SOP No.	Revision	Issue date	Page 1 of .....
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Effective date			Prepared by:
Standard Operating Procedure			Reviewed by:
			Authorized by:

COSMETICS, DEVICES & DRUGS REGULATORY AUTHORITY PROCEDURES

STANDARD OPERATING PROCEDURE FOR REGISTRATION OF PRODUCT DOSSIERS

Purpose:

Purpose of this document is to describe the procedure for registration of product dossiers..

Scope:

This procedure applies …….

Responsibility:

Procedure

Step 1 — Applicant submits **duly compiled application [Annexre A& B; Schedule IV, Form A/Form B, Regulation 5(3)] along with the duly completed check list, Sample Licence, company approval letter, COPP(original), COA (original), Stability Data (Original), numbering (bottom to top) and Valid wholesale Licence to pharmacist (1).**

Step 2 — Pharmacist (1) verifies against check list **(Annexure….**Checklist (to be developed)**)**.

Step 3 — Pharmacist (1) decides the category of payment (whether NCE, Generic or NDF) and issues payment letter.

Step 3 — Applicant makes the payment to the shroff counter of the Ministry of Health. The applicant receives a yellow receipt from the shroff.

Step 4 — Yellow receipt is date stamped at the CDDA and **entered in a register** by the Health Management Assistant (1).

Step 5 – — Date stamped yellow receipt, copy of the date stamped payment letter and acknowledgement letters (2) [Annexure E] is submitted to pharmacist (1). Pharmacist (1) cancels the yellow receipt.

Step 7 — pharmacist (1) signs and date stamp acknowledgement letters, allocates a serial number to the application, enters the serial number **(with coding)** in the yellow receipt and an acknowledgement letter is returned to the applicant while keeping one acknowledgment letter with the application. Two samples have to be submitted by the applicant to the pharmacist (1) at the same time.

Step 8 — Samples are sent to the sample room by the pharmacist (1). Samples that have to send to the NDQAL **(specify criteria: Annex)** are forwarded to the pharmacist (2).

Step 9- The data regarding the submitted dossiers are fed to the database and applications are forwarded to the record room. Health Management Assistant (1) accepts the applications and acknowledge.

Step 10 Health Management Assistant (1) enters the serial numbers of received applications into a register and forwards to the D/MT&S. D/MT&S assigns the applications to Pharmacists in sequential order for evaluation.

Step 11 Applications are forwarded to the pharmacists (3) along with the sample (pharmacist 2).

Step 12 Pharmacist (3) makes recommendations upon evaluation and forwards to D/MT&S for signature.

Step 13 **D/MT&S approves/rejects, signs and forwards to pharmacist (4) to table at the DESC for the final approval.**

Step 14 After submitting to the DESC, pharmacist (4) forwards file to Health Management Assistant (2) & (3). If any changes are made by the DESC, pharmacist (4) re-evaluates the application.

Step 14 Health Management Assistant (2) sends the rejected dossiers to the record room and enters in a register. Inform to the applicant.

Step 15 Health Management Assistant (3) receives approved dossiers. Health Management Assistant (3) issues Payment Letter.

Step 16 Applicant makes the payment to the shroff counter of the Ministry of Health. The applicant receives a yellow receipt from the shroff.

Step 17 Applicant submits date stamped Yellow Receipt within 14 days to Health Management Assistant (3) <u>If not, Application will be sent to Record room.</u>

Step 18 Health Management Assistant (3) cancels the yellow receipt, attach the registration certificate to be typed [Annexure ….; Schedule IV, Form D,

Regulation 6(2)] to the application and indicates the relevant certificate number & date in the yellow receipt.

Step 19 Health Management Assistant (3) forwards the certificate along with the other documents to the typist for typing.

Step 20 Typist submits the typed registration certificate with two copies to Health Management Assistant (3).

Step 21 Health Management Assistant (3) will submit typed registration certificate with two copies to pharmacist (4) for checking. **Pharmacist checks the licence. If any corrections are noted, send back to the typist/ Health Management Assistant.**

Step 22 Pharmacist (4) will sign in a copy (green/blue) of the registration certificate after checking, enter in a register and forward the registration certificate with two copies to D/MT& S for signature.

