GUIDANCE DOCUMENT FOR CLINICAL TRIALS OF BIOLOGICAL PRODUCTS (MANUFACTURE LOCALLY)

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Drug Regulatory Authority of Pakistan Islamabad - Pakistan.

GLOSSARY

ACRONYMS

API	Active Pharmaceutical Ingredient
CoPP	Certificate of Pharmaceutical Product
CoA	Certificate of Analysis
CTD	Common Technical Document
DML	Drug Manufacturing License
DRAP	Drug Regulatory Authority of Pakistan
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonization
LR&A	Licensing, Registering & Advertising
RRA	Reference Regulatory Authority
WHO	World Health Organization

Table of Contents

1

HISTORY

This is the first edition of these guidelines.

SCOPE

The scope of this Guideline is limited to application on Form-5F (CTD) for registration of Biological drug products for human use manufactured locally.

APPLICATION[1] - Guidance for Industry.

This document is applicable to the firms who intends to apply for registration / Marketing Authorization of Biological drug products for human use manufactured locally.

1. INTRODUCTION

This guidance is developed to assist manufacturers in developing their applications for registration of human Biological drug products. This guidance document is developed on the basis of best available knowledge and scientific data / evidence.

1 **The Guidance document is prepared by Drug Regulatory Authority of Pakistan for better illustration of data requirements on conduction of clinical trials on biological drugs manufactured locally. However, content of guidance document only reflects the current thinking perspective of the Authority on the subject and does not create or confer any rights for or on any person and does not operate to bind the Authority or the public.**

2. LEGAL PROVISIONS

Section 7 (c) (ix) of DRAP Act 2012, mandated the systematic implementation of internationally recognized standards of World Health Organization, International Conference on Harmonization (ICH), and Food and Drug Administration guidelines etc.

3. GENERAL GUIDANCE FOR APPLICANTS

Applicant needs to follow the following general instructions/guidance to ensure proper submission. Data requirements for issuance of registration of locally manufactured biological drugs. In DRAP's Act, 2012 there are four categories of Biological drugs, Finished Form, Ready to fill form, concentrated form and naked vials:

3.1 Biological Drugs (Concentrated Form/Ready to fill Form).

a) The firms shall provide legalized GMP certificate of biological drug substance manufacturer abroad (who will provide concentrate / ready to fill bulk of biological drug to Pakistani manufacturers for further processing) as an evidence that the manufacturer is an authorized manufacturer of biological drug in the country of origin.

b) The firms shall provide legalized free sale certificate/CoPP either from country of origin or by any reference regulatory authority as adopted by Registration Board of finished product as evidence that the final product has been manufactured by same concentrate/ready to fill bulk after submission of data to the concerned regulatory authority.

c) The firm shall provide the complete Bio-similarity studies of the finished product of same source (bulk concentrate or ready to fill) manufactured either from country of origin or by any reference regulatory authority as adopted by Registration Board to demonstrate the bio-similarity.

d) The firm shall provide the lot release certificate of the finished product manufactured by same bulk concentrate/ ready to fill from country of export (If applicable).

e) The firm shall provide the accelerated and real time stability studies for drug substance.

f) The local manufacturer shall manufacture three trial batches of the finished biological product to finalize the formulation and then perform analytical studies(Physicochemical and biological) including protein content, appearance, pH, Osmolarity, composition of key excipients including stabilizers (if formulation is same), visible/subvisible particles, identity testing to parent molecule, purity testing, in vitro biological activity, sterility, Pyrogen content, safety, potency and toxicity with support of iso-electro focusing data, gel

electrophoresis, Western-Blot and other analytical techniques). The firm shall submit the results for processing of registration application.

g) The manufacturer shall perform all tests locally as detailed on Certificate of analysis.

h) The firm shall also provide the list of finished products being manufactured from same bulk concentrate or ready to fill form in any country of the world (if available).

i) The firm shall provide the agreement with the source (of bulk concentrate/ready to fill) that if there shall be any critical change in manufacturing process, biological systems used to manufacture, etc. the firm shall inform DRAP immediately along with relevant documents.

j) Regular monitoring through pharmacovigilance reporting system shall be observed through proper pharmacovigilance cell of the manufacturer and report will be forwarded to the National Pharmacovigilance Centre, Division of Pharmacy Services and Biological Division of DRAP. In case of any adverse event, immediate mandatory reporting procedure shall be followed.

k) The firm shall inform DRAP if there shall be any adverse event or ADR reporting from the country of manufacture of concentrate/ready to fill bulk and finished product as required vide Rules 30 of Drug (LR&A) Rule.

l) If any of the conditions is not fulfilled or public health risk reported at any stage, the drug registration shall stand cancelled with immediate effect.

m) All the provisions as contained in the Drugs Act, 1976 and rules made there under including provisions of Lot Release certification from National Control Laboratory for Biologicals shall be strictly adhered to.

n) For the already registered drugs for local manufacturing the current guidelines shall apply.

3.2 BIOLOGICAL DRUGS (finished form/ Naked Vials).

a) The importer shall provide the complete bio similarity studies including analytical studies (Physicochemical, Biological), animal studies and clinical studies (immunogenicity studies, PK, PD) of the finished product from the exporter.

b) The importer shall provide the guidelines for evaluation of bio therapeutics in the country of export (Non-reference authorities) as evidence that the submitted data is in accordance with the said guidelines.

c) The importer shall provide the lot release certificate of the country of export for the same drug (if applicable).

3.3. Other manufacturing processes:

For products where process like PEGylation are performed locally, then complete clinical data shall be required by the manufacturer.

REFERENCES:

1. The DRAP Act, 2012.
2. The Drugs Act 1976.
3. The Drugs (Licensing, Registering and Advertising) Rules, 1976.
4. Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part (Annex 6 of WHO Technical Report Series No. 986, 2014).
5. ICH -M4Q (R1) Guidelines.
6. WHO QUALITY OVERALL SUMMARY: PRODUCT DOSSIER (QOS-PD) TEMPLATE

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