CURAÇAO

INSPECTORATE OF PUBLIC HEALTH

BUREAU OF PHARMACEUTICAL AFFAIRS

NEW DRUG APPLICATION

Applicant

An applicant can be a person or agency who holds a license to function as a wholesaler of pharmaceutical products on Curaçao.

Application Form

An official application form has to be filled and signed by the applicant or his/her asignee. This application form can be obtained at the Secretariat Drug Registration, Bureau of Pharmaceutical Affairs.

Language

The application and registration dossiers are accepted in English, Dutch, and Spanish (special permission required).

Drug Registration Fee

New Drug Application	Naf 500.00
Abbreviated Drug Application	Naf 500.00
Re-registration	Naf 250.00

Payment can be made by depositing the sum on a Drug Registration Board (DRB) account.
Giro account number: 1500047
A proof of payment has to be included with the official application form.

Registration Procedure

The first step after the submission of a registration dossier is to check whether it is complete. If the file is not complete, it is sent back to the applicant for additional information. (The official application date is the date when a complete registration file is submitted.)
The file is then reviewed by the secretary and members of DRB and a report of findings and recommendation is made. The report is discussed by the committee during its meetings, and a decision is then taken.
The analytical part of the registration dossier is sent to the laboratory for quality control tests. A negative result from the lab results in denial of registration. The outcome of the DRB meeting is processed by the administrative personnel of the Secretariat. Notice of Registration or Reregistration with the official registration number, country of origin and sales-category status is then sent to the applicant.
The duration of registration procedure is approximately 4-6 months.

Maintenance of Registration (Renewals)

The registration of a pharmaceutical product is valid for 5 years after the date of registration. After the 5 years, an official re-registration procedure has to be followed. It is not an automatic procedure. The DRB will re-evaluate the application. Reregistration of a pharmaceutical product requires the following information:

- A recent (at the most 1 year from date of issue) or valid 'Free Sale Certificate' (FSC) or Certificate of Pharmaceutical Product (CPP).
- The complete composition of the pharmaceutical product.
- Samples of labels, packages, and inserts.
- Proof of payment.

At the end of the 5-year registration period of a product, the Secretariat will send a letter of notification to the agent. If the agent does not respond within the deadline specified in this letter, the registration of the product will be canceled automatically. In order to re-register the product, an abbreviated drug application procedure will apply.

Cancellation of Registration

For reasons of safety, efficacy and/or quality, the Minister of Health, Environment and Nature or the DRB may decide that a particular pharmaceutical product can not continue on the market on Curaçao, and subsequently the registration of the product will be suspended or cancelled.

Changes

The DRB must be immediately notified, in writing, of any changes in for example, formulation and/or presentation of the pharmaceutical product. The change(s) and reason(s) for the change(s) have to be described accurately, and accompanied by relevant pharmaceutical and chemical data. When necessary, toxicological and clinical data will be requested.

Contact/Correspondence:

The Secretariat of the Drug Registration Board can be reached at:

The Inspectorate of Public Health, the department of Pharmaceutical Affairs.
Schouwburgweg 24-26, APNA-Plaza, Gebouw “E”
P.O. Box 3824 (for correspondence)
CURAÇAO.

Phone: +599-9-466.9366
Fax: +599-9-466.9367
Email: **cleopatra.hazel@gobiernu.cw**

GUIDELINES FOR THE COMPILATION OF REGISTRATION DOSSIERS FOR CURAÇAO

When an application is made for the registration of a pharmaceutical product, the following information is to be submitted:

I. General Information
II. Chemical and Pharmaceutical Data
III. Toxicological and Pharmacological Data
IV. Clinical Data

The registration dossier has to be arranged in four separate parts:

- *Part One* containing **I. General Information.**
- *Part Two* containing the duplicates of **II. Chemical and Pharmaceutical Data.** This is to facilitate the registration procedure, since the analytical part can be sent to the committee members and to the laboratory at the same time.
- *Part Three* containing **III. Toxicological and Pharmacological Data.**
- *Part Four* containing **IV. Clinical Data.**

All data are to be arranged in the dossier in such a way as to make the information provided easily retrievable. Reference to the numbering applied in these guidelines is recommended. For names of active ingredients only official nomenclature (INN, USAN, a pharmacopeia) should be used. Metric units (SI specifications) should be used for quantitative descriptions.