Step 23 D/MT& S will sign and forward to Health Management Assistant (4).

Step 24 Health Management Assistant (4) issues the Registration Certificate to Importer while attaching a copy to the dossier and sending the other copy to the data entry operator. The data entry operator enters the required data in the database and return **to the Health Management Assistant (4). Bind..**

Pre requisites for applying for product registration.

(i) Company profile needs be approved.

(ii) Sample Licence needs be submitted.

(iii) Dossiers need be indexed in ascending and descending order and fully complied as per stipulations.

(iv) Duly completed checklist

(iv) Importers regulatory Pharmacist need provide certification to state that Dossiers has been complied as per check list i.e. in addition to that as at schedule iv Form B of CDDA.

Notes: 1. NCE, NDF and vaccines are sent to the DESC before starting the evaluation.

2. Vaccines - Submitted to MRI with samples to the external evaluator ensuring storage requirements.

3. Generics - (a) Established manufacturers

(b) New Manufacturers – Samples to be submitted to NDQAL

(c) Products requiring DESC Opinion and Quality Analysis

ANNEXURE "A"

Form B

Regulation 5(4)

SCHEDULE IV

APPLICATION FORM FOR CERTIFICATE OF REGISTRATION OF A DRUG BY AN IMPORTER

(To be filled in triplicate by applicant)

I/We ..... of .....hereby apply for registration of the drug namely .....details of which are enclosed herewith.

Signed :.....,

Address :.....,

Designation of applicant :.....

For official Use only

Application No. :..... Dated :.....,

Decision : Registered/Not registered. Dated :.....

Registration No :..... Dated :.....

Fees paid :..... Receipt No :.....

Date :..... Signature :.....

Authority

Annexure "B"

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.

ANNEXURE "C."

FORM AP 1

To be filled in duplicate.

ACKNOWLEDGEMENT OF APPLICATION FOR REGISTRATION OF A DRUG

1. Name of Local Importer : ……
   Address : ……

   ……

   ……

2. Name of Drug-Generic : ……
3. Dosage form : ……
4. Strength : ……
5. Name of Manufacturer : ……
6. Country of Origin : ……
7. Two Samples : ……

8. Sample Licence No. : ……

9. Processing Fee : ……

Payment Receipt No.: ……..

Date : ……

Received the above application.

Date …… …….

Signature of the Receiving Officer

ANNEXURE "D"

Form D

Regulation 6(2)

SCHEDULE IV

CERTIFICATE OF REGISTRATION

Certified that the following drug is hereby registered under the Cosmetics, Devices and Drugs Act No. 27 of 1980.

Name of Drug :.....

Dosage form :.....

Name of manufacturer :.....

Country of manufacture :.....

Name of Importer :.....

Registration No. :.....

Date of Registration :.....

Type of Registration :.....

Full Registration :.....

Provisional Registration :———.

Period :.....

Schedule :

Full registration shall be valid for a period of 5 years unless earlier suspended or cancelled.

Provisional registration shall be valid for the period stipulaed.

Date of issue :.....

.....,
Authority.

ANNEXURE "E"

Evaluation form – Drug Registration Applications

Pharmaceutical Documentation

Application Number:

Date of submission of the application:

Date taken for evaluation:

Name of the evaluator:

A	**History of quality failures**		
	Product withdrawals/ batch withdrawals report with this manufacturer	Yes	No
	If Yes, attach a report		

B	**Application Type**			
		Check		
	1. New Chemical Entity (NCE)		DESC approval	
	2. New salt or ester of an existing drug		DESC approval	
	3. New Generic Product (NGP)		-	
	4. New Combination Products (NCP)		DESC approval	
	5. New dosage form of an existing drug		DESC approval	

	6. New strength		DESC approval	
	7. Vaccine		DESC approval / Expert comments	
	8. Blood product		DESC approval/ Expert comments	
	9. Bio-tech Innovator Product		DESC approval	
	10. Bio-similar product		DESC approval/ Conformity to guidelines	

C	**Availability of office documents**		
	1. Approval letter of the manufacturer		
	2. Sample importation licence		
	3. Wholesale licence		
	4. Form A, Schedule IV		
	5. Form B, Schedule IV		

D

1	Generic name (INN)	
	Trade Name	
	Whether this trade name is already registered?	
	If Yes, to change the brand name	
2	Dosage form	

3	Strength	

5	**Type of Manufacturer**	
	1. Local	**2.** Foreign

6	**Foreign manufacturer**				
	Actual manufacturer	Licence holder	Contract manufacturer	Distributor	
	1. Is the applicant is authentic to submit application of this manufacturer				
	2. Is this **manufacturer/plant** is approved?				

