The Gazette of Pakistan

EXTRAORDINARY
PUBLISHED BY AUTHORITY

ISLAMABAD, TUESDAY, SEPTEMBER 18, 2017

PART II

Statutory Notifications (S.R.O.)

GOVERNMENT OF PAKISTAN

Ministry of National Health Services, Regulations and Coordination
Drug Regulatory Authority of Pakistan

NOTIFICATION

Islamabad, the 13th September, 2017

S.R.O. 932(I)/2017. – The following draft of certain further amendments in the Drugs (Licensing, Registering & Advertising) Rules, 1976, which is proposed to be made in exercise of powers conferred by section 23 of the Drug Regulatory Authority of Pakistan Act, 2012 (XXI of 2012), read with clause (a) of section 7 thereof and section 43 of the Drugs Act, 1976 (XXXI of 1976), is hereby published, as required by sub-section (3) of said section 43, for the information of all persons likely to be affected thereby and notice is hereby given that the draft will be taken into consideration after seven days of its publication in the official Gazette.

Any objection or suggestion which may be received from any person in respect of the said draft, before the expiry of the said period, will be considered by the Drug Regulatory Authority of Pakistan.

DRAFT AMENDMENTS

In the aforesaid Rules, -

(1) in rule 26.-

(a) in sub-rule (1), at the end , words and expressions "or on Form 5-F *(Common Technical Document)* as notified by the Drug Regulatory Authority of Pakistan; and the Registration Board may issue necessary explanations and exemptions in this regard if needed" shall be added;

(b) in sub-rule (1), for full stop, at the end a colon shall be substituted and thereafter the following proviso shall be added, namely:-

"Provided that an applicant may submit registration application(s) on existing forms (Form 5 or 5-A or 5-D or 5-E) for a period of 6 months, which may be extended on justifiable reasons for further period by the Authority, after notification of Form 5-F by the Drug Regulatory Authority of Pakistan.";

(2) in Schedule A,-

(a) after Form 5 (E), the following new form shall be added, namely:-

"**FORM 5-F**"

[See rule 26 (1)]

Common Technical Document (CTD) for Registration of Human Drugs

Contents of Module 1: Administrative part

Section	Sub-Section	Heading
1.1		Covering Letter and Fee Deposit Slip
1.2		Table of Contents (From Module 1 to Module 5)
1.3		**Applicant Information**
	1.3.1	Name, address and contact details of Applicant / Marketing Authorization Holder:
	1.3.2	Name, address and contact details of Manufacturing site.
	1.3.3	Specify whether the Applicant is: a. □ Manufacturer b. □ Importer c. □Is involved in none of the above (contract giver)
	1.3.4	Valid Drug Manufacturing License (DML) of manufacturer / Applicant or Drug Sale License, whichever is applicable.
	1.3.5	Evidence of approval of manufacturing facility / Approved Section from Licensing Authority
	1.3.6	List of already approved registered drugs in this section
	1.3.7	Identification of Signature(s) of authorized persons, Incharge Production, Quality Control and Incharge Quality Assurance
	1.3.8	Manufacturer's Site Master File and Credential (for importer)
1.4		**Type of Application**
	1.4.1	Application is for the registration of: □ New Drug Product (NDP) □ Generic Drug Product (GDP)
	1.4.1	Pharmaceutical product is intended for: □ Domestic sale □ Export sale □ Domestic and Export sales
	1.4.2	For imported products, please specify one of following: □ Finished Pharmaceutical Product Import □ Bulk Import and local repacking (specify status of bulk) □ Bulk Import Local Repacking for Export purpose only