I. General Information:

1. Application form filled and signed by the applicant or his/her asignee. For each pharmaceutical product and for each dosage form, a separate application for has to be submitted. For the same dosage form but in different strengths, one application form including all the strengths may be submitted.

2. Administrative Data.
   Name of the pharmaceutical product;
   Name and quantity of active ingredients;
   Dosage form and strength;
   Name and address of the manufacturer;
   Three each of labels, cartons, package inserts, trade packages and other material promoting the Pharmaceutical product in actual size.

3. Summary of product characteristics: clinical and pharmaceutical particulars.

- *The clinical particulars:*
  Therapeutic indications;
  Dosage and method of administration;

Contra-indications (also rare cases where the product should never be given, this must be specifically outlined);
Special warnings and special precautions for use;
Interaction with other medications and other forms of interactions;
Pregnancy and lactation;
Effects on ability to drive and use machines;
Adverse events and adverse drug reactions;
Overdose (animal and man);

- *The pharmaceutical particulars:*
  Incompatibilities;
  Shelf life;
  Storage conditions;

4. Free Sale Certificate.
   According to the current laws, at the time of registration (new drug application), a recent (at least 1 (one) year from date of issue) or valid 'Free Sale Certificate' (FSC) or Certificate of Pharmaceutical Product (CPP) should be included in the application-dossier.
   A Free Sale Certificate is a certificate issued by the competent authority in the country of drug origin stating that the pharmaceutical product mentioned on the certificate is:

   a) *if it concerns a pharmaceutical product:*
   - manufactured in that country;
   - the production is done according to GMP-rules;
   - the manufacturing plant is inspected on a regular basis by the competent health authorities;
   - the product is duly registered and actually being sold in the country of drug origin;

   b) *if it concerns a product which in the country of origin is not considered a pharmaceutical product:*
   - a certificate from a competent authority (on food, medical devices, commodities, etc) stating the product is manufactured in that country;
   - is actually permitted and being sold on the market of the country of origin, without any special restrictions.

By definition, drug origin is the company and country where the last pharmaceutical handling takes place. If more than one company are involved, it has to be clearly stated which company does which procedure.

5. List of countries where the pharmaceutical product is registered and/or is withdrawn from the market, specifying the year of licensing and/or withdrawal. In case of a withdrawal, an explanation should be provided.

II. Chemical and Pharmaceutical Data

A. Composition

1 Complete quantitative and qualitative composition of the pharmaceutical product.

B. Method of Preparation

1 Manufacturing Formula

The names, grades and actual quantities of the active ingredient(s) and constituent(s) involved in the manufacturing procedure are to be stated.

Overages are to be indicated in quantitative terms and the reasons for them are to be given.

2 Manufacturing Process

The manufacturer of the pharmaceutical product should proceed under conditions that comply with the Code of Good Manufacture Practices (GMP).

A concise description of the manufacturing process has to be stated. A step by step description of the pharmaceutical assembly process should be outlined.

C. Analytical Procedures

1 Control of Starting Material

The requirements for quality and standards of all materials used are to be stated, and reference made to an official pharmacopoeia. Pharmacopoeia recognized by DRB are: European, British, Dutch, and United States Pharmacopoeia. If no official pharmacopoeia can be referred to, mention is to be made of specific identification reactions, requirements for purity and method for determining this purity together with the variations allowed (if possible with some reference to the literature available).

2 *Control of Intermediate Products*

In-process controls are to be stated. Methods for indication and specifications of intermediate products are to be described, especially in cases where in-process control is of importance for quality parameters that can not be checked on the final product.

3 Control of Finished Products

I Identification tests

Method of identification of all active and inactive ingredients in the final product.

The identification reactions must be as specific as possible and a complete description is to be given.

- The quality specifications should include:
  Information on appearance of the product, color, shape, dimensions, and other distinguishing features
- Tests for content uniformity, particle size, dissolution rate, pH, etc.

