Check list for Scrutinization of Registration Application / Dossiers

In DRAP's Act, 2012; Pharmaceutical Evaluation & Registration Directorate was established. Accordingly, Pharmaceutical Evaluation Cell has been setup and tasked with evaluation of applied registration applications.

Registration Board in 240th meeting approved check list for evaluation of registration dossiers. The check list will also serve as a guideline for filling applications / dossiers for registeration of drugs.

Registration Board approved following check list for implemetation:

S. No.	Contents of Form-5 & it's enclosures	Required Document/Data to be submitted
1	A cover letter	Letter signed by the director/owner of the company or person specifically authorized on behalf of onwer(s)
2	Evidence of fees paid	i. Bank reciept duly endorsed by STO. ii. Fee required as per Schedule-F of Drugs Act, 1976.
3	Application type on relevent prescribed form	Form-5 (Application form for registration of a drug for local manufacture). Each page signed (original) by authorized / approved production and Quality Control Incharge.
		Form -5 A
		Form 5 D
		Form 5 E
4	Title, name and address of the applicant	i. Attested Copy of DML / Renewal of DML (In case of more than 5 years)
5	Dosage form	Complete Description of dosage form of drug e.g., i. Flim coated tablet ii. Bilayered Layered Tablet (one immediately released and other is sustained released). iii. Capsule with enteric coated pellets iv. Powder for suspension etc.
6	Brand Name of Drug Product	i. Written in capital letters ii. An undertaking that in case of

		resemblance / similarity, the applicant would be liable to change the brand name. In case of approval of drug, the brand name will be checked for resemblance / similarity.
7	The drug product name (proprietary, INN or generic name, pharmaceutical form, strength) with relevant information;	Proprietary, INN or generic name of the applied drug.
8	Strength of API per unit	Strength of applied drug.
9	Pharmacological Group	Reference document of common Pharmacological drug classification or Proposed *ATC* (anatomical-therapeutical-chemical) classification
10	Recomended clinical use Documented evidence based information (Indication, side effects, contraindications, drug-drug and drug-food interaction, overdosage, atc)	i. Evidence of approval by any competant DRA (attach copy) or ii. Authentic Reference Book
11	Proposed rout of administration	Details e.g, oral, etc
12	Proposed Dosage and administration	Detail of dosage e.g, adult, paedeatric and administration procedure, etc.
13	Proposed shelf life and storage conditions	An undertaking stating that before sale of the product; accelerated and real time stability studies of 6 months with undertaking to conduct real time stability studies up to assigned shelf life & report if any result falls outside specifications (with proposed action). The responsibility of genuineness of the data will lie with the applicant.
14	Unit price	Proposed Price & Pack size As per DRAP policy
15	International (name of drug, country where registered or sold and name of company selling the drug or having registration of drug (include supporting documents/proof of international registration)	Complete details regarding international availability specially in FDA, EMA, Health Canada, TGA & MHLW (Japan) i.e., same generic, dosage form & strength etc.
16	Brands available in Pakistan along with name of manifacturer	Complete details i.e., same generic, dosage form & strength etc.
17	Composition (actives and excipients) including statement of quantitative composition, giving the weight or measure for each active substance used in the manufacture of the dosage form	Master formulation with quantities of all the ingredients including excipients.
		Batch size
		Quantities to be used per Batch
		Source of active and inactive starting materials
		Role of inactive starting materials and the Justification of their quantities used. Before marketing of the product an undertaking of submitting data regarding

		Pharmaceutical deveoplemnt. The responsibility of genuineness of the data will lie with the applicant.
18	Outline of Manufacturing method	Evidence of approval of section / manufacturing facility of applied drug (especially in case of dedication).
		Stepwise details of manufacturing process including.
		Precautions/Control required to produce specified quantities of the drug applied for registration and demonetration of cleaning validation procedures.
		Identification & description of Critical steps which may alter the results.
		Data of tests for IPQC including weight variation, hardness, friability, water content, etc.
		Before marketing of the product an undertaking of submitting data regarding Process validation data. The responsibility of genuineness of the data will lie with the applicant.
		Expected yields.
19	Persons under whose direct supervision and control the drug is manufactured with the details i. total number of technical staff and ii. name, qualification and designation of the persons directly supervising the manufacture of the drug applied for registration and any change shall be properly documented and record maintained by the manufacturer.	Total number of technical staff in the Production area along with evidence of approval from Licensing section.
		Name, qualification and designation of the person directly supervising the manufacture of the drug applied for registration.
		SOPs / procedure to record and inform about the change of person.
20	Name of equipment that will be used in the manufacture of the drug applied for registration cGMP compliant or not	List of particular equipment used showing its model, make, serial No., and date of purchase of equipment and capacities along with their status of cGMP compliance.
21	Full description of specifications and analytical methods necessary to assure identity, strength, quality, purity and homogeneicity throughout shelf life drug product.	Specfications of active starting material(s) i.e., API (Active Pharmaceutical Ingredient)
		Specfications of inactive
		Specifications of finished product must be phamacopial (if included) otherwise submit validaion for inhouse specifications, alongwith certificate of analysis of API manufacturer. i. List of all the tests for the applied dosage form (e.g, for tablets, capsules, ointments, sterile products, etc.) ii. stepwise analytical description with