	1.4.3	Contract Manufacturing as per Rule 20-A of Drugs (Licensing, Registering and Advertising) Rules, 1976. □ Domestic Manufacturing □ Export Purpose Only
1.5		**Detailed Information of Drug, Dosage From & Labelling Claims**
	1.5.1	Generic name with chemical name & synonyms of the applied drug.
	1.5.2	Strength / concentration of drug of Active Pharmaceutical ingredient (API) per unit
	1.5.3	The proposed proprietary name / brand name under which the drug is intended to be sold with trade mark certification / clearance.
	1.5.4	Proposed Pack size and Proposed unit price of drug e.g., per tablet / capsule. Maximum Retail Price (MRP) per pack shall also be mentioned.
	1.5.5	Pharmacotherapeutic Group of Active Pharmaceutical Ingredient (API)
	1.5.6	Pharmacopoeial reference / Status of applied formulation
	1.5.7	Route of administration
	1.5.8	For Generic Drug Product, reference of other similar approved medicines with information pertaining to Manufacturer name, brand name, strength, composition, registration number & dosage form, Pack size and Price.
	1.5.9	The registration status of applied drug in same molecule and salt, strength, dosage form, container closure system, indications and route of administration etc. in other countries. The status in reference regulatory authorities is mandatory to mention.
	1.5.10	Dosage form of applied drug
	1.5.11	Proposed label (outer (secondary) & inner (primary)) & colour scheme in accordance with Drug (Labelling & Packing) Rules, 1986 along with specimens
	1.5.12	Description of Batch numbering system
	1.5.13	Training evidence of technical staff with respect of manufacturing of applied drug (mandatory in case of specially designed pharmaceutical product / Novel Dosage Form).
	1.5.14	Summary of Product Characteristics (SmPC) including Prescribing Information (PI) along with Patient information Leaflet (PIL) of the Finished Pharmaceuticals Product (FPP).
	1.5.15	Commitment / Undertaking that after registration of applied drug, the Pharmacovigilance department of the applicant / manufactureis liable to impose similar restrictions, addition of any clinical information (like in Indications, Contra-indications, Side effects, Precautions, Dosage & Adverse Drug Reactions etc. in Summary of Product Characteristics (SmPC), Labelling & Promotional material) or withdraw the drug from market in Pakistan within fourteen days after knowing that such information (which was not available or approved by the DRAP at the time of registration) / actions taken (for safety reasons) by any reference / stringent drug regulatory agency / authority & also inform the DRAP (Drug Regulatory Authority of Pakistan) for further action in this regard.
	1.5.16	Commitment / Undertaking that the applicant shall recall the defective Finished Pharmaceutical Products (FPP) and notify the compliance to the authority along with detail of actions taken by him as soon as possible but not more than ten days. The level of recall shall also be defined.
	1.5.17	Commitment / Undertaking that in case of any false claim / concealing of

		information, the DRAP has the right to reject the application at any time, before and even after approval or registration of the product in case if proved so.
	1.5.18	Commitment / Undertaking that the firm shall follow the official pharmacopoeia specifications for product / substance as published in the latest edition & shall update its specification as per latest editions of the same. In case, the specifications of product / substance not present in any official pharmacopoeia the firm shall establish the specifications. In both cases, the validation of specifications shall be done by the applicant.
	1.5.19	Commitment / Undertaking that in case of any post approval change, the applicant shall ensure that the product with both approvals shall not be available in the market at the same time. And the product with new approvals shall be marketed only after consumption / withdrawal of stock with previous approvals. The company shall be liable to inform the same regarding marketing status of product to the DRAP after getting such post-registration approvals.
	1.5.20	Other commitment e.g., regarding stability studies etc.
	1.5.21	Protocols along with the commitment to follow Good Laboratory Practices (GLP) by the Manufacturer.
	1.5.22	Protocols to implement Good Pharmacovigilance Practice by the Pharmacovigilance department/section of the Manufacturer / Company.
1.6		**Miscellaneous Information**
	1.6.1	Information on Prior-related Applications
	1.6.2	Appendix
	1.6.3	Electronic Review Package
	1.6.4	QIS (Quality Information Summary)
	1.6.5	Drug Substance related Document including following: a. Name and address of API manufacturer. b. Approval of manufacturing facility of API by regulatory body of country and validity. c. Vendor qualification / audit is □ Document based □ Site inspection based d. Reason for point c.

Contents of Module 2: Overviews and Summaries

Module	Section	Sub-section	Contents
2	2.1		Overall CTD Table of Content
	2.2		CTD Introduction
	2.3		Quality Overall Summary (QOS)*
		2.3	Introduction
		2.3.S	Drug Substance
		2.3.P	Drug Product
		2.3.A	Appendices
		2.3.R	Regional Information
	2.4		Non-Clinical Overview
	2.5		Clinical Overview
	2.6		Non-Clinical Written and Tabulated Summaries (Normally not required for generics)
	2.7		Clinical Summary

