I. Guidelines for regulatory requirements of Biological drugs using rDNA technology.

Two meetings of committee on Biological drugs constituted by Registration Board in its 273rd meeting were held on20th November, 2017& 16th January, 2017 in the Committee Room, Drug Regulatory Authority of Pakistan, G-9/4, Islamabad. The meeting was attended by the following:

1.	Maj.Gen.Dr. TahirMukhtar Syed	Chairman
2.	Dr Noor us Saba, Director (Biological)	Member
3.	Dr.Qurban Ali, Member Registration Board	Member
4.	Dr. Obaidullah, Director (PE&R)/Chairman Registration Board	Co-Opted Member
5.	Mr. Abdullah Add. Director (PE&R) / Secretary Registration Board	Co-Opted Member (2nd meeting)
6.	M. Akhtar Abbas Khan, Dy Director Biological	Secretary

Mr. ZubairMasood AD (Bio), Mr. Muneeb Ahmad Cheema AD (Bio) Mr. Muhammad Sarfraz Nawaz AD (Bio), Mr. Khurrum Khalid AD (Bio) and Mr.Saadat Ali Khan, AD (Bio) assisted with relevant agenda. Mr. Hamid Raza & Mr. Muhammad Imran in first meeting while Mr. Farooq Mustafa & Dr.Syed Salman A Zaidi represented PPMA in 2nd meeting, Mr. Abdul Samad and Dr.Ali Shehzad reperesented PharmaBeauru and PCDA respectively in both meetings. Mr.Ajmal Nasir (BF Bioscience) was called for 2nd meeting on his request as the firm is not member of PPMA.

In the 1st meeting PPMA was asked by committee to provide the details of the testing facilities available in the reference countries for the complete testing of bio-similar products. After many verbal reminders the information was not provided by the PPMA. Later on bio-similar testing Labs who have online contact details were contacted to get the information on availability of tests and their cost for analytical characterization. It is submitted that there are labs available in the Europe, USA and other countries that provide the bio-similar testing services at different negotiable rates. A list of the required tests for analytical characterization was also searched. There are various guidelines which provide details of the Physicochemical and Biological characterization methods to be used for r-DNA derived products however the Guideline on similar biologics India have outlined the list of routine analytical tests to be included for comprehensive quality comparability exercise of Critical and Key Quality Attributes is given in Annexure-II of Guidelines. The list from a testing lab of a Europe/USA was also placed for further consideration of the committee.

The committee discussed regulatory requirements in Pakistan and deliberated on the Registration Board's previous decision of 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.

The committee gave its recommendations as follows: -

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<u>either from country of origin or by any reference regulatory authority as adopted by Registration Board</u>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) <u>The firm shall provide the open part of DMF of Drug Substance (Concentrate/Ready to fill).</u>

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

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

f) The firm shall provide the 6 months accelerated and real time stability studies for drug substance.

g) The local manufacturer shall be authorized to manufacture the finished biological product and then perform analytical studies(Physicochemical and biological) including <u>protein content, appearance, pH, Osmolarity, composition of key excipients including stabilizers (if formulation is same), visible/subvisible particles, identity testing to parent molecule</u>, purity testing, in vitro biological activity, <u>sterility, Pyrogen content, safety</u>, potency and toxicity with support of iso-electro focusing data, gel electrophoresis, Western-Blot and other analytical techniques).

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) *<u>The manufacturer shall perform all tests locally as detailed on Certificate of analysis.</u>*

j) 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.

k) 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 severe adverse event, immediate mandatory reporting procedure shall be followed.

l) <u>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.</u>

m) 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.

n) 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.

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

2. Biological Drugs, finished form/ Naked Vials

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

b) The firm shall provide the open part of DMF of Drug Substance (Concentrate/Ready to fill).

c) The importer shall provide the guidelines for evaluation of biotherapeutics in the country of export as evidence that the submitted data is in accordance with the said guidelines.

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

3. Other manufacturing processes: For products where process other than listed above (Finished Form, Ready to fill form, concentrated form and naked vials) is done locally likePEGylation, then complete clinical data shall be required by the manufacturer.

Above recommendations are submitted for the consideration of the Registration Board with the suggestion that the firms must first produce at least three trial batches to finalize the formulation and testing protocols as mentioned above and submit results to the RB before they are issued registration letter.

Decision: Registration Board appreciated the work of committee for drafting guidelines for registration of Biological drugs and decided to adopt the following guidelines as regulatory requirements for the registration of rDNA therapeutic proteins:

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 6 months 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 severe 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.

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 biotherapeutics 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. Other manufacturing processes:

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