Form A Regulation 5(3)

SCHEDULE IV

INFORMATION REQUIRED FOR REGISTRATION OF A DRUG.

1. Name of applicant.....

2. Address.....

3. Status of applicant:

Manufacturer ……..

Importer .....

If applicant is Importer, the name and address of the Manufacturer must be given.

4. Name of the drug.....

(1) Brand name (if any):.....

(2) Official or approved name indicating the official body that has given the name (whether B.P., U.S.P. etc.).

5. Dosage form of the drug. e.g. tablet, syrup, injection.

6. Composition.-
All ingredients, active and inactive, should be listed by their official or approved names and
should include their exact quantities as per unit dose or if it is not practical, as percentage
of the total formulation.

7. Main pharmacological group and ATC-class (if known) to which the drug belongs: (e.g.diuretic etc. C 03 C A 01).

8. A certificate from the health authorities of the country in which it is produced, confirming
that the drug is in use there and the period of use and if not, reasons for not marketing it in
the country of origin (Free Sale Certificate, Certificate according to the W.H.O. Certification Scheme on Pharmaceutical Products moving in International Commerce – the
recommended format should be used).

9. Published reports on controlled clinical trials.-establishing the therapeutic efficacy of the drug. (Uncontrolled studies would be accepted only if controlled clinical trials are not necessary to prove efficacy). In the case of combination drugs, evidence must be

provided
to justify the inclusion of all the active constituents in the formulation.

10. Summary of toxicity tests and tests for teratogenicity indicating the safety of the drug.

11. Data sheet giving the following information:

A) Pharmacology

Pharmacological actions
Mechanism of action (if known)
Relevant Pharmacokinetic data
Bioequivalence/Bioavailability data (when necessary)

B) Clinical Information

Indications
Contraindications
Precautions
Warnings
Adverse effects
Drug interactions
Dosage regimen
Average dose and dose range for adults and children
Dosing interval
Average duration of treatment
Dosage in special situations e.g. renal, hepatic and cardiac insufficiency

Overdosage:

Brief clinical description of symptoms
Treatment of overdosage
Post-marketing surveillance data for new drugs (new chemical entities)

C) Pharmaceutical Information

a. Dosage form and strength.
Separate applications have to be submitted for different strengths of the same product/dosage form.

b. Description of the product.
Description of the physical characteristics of the product. This should include where

applicable:- shape, size, superficial markings for identification purposes, colour, odour, taste, consistency, type of tablet coating (e.g. sugar-coated, film-coated, enteric-coated, delayed release, etc.).

When describing liquids, state clearly whether it is in the form of a solution, suspension, emulsion, etc.

c. Packing and Package sizes.

State here briefly the types of immediate container or packing and the pack sizes e.g.

Tablets - bottles of 100's, 500's, blister pack - 50's etc.
Details must be provided under H.

d. Manufacturing formula.

Names, quantities and reference to quality standards of all ingredients including those

which will disappear during the manufacturing process (i.e. water, alcohol used for granulation etc.).
If the quality standard of an ingredient is not included in one of the official pharmacopoeias, the manufacturers own specification and test method must be submitted.
For injectable preparations total content in each unit container should be given.

Overage.

Where an overage is included, state name of the ingredient and amount.
State also the reason for including overage, i.e. whether overage is to cover loss of potency on storage, to permit withdrawal and administration of labelled volumes, required doses, etc. supporting data for inclusion of overage should be enclosed.

e. Manufacture of Product.

If desired, information required under this heading can be enclosed in a sealed envelope marked "Confidential".

Complete Manufacturing Master Formula.

Give the actual batch manufacturing master formula with names and quantities of all ingredients (active and inactive) Substances which are removed in the course of manufacture should be included.

Manufacturing process.

A description of all stages involved in the manufacture of the dosage form is required,

eg. manufacture of tablets:

Stage 1 : Mix ingredients

Stage 2 : Moist granulation

Stage 3 : Fluid bed drying at 60 C

Stage 4 : Rotary punching

In the full description of the manufacturing process (to be enclosed separately) there should be sufficient details to cover the essential points of each stage of manufacture, such as steps in the comminution of ingredients, method of mixing, order of incorporation of ingredients, fluid media used in moist granulation, drying process, clarification process, formation of final dosage form etc. including methodology, equipment, operating parameters (e.g. temperature, pH adjustments, processing time, sterilization conditions) used in each stage of manufacture. For sterile products, description should include preparation and sterilization of components (i.e. containers,

closures etc.).

Validation of important manufacturing operations.

Important production processes have to be validated and the relevant reports submitted.

Validation is defined as "the obtaining and documenting of evidence to demonstrate that

a method can be relied upon to produce the intended result within defined limits". Validation should be able to prove that a process yields e.g. homogeneous tablets, capsules or suppositories, or sterile drugs.

Packaging operations.

A description of the packaging of the product into the final containers (immediate and

outer) with information on any special precautions taken,
e.g.:
Stage 1 : bulk cream filled into 10 g jars by automatic dispensers.

Stage 2 : automatic weight check

Stage 3 : automatic labelling

Stage 4 : manual transfer to cardboard boxes and sealed.

In details enclosed separately, describe the steps, equipment, flow and precautions for

each of the packaging operations.

f. Quality Control.