*QOS has been explained by a WHO QOS - PD template **MODULE 2.3**

Contents of Module 3: Quality / CMC

Module	Section	Sub-section	Contents
3	3.2.S		DRUG SUBSTANCE
		3.2.S.1	General Information
		3.2.S.2	Manufacture
		3.2.S.3	Characterization
		3.2.S.4	Control of Drug Substance
		3.2.S.5	Reference Standards or Materials
		3.2.S.6	Container Closure System
		3.2.S.7	Stability
	3.2.P		DRUG PRODUCT
		3.2.P.1	Description and Composition of Drug Product
		3.2.P.2	Pharmaceutical Development
		3.2.P.3	Manufacture
		3.2.P.4	Control of Excipient
		3.2.P.5	Control of Drug Product
		3.2.P.6	Reference Standards or Materials
		3.2.P.7	Container Closure System
		3.2.P.8	Stability

Module 3 has been explained by following guidelines M4Q__R1__3, M4_Quality_Questions_Answers_R1(Location Issues), WHO TRS 970 annexure 4

Details of Module: 3 (Quality / CMC)

- 3.1 Table of Contents of Module 3
- 3.2 Body of Data
- **3.2.S Drug Substance**
  - **3.2.S.1 General Information**
    - 3.2.S.1.1 Nomenclature
    - 3.2.S.1.2 Structure
    - 3.2.S.1.3 General Properties
  - **3.2.S.2 Manufacture**
    - 3.2.S.2.1 Manufacturer(s)
    - 3.2.S.2.2 Description of Manufacturing Process and Process Controls
    - 3.2.S.2.3 Control of Materials
    - 3.2.S.2.4 Controls of Critical Steps and Intermediates
    - 3.2.S.2.5 Process Validation and/or Evaluation
    - 3.2.S.2.6 Manufacturing Process Development
  - **3.2.S.3 Characterisation**
    - 3.2.S.3.1 Elucidation of Structure and other Characteristics
    - 3.2.S.3.2 Impurities
  - **3.2.S.4 Control of Drug Substance**
    - 3.2.S.4.1 Specification
    - 3.2.S.4.2 Analytical Procedures
    - 3.2.S.4.3 Validation of Analytical Procedures
    - 3.2.S.4.4 Batch Analyses
    - 3.2.S.4.5 Justification of Specification
  - **3.2.S.5 Reference Standards or Materials**

- **3.2.S.6 Container Closure System**
- **3.2.S.7 Stability**
  - 3.2.S.7.1 Stability Summary and Conclusions
  - 3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment
  - 3.2.S.7.3 Stability Data

- **3.2.P Drug Product**
  - **3.2.P.1 Description and Composition of the Drug Product**
  - **3.2.P.2 Pharmaceutical Development**
    - 3.2.P.2.1**Components of the Drug Product**
      - 3.2.P.2.1.1Drug Substance
      - 3.2.P.2.1.2 Excipients
    - 3.2.P.2.2 **Drug Product**
      - 3.2.P.2.2.1Formulation Development
      - 3.2.P.2.2.2Overages
      - 3.2.P.2.2.3Physicochemical and Biological Properties
    - **3.2.P.2.3Manufacturing Process Development**
    - **3.2.P.2.4Container Closure System**
    - **3.2.P.2.5Microbiological Attributes**
    - **3.2.P.2.6 Compatibility**
  - **3.2.P.3 Manufacture**
    - 3.2.P.3.1 Manufacturer(s)
    - 3.2.P.3.2 Batch Formula
    - 3.2.P.3.3 Description of Manufacturing Process and Process Controls
    - 3.2.P.3.4 Controls of Critical Steps and Intermediates
    - 3.2.P.3.5 Process Validation and/or Evaluation
  - **3.2.P.4 Control of Excipients**
    - 3.2.P.4.1 Specifications
    - 3.2.P.4.2 Analytical Procedures
    - 3.2.P.4.3 Validation of Analytical Procedures
    - 3.2.P.4.4 Justification of Specifications
    - 3.2.P.4.5 Excipients of Human or Animal Origin
    - 3.2.P.4.6 Novel Excipients
  - **3.2.P.5 Control of Drug Product**
    - 3.2.P.5.1 Specification(s)
    - 3.2.P.5.2 Analytical Procedures
    - 3.2.P.5.3 Validation of Analytical Procedures
    - 3.2.P.5.4 Batch Analyses - for **Biologics Drugs** & for **Pharmaceutical Drugs**
    - 3.2.P.5.5 Characterisation of Impurities
    - 3.2.P.5.6 Justification of Specification(s)
  - **3.2.P.6 Reference Standards or Materials**
  - **3.2.P.7 Container Closure System**
  - **3.2.P.8 Stability**
    - 3.2.P.8.1 Stability Summary and Conclusions
    - 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment
    - 3.2.P.8.3 Stability Data
- **3.2.A Appendices**
  - 3.2A.1 Facilities and Equipment