II Assay

Validated analytical methods for the quantitative analysis of all active constituents are to be stated. These methods should be clearly described and should be up to date with the present scientific procedure and results should be reproducible. The description is to be such as to enable the test to be repeated in the Government Laboratory. Bulk drug in sufficient quantities (roughly 1gram) to allow repetition of the assays and verification of control procedures should be submitted. A signed certificate of analysis should be submitted. Information to be included are:

- Principles
- Apparatus
- Reagents
- Standards / Reference materials
- Procedures
- Calculations and formulae used

An additional fee of NAFl. 800.00 will be required by the lab for testing.

III Impurity tests

Validated analytical methods to assess the purity of the drug substance. Possible Impurities should be stated and the allowable quantities are to be specified.

IV Dissolution tests

For solid dosage forms, dissolution tests are to be included.

D. Stability Data

1 Chemical Stability and Physical stability of the Finished Product

The criteria for the evaluation of stability have to conform to tropical conditions, i.e. temperature ± 30° C and relative humidity of ± 60 %. The length of the stability studies should be at least 12 months. Frequency of testing should be every 3 months over the first year, every 6 months over the second year, and then every year.

Validated stability indicating testing methods must be applied and clearly stated. The results of the stability tests of at least three batches are to be tabulated, with the testing conditions (initial values, type of container, humidity, temperatures, and times of storage) clearly defined. The results of accelerated tests, at 40° C and relative humidity of 70% for six months, are accepted. However, tests covering at least 12 months or the whole shelf-life have to be submitted as soon as available.

The data submitted should reflect the shelf-life claimed by the manufacturer. The method of shelf-life calculation should be included.

Finally, the conclusion with the shelf-life and storage conditions that the manufacturer intends to print on the pack has to be stated.

E. Bio-equivalence studies (for Generics only).

III. Toxicological and Pharmacological Data

A. Toxicology

1 Acute toxicity

Toxicity testing after one-dose should be summarized. Toxic symptoms should be described as well as any other relevant information.

2 Sub-chronic and chronic toxicity

Toxicity testing after prolonged administration should be summarized. The duration of the test, route of administration and the species used in the testing should be specified. For each investigation the dosage is to be stated as well as the number of animals per dose level, the sex of the animals and how frequently the drugs have been given.

3 Fetal toxicity and fertility studies

A test for teratogenic and other embryotoxic effects should be summarized. For each investigation the dosage is to be stated as well as the number of animals per dose level, the sex of the animals, and how frequently the drugs have been given.

4 Mutagenicity

Summaries of the tests of mutagenic effects stating the animal species, route of administration, and dosage. The mutation rate is to be reported for each dosage or concentration.

5 Carcinogenicity

Carcinogenicity testing must be done for substances which resemble known carcinogenic chemical compounds, and for substances intended for long periods (such as in chronic diseases).

B. Pharmacology

1 Pharmacodynamic

The mechanism of action of the active ingredient should be explained.

The primary effects, i.e. the action relevant to the therapeutic uses, are to be adequately described.

State the results in terms of dose-effect curves, time effect curves, the optimum dose and the therapeutic index.

The secondary effects, i.e. any action other than that relevant to the therapeutic uses, are to be included.

The activity of the active ingredient should be compared with a substance of which the activity is well known.

2 Pharmacokinetics

For the intended routes of administration, the following pharmacokinetics data should be provided:

Absorption.

Distribution.

Metabolism.

Excretion.

IV. Clinical Data

A. Clinical Data

The minimum requirements are: three controlled studies, one open study, and the experts reports.

The aim of the clinical study should be clearly stated. The study has to be described in terms of its type (controlled, open), its design (parallel groups, crossover techniques), blind technique (double blind, simple blind) and randomization (method and procedure).

The patient group selection criteria (inclusion, exclusion) should be described, with the number of patients included in the study and a justification thereof.

The route of administration, dosage form, dosage, dosage interval, and treatment period for the drug tested and the drug being used as control are to be stated.

Any possible drug - drug interactions and/or interactions with environmental factors should be studied and the findings should be reported.

Pre-marketing studies to assess adverse drug reactions are to be described and the results recorded.

If post-marketing surveillance reports are available, then they should be included.