		authentic reference (approved by regulatory body or refernce book) iii. Limits with authentic reference (approved by regulatory body or refernce book)
		Details of Reference standard being used: a) Primary or b) Secondary
22	Name, qualification and designation of the persons who will be responsible for the quality control of the active raw material and finished products	i. Name, qualification and designation of the persons who will be responsible for the quality control of the active raw material and finished products. ii. Evidence of approval the persons working in qualitty control from Licensing section
23	Description of equipment to be used in for quality control of the raw material and finished product	i. List of specific equipments / instruments required for tests of applied drug. e.g., Atomic Absorption Spectrophotometer is required for analysis of minerals. ii. List of equipment used showing its model, make, serial No., and date of purchase of equipment and capacities along with their status of calibration.
24	Labelling and Prescribing information (to be mentioned on the pack/leaflet). specimen or the draft shall be submitted for the following class of drugs. i. CNS drugs ii. Drugs affecting uterine motility iii. Drugs inhibiting Hormonal production iv. Harmones and other steroidal drugs excluding preparations for external & topical use. v. Narcotic/psychotropic drugs	Prescribing information (PI), Patient Information Leaflet (PIL) and Summary of product characteristics (SmPC) as per Approved by Drug regulatory agencies or authorities of FDA, EMA, TGA, Health Canada and MHLW (Japan) for following classes of drugs. i. CNS drugs ii. Drugs affecting uterine motility iii. Drugs inhibiting Hormonal production iv. Harmones and other steroidal drugs excluding preparations for external & topical use. v. Narcotic/psychotropic drugs
	Specimen of lable to be submitted by the manufacturer at the start of production.	Undertaking to submit the specimen of label (for approval) by the manufacturer at the start of production.
25	Facility of water processing with specifications	i. Source of water. ii. Specifications iii. Data regarding test / analysis of water

26	Environmental control processing with details	i. Complete detail of HVAC under which the applied drug will be manufactured Attach data for the following parameters: Particulate matter (Mention the class of area (A, B, C, D or class 100, 10000, 100 000). Humidity, temperature, air velocity and air pressure ii. Detail of waste managemnet.
27	Last GMP report	Last / latest inspection report that should be conducted with in six months from the date of evaluation of dossier and having detailed assessment of facility in which the applied drug will be manufactured whether it is GMP compliant or not.
28	Types of container / packaging	a. Specifications (Physical & Chemical Characteristics) of the container closure system (Primary Packaging, Secodary Packaging & Associated components e.g., caliberated spoon etc.) fulfilling the compendial requirement. b. Before marketing of the product an undertaking of submitting Description of Suitability of container closure system comprising of following parameters: a. Protection of Drug b. Compatibility of Drug c. Safety of Drug d. Performance of Drug Stability studies will establish the final suitability of container closure system. The responsibility of genuineness of the data will lie with the applicant.
29	Undertaking	An undertaking by the production and quality control incharges about the correctness of contents of the dossier.
30	CD	i. Check for the CD whether given or not. ii. An Undertaking that the CD contains the same information / data as submitted by the applicant in the dossier. And that the CD is in operative condition.
31	Contact details	i. e-mail address. ii. mobile & phone no.
32	In case of Pellets	Submission of:

		i. COA ii. Stability studies iii. GMP of source of pellets.
33.	In case of XR / CR / DR / SR / MR etc.	Before marketing of the product an undertaking that they shall submit the comparative dissolution profile with the established brand and the data shall be supported by relevant documents to the DRAP which will include: a. Purchase of raw material, b. Certificate of Analysis, c. Testing protocols, d. SOPs, e. Analytical data and f. Finished Product sample.

For Imported Drug: Following additional data would be asked from the applicant.

a. Original and legalized Certificate of Pharmaceutical Product as per WHO format for applied product OR Original and legalized GMP certificate of new manufacturing site with free sale certificate from regulatory body of country of origin.
b. Sole Agency Agreement with complete contact detail of exporter.
c. Credentials / Site master file.
d. Prescribing information (PI), Patient Information Leaflet (PIL) and Summary of product characteristics (SmPC) as per Approved by Drug regulatory agencies or authorities of country of origin or FDA, EMA, TGA, Health Canada and MHLW (Japan)
e. Stability Studies conducted under the Zone IV-A conditions as per ICH / WHO guidelines.
f. Authentic Clinical Data / Clinical trials
g. Clinical justification

For New Drug molecule / Dosage form / Strength / combination Following additional data would be asked from the applicant.

a. Prescribing information (PI), Patient Information Leaflet (PIL) and Summary of product characteristics (SmPC) as per Approved by Drug regulatory agencies or authorities of country of origin or FDA, EMA, TGA, Health Canada and MHLW (Japan)
b. Stability Studies conducted under the Zone IV-A conditions as per ICH / WHO guidelines.
c. Clinical Data / Clinical trials
d. Clinical justification
e. International availability specially in FDA, EMA, Health Canada, TGA & MHLW (Japan) of same generic, dosage form & strength etc.