This section must give a complete account of the tests which will be carried out routinely

on each batch of product and its ingredients and must state the specifications with which

any sample (ingredient or finished product) would be expected to comply.)

Name(s) and address(es) of person(s)/organization(s) performing quality control tests, if

not done by the manufacturer's own quality control department must be given.

Quality control of starting materials (active and inactive).

Specifications and test methods are required for each ingredient used in the manufacture of the product.

Where an ingredient is subject of a current pharmacopoeia it is sufficient to make appropriate references. Copies of relevant monographs need not be attached.

Where specifications are those of the manufacturer's supplier's or any other source, full details of specifications and test methods must be submitted. Source of specifications and test methods must be indicated.

Test methods should be in sufficient detail so as to be reproducible in tests carried out by another laboratory.

If any specification or test is omitted or modified in any way from the original documents, such omissions/modifications must be clearly stated with reasons. This includes additional tests, variations and changes in test conditions, reagents etc. Modifications, additions, substitute tests, etc. must be described in detail.

Indicate clearly whether the ingredients are bought to a purchase specification with a certificate of analysis, or tested by the manufacturer (or his behalf) for compliance of specification.

Control of intermediate products - in-process control.

Specifications and test methods for in-process control must be submitted especially in cases where such control is of importance to quality parameters that can not be checked in the final product.

A detailed description is particularly important when the finished product contains low dose of active ingredient or if the product is sterile.

Control of procedures in filling, labelling and packaging operations must be described.

Control of the finished product.

The quality specifications of the finished product must be submitted. These should include the appropriate tests and requirements concerning the pharmaceutical properties of the dosage form such as uniformity of mass, content uniformity, disintegration. In addition the following tests should be considered: Particle size, dissolution rate, pH etc.

If bioavailability/bioequivalence studies for tablets and capsules are not performed, at least dissolution tests must be performed on tablets/capsules contained in the USPXXII even though the product is subject to a monograph which does not specify a dissolution test.

The specification should also cover:

- identification of active ingredient(s)
- quantitative determination of active ingredient(s) and preservatives.
- tests for impurities
- tests for degradation products

If a product is subject of a monograph in a current pharmacopoeia, it is expected to comply with the specification for that product as well as the general requirements of the general monograph for the dosage form.

Availability/Release rate of active ingredients (in-vitro tests):

Evidence of dissolution rates is particularly important for the following:

where the drug is of sufficient potency and importance to warrant such investigation.

where the therapeutic dose of the drug is close to its toxic dose.

where solubility or other physicochemical properties of the drug indicate that any change in formulation, or source of ingredient might alter the therapeutic efficacy or safety of the drug.

where specific excipients, coating and other ingredients may affect or alter the dosage form performance e.g. dissolution, disintegration, drug release rate, etc. special formulations e.g. controlled release tablets, depot injections, etc.

g. Information concerning shelf-life, stability and storage conditions.

State proposed shelf-life of the product with recommended storage conditions (temperature, humidity, light, oxygen etc.)
The recommended storage conditions must be included on the label.

If the product is to be reconstituted before use, the shelf-life/expiry period of the original product as well as the reconstituted product should be stated.
The manufacturer must provide evidence to the effect that the product retains acceptable strength and pharmaceutical quality throughout its shelf-life.

Describe stability studies performed and completed on the product, outlining study protocols, conditions and parameters, characteristics/degradation products monitored, results and conclusion of studies.
Results must be presented in an illustrative form, tables or graphs. Batch number, type of container and storage conditions have to be stated in the reports.

The stability studies must be carried out on the product packed in the container in which it is going to be marketed (sales container).
If the stability studies are carried out on product not packed in the sales container, evidence must be given that the container used is equivalent to the sales container.

In view of the fact that sufficiently long experience of storage of new products has

often not been accumulated when an application is made, the results of accelerated tests may be accepted for a preliminary shelf-life. Stability of the product must be followed up at suitable frequency in relation to its shelf-life, on a suitable number of regularly produced batches.

The manufacturer must outline his programme for further stability studies (frequency, number of batches, storage conditions etc.).

Analytical methods used in stability studies must be given, supplemented with documentation of their ability to detect possible changes.

Changes in composition, the manufacturing process or the container or packaging material may necessitate renewed stability studies and revised shelf-life.

h. Packaging materials.

The manufacturer should supply data on the material from which the container and the closure are produced. For plastics, the name of the material, name of manufacturer, chemical structure and physico-chemical properties must be submitted.

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

Quality specifications of the container and closure must be submitted.

12. List of countries in which the drug (the applicant's formulation/product) is approved or registered for sale.

13. .Fully packed samples of the drug in the form that it will be offered for sale should also be sent,
to enable analysis of the product with Certificate of Analysis of the product.

15. A sample of the label(s) used on the container should be supplied.

16. Product information leaflet (PIL).

17. All data should be submitted in English, organized as this schedule IV, with an index in a hard
file cover. (A copy should be kept with the applicant.)

18. All pages should be numbered (starting from the last page).

19. A blank sheet should be pasted on the inner side cover to be used as a minutes sheet.

APPLICATIONS MADE WITHOUT THESE REQUIREMENTS WILL NOT BE ACCEPTED.