated active chemical substance, usually a powder or a liquid, in the form in which it is used to manufacture the dosage form, usually in combination with excipients.

Direct Scales: Products are said to be direct scales if the same granulated or mixture of powders is used to manufacture the various strengths, but the products are compressed or filled at varying weights corresponding to the various strengths.

Dosage Form: The pharmaceutical form in which a product is presented for pharmaceutical administration, for example, tablet, injection, cream, suppository, etc. Note that modified release formulations are not the same dosage form as their conventional counterparts, for example, a sustained release tablet and a conventional tablet: a depot injection and an aqueous solution for intramuscular injection.

Finished Product: For the purposes of this document, the finished dosage form when all stages of manufacture have been completed to the stage of packaging in the immediate container (e.g. ampoule, tube, sachet, blister etc.)

Labels: The labels on the container (e.g. ampoule, tube, sachet, blister etc) and on any carton or other overwrap which is part of the primary pack.

Impurity: An unintended component of a substance or product. Impurities include degradation products, by-products of chemical synthesis and contamination from any other source. A degradation product may be an isomer, for example, following racemisation.

Pharmaceutical Data includes:

- the method of synthesis or biosynthesis, proof of structure and purification of the active raw material
- the formulation, method of manufacture and stability of the finished product
- specifications (including test methods) of the active raw material, excipients and finished product
- labelling, including shelf life, storage conditions and recommendation for processing prior to use (e.g. reconstitution of a powder for injection)
- bioavailability as applicable

Pilot Production Batch: A quantity of product which is identical in formulation and equivalent in terms of manufacturing equipment and manufacturing method to a production batch, except for scale.

Semiquantitation: "ballpark" assays and therefore less desirable than true quantitation. Two techniques are common:

1. for unknown impurities, a result is assigned on the basis of comparison with known concentrations of the drug substance, e.g. by colour depth on a TLC plate. This technique is not preferred as (1) the assumption of similar physicochemical properties for the degradation product and the drug substance may be incorrect, and (2) even if the assumption is correct, the technique is only approximate. It is generally used only in cases where the degradation product has not been identified and is present in only trace amounts.
2. where the degradation product has been identified but is present in very small quantities, a result is assigned on the basis of comparison with known concentrations of the authentic degradation product.

In both cases, results are expressed as, for example, 'less than 0.055' or 'between 0.01 and 0.055'. Expression of results as "trace amounts" is discouraged as there should normally be some estimate of the limit of detection.

Stability Guidelines References

1. "British Pharmacopoeia 1993" Department of Health and Social Security, UK (1993)
2. "United States Pharmacopoeia" XXIII United State Pharmacopeial Convention (1995)