- 3.2.A.2 Adventitious Agents Safety Evaluation
- 3.2.A.3 Excipients

- **3.2.R Regional Information**
  - 3.2.R.1 Production Documentation
    Human Blood Product with required supporting documents
  - 3.2.R.2 TSE Checklist with required supporting documents
  - 3.2.R.3 Product Interchangeability (Bioequivalence Study Reports)
    - BE test product uses same DS and DP manufactured at same site as proposed in application
    - Reference product used in BE study
    - If BE RP not from same DP site then bridging data (comparative dissolution) will be required
    - Batch size, manufacturing date & expiry date for test product are stated
    - Expiry date & manufacturing site for BE RP (Reference product) are stated
    - CoA of both test product and BE RP are provided
    - IRB & protocol approval are provided
    - Analytical validation reports are provided
    - BE inspection report is provided
    - If BE study is not provided, then justification for bio-wavier is required, with supporting documents
    - Lot Release Documentation (for Biological Drugs)
  - 3.2.R.4 Blank Production Batch Record
    - Yearly Biologic Product Reports (Biological Drugs only)
- **3.3 Literature References**

- **Bioequivalence or Comparative Dissolution Testing is discussed in 3.2.P.2.2.1Formulation Development and 3.2.R.3 Product Interchangeability**

Module 4: Non-clinical / Safety

4.1 Table of Contents
4.2 Study Reports
4.2.1 Pharmacology
- 4.2.1.1 Primary Pharmacodynamics
- 4.2.1.2 Secondary Pharmacodynamics
- 4.2.1.3 Safety Pharmacology
- 4.2.1.4 Pharmacodynamic Drug Interactions

4.2.2 Pharmacokinetics
- 4.2.2.1 Analytical Methods and Validation Reports
- 4.2.2.2 Absorption
- 4.2.2.3 Distribution
- 4.2.2.4 Metabolism
- 4.2.2.5 Excretion
- 4.2.2.6 Pharmacokinetic Drug Interactions (non-clinical)
- 4.2.2.7 Other Pharmacokinetic Studies

4.2.3 Toxicology

4.2.3.1 Single-Dose Toxicity (in order by species, by route)

4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)

4.2.3.3 Genotoxicity

4.2.3.3.1 In vitro

4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)

4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)

4.2.3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity orpharmacokinetics)

4.2.3.4.3 Other studies

4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly.)

4.2.3.5.1 Fertility and early embryonic development

4.2.3.5.2 Embryo-fetal development

4.2.3.5.3 Prenatal and postnatal development, including maternal function

4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.

4.2.3.6 Local Tolerance

4.2.3.7 Other Toxicity Studies(if available)

4.2.3.7.1 Antigenicity

4.2.3.7.2 Immunotoxicity

4.2.3.7.3 Mechanistic studies (if not included elsewhere)

4.2.3.7.4 Dependence

4.2.3.7.5 Metabolites

4.2.3.7.6 Impurities

4.2.3.7.7 Other

4.3 List of Literature References

Module 5: Clinical / Efficacy

- **5.1 Table of Contents of Module 5**
- **5.2 Tabular Listing of All Clinical Studies**
- **5.3 Clinical Study Reports**

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.1 Bioavailability (BA) Study Reports

5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports

5.3.1.3 *In vitro-In vivo* Correlation Study Reports

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials

5.3.2.1 Plasma Protein Binding Study Reports

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies
5.3.2.3 Reports of Studies Using Other Human Biomaterials

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports
5.3.3.2 Patient PK and Initial Tolerability Study Reports
5.3.3.3 Intrinsic Factor PK Study Reports
5.3.3.4 Extrinsic Factor PK Study Reports
5.3.3.5 Population PK Study Reports

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

5.3.4.1 Healthy Subject PD and PK/PD Study Reports
5.3.4.2 Patient PD and PK/PD Study Reports

5.3.5 Reports of Efficacy and Safety Studies

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
5.3.5.2 Study Reports of Uncontrolled Clinical Studies
5.3.5.3 Reports of Analyses of Data from More Than One Study
5.3.5.4 Other Clinical Study Reports

5.3.6 Reports of Post-Marketing Experience

5.3.7 Case Report Forms and Individual Patient Listings

- **5.4 Literature References "**

[No. F.2-2/2017(Reg-I)/DRAP]

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