7	**Regulatory situation (licensing status) in other countries**	
	List other countries where the product is registered and currently marketed :	

8	**Local Manufacturer**		
	1. Formulation approval		
	2. GMP approval for the product		

9	**Certificate of a Pharmaceutical Product**		

	1. Original	Yes	No
	2. Addressed to Sri Lanka	Yes	No
	3. Valid at the point of submission	Yes	No
	4. Signed by the designated person	Yes	No
	5. Product registered and currently marketed		
	6. Product registered for marketing in the country of manufacturing but not currently marketed	Yes	No
	7. Product registered for export only	Yes	No
Comments			

10	**Packaging**			
	Pack type	Primary pack	Secondary pack	
	Pack size	Primary pack	Secondary pack	
	Whether the secondary pack include any other (Ex. Dropper or other measuring device, syringe, solvent pack etc) . Specify:			

	Comments		
11	**Composition of the products** All ingredients, active and inactive are listed by their official or approved names and include their exact quantities as per unit dose or if it is not practical, as percentage of the total formulation.	**Yes**	**No**
	Dosage form and strength.		
	Description of the product. (specify)		
	Manufacturing formula.		
	a. Master Formula		
	b. Specifications and test methods of all ingredients		
	Comments		
	Method of manufacture		
	Comments		
	Validation of important manufacturing operations -		
	a. Reports available - Sterilization		
	b. Reports available - Filling		

12	**Quality Specification**			
	Finished product	Pharmacopoeia: Specify:	In-House	
13	**Active Pharmaceutical Ingredients(s) (APIs)**			
	API quality standard: ☐ BP Edition : …….. ☐ EP Edition : …… ☐ USP Edition :…… ☐ IP Edition: …… ☐ Other specifications or additional			
	Certificate of analysis is attached			
	Name; country of API manufacturer is stated			
	A technical file (including the synthesis route, the site(s) of manufacture, the potential by-products and the potential impurities) is submitted			
	API manufacturer GMP compliance has been certified:			
Comments				
14	**Finished product quality specifications and test methods**			
	☐ BP Edition : …… ☐ USP Edition :…… ☐ Other (*) : ……			

	Attach a copy of the finished product specifications		
	Limits in % for the assay in active ingredient(s) : ☐ 95-105% ☐ 90-110 % ☐ other : ……		
	In case of in-house specifications, test method validation reports are provided		
	The specifications cover:		
	a. identification of active ingredient(s)		
	b. Quantitative determination of active ingredient(s) and preservatives.		
	c. tests for impurities		
	d. tests for degradation products		
	e. dissolution		
	Attach a certificate of analysis for batch release.		
Comments			

15. Evaluation of analytical validation data		
Item	Data provided by the applicant	Acceptable or not? Give comments separately
Is a chromatogram or similar provided		
Specificity		

Linearity		
Range		
Accuracy		
Precision		
Other comments		

16	**Stability**		
	Stability testing data available	**Yes**	**No**
	Claimed shelf-life		
	Recommended storage condition		
	Type of study	Real time	Accelerated
	satisfactory with respect to conditions of study		
	Temperature		
	Relative Humidity		
	Intervals of testing		
	Period of testing		
	Type of container		
Other comments			

17	**Data sheet giving the following information**		
	A) Pharmacology		
	Pharmacological actions		
	Mechanism of action		
	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		
Comments			

18	**Comparison of PIL with the data sheet**

19	**Comments on the sample provided**

20	**Bio- availability**		
	Demonstrated by in vivo bioequivalence study	Yes	No
	Reference product (name + company) :		
	Number of volunteers		
	Performed year		
	Country of study		
Comments:			

21	**Label**		
	Attached a copy	Yes	No
	Comply with regulations		

	Compared with the sample provided		
Comments:			

Recommendation:

Date :…… Evaluator's Signature :……