Checked by _____ Verified by_____

Commitments / undertakings

We give commitment / undertake that:-

1. We are submitting a proposed master formulation based on physicochemical characteristics of Active & Inactive components of formulation. Before marketing of the product, we will prepare trial / pilot scale batches for adjustment of said formulation in which proposed quantities of inactive ingredients may vary. After adjustment of formulation, the final formulation shall be submitted to DRAP alongwith the Pharmaceuticals Development studies.
2. Before marketing of product, we shall perform / conduct following studies for our product (Brand name with generic, dosage form & strength etc.) as per Guidelines approved / recommended by the Registration Board & the same shall be submitted to DRAP for becoming the part of our dossier of said product:
    a) Stability studies
    b) Pharmaceutical Development Studies
    c) Validation of analytical testing methods and
    d) Process validation

Quality Control Manager_____ Production Manager_____

Director/ Managing Director

Pharmaceutical Development studies

1. **Proposed Master Formulations**

S. No.	Name of ingredient (active/inactive)	Role	Safe Range/Limits		Proposed		Overage (if any alongwith justification)
			Qty.	%	Qty.	%	
1.	Active	X	X	X	√	X	-
2.	Inactive	Diluent	√	√	√	√	X
3.	Inactive	Binder	√	√	√	√	X
4.	Inactive	Disintegrant	√	√	√	√	X
5.	Inactive	Lubricant	√	√	√	√	X

Proposed average weight:_____

2. **Rational of Formulation Based**:

Based on following described physico-chemical characteristics of components of formulation, the Proposed Master Formulation has been designed.

3. **Description of Physico-chemical characteristics** of ingredients / components of proposed formulation:

Not required in table form table is just for idea about information

S. No.	Name of ingredient (active/inactive)	Pka	M.P.	Solubility	Particle size	Polymorphic Form
1.						
2.						
3.						

Details of Drug substance:

Chemical Name: [full chemical name]

CAS #: [CAS#]

USAN: XXX

Molecular Structure: [chemical structure]

Molecular Formula: CxHyOzN

Molecular Weight: XXX

Physical Description: XXX is a white, crystalline powder, practically insoluble in water at pH 7.0, freely soluble in XY organic solvent, sparingly soluble in acetone and alcohol.

pKa: The pKa of in XX is 5.5.

Polymorphism: There are two anhydrous polymorphic forms, Forms I and II, and no known hydrate forms. Form I is the most stable form and is used for the manufacture of the drug product. Form I and II can be produced by crystallization from ethanol at different cooling rates.

For detail guidance please see:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072866.pdf

Solubility Characteristics: The aqueous solubility at __pH at 37º C is___.

Solvent Media	Solubility Form I	Solubility Form II
0.1 N HCl, pH 1.2	0.10 mg/ml	0.40 mg/mL
0.15 M acetate buffer, pH 3.0	0.09 mg/ml	0.40 mg/mL
0.15 M acetate buffer, pH 4.5	0.011 mg/mL	0.033 mg/mL
0.15 M phosphate buffer, pH 6.8	(< 0.001 mg/ml)	(< 0.001 mg/ml)

Hygroscopicity: Water uptake for the drug substance was less than 0.1% by weight after one week at 25ºC/75±5% RH. (Details in 3.2.P.2.1.1)

Melting Point: The melting point of Form I and Form II are 225 ºC and 210 ºC, respectively.

Partition Coefficient: ClogP = 4.25

Control of API

Tests	Acceptance criteria	Analytical procedure	Test results for Lot#15531
Appearance	A white, crystalline powder.	Visual	Complies
Identification A: IR B: UV	A. IR: Corresponds to RS B. UV: Absorptivities at xxx nm, do not differ by more than 3.0% from the reference standard.	USP<197M> USP<197U>	Complies Complies
Heavy metals	NMT 20 ppm	USP<231>	LT 20 pm
Assay	98.0-102.0%	USP method	99.5%
Residual solvents	Methanol: NMT 3000 ppm Methylene Chloride: NMT 600 ppm Toluene NMT 890 ppm	USP <467>	 300 ppm 150 ppm 80 ppm
Related Substances	Specified Impurities* RC 1: NMT 0.15% RC 2: NMT 0.25% RC 3: NMT 0.25 % Any unspecified impurity: NMT 0.10% (each) Total impurities: NMT 0.75%	method #41	 LT 0.05% LT 0.05% 0.10% LT 0.05% 0.30 %
Polymorphic Form (XRD)	Ratio of peak at 2θ= xx to peak at 2θ=yy: LT 5%	method #47	LT 1%
Particle size (Laser Diffraction)	D90: NMT 30 µm D50: NMT 15 µm D10: NMT 5 µm	method #48	20 µm 10 µm 2.5 µm