



REGULATORY GUIDANCE FOR LOCAL MANUFACTURE OF BIOLOGICAL PRODUCTS USING IMPORTED BULK CONCENTRATE OR READY-TO-FILL BULK

(Quality, Non-Clinical & Clinical Expectations)

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Table of Contents

1. Introduction	3
2. Objectives.....	3
3. Scope.....	4
4. Definitions	4
5. Regulatory Principles.....	7
6. Regulatory Documents.....	7
7. Quality Requirements	8
8. Non-Clinical	11
9. Clinical Requirements.....	12
10. Post-Marketing Safety and Pharmacovigilance.....	13

1. Introduction

The Drug Regulatory Authority of Pakistan (DRAP) is mandated to ensure the quality, safety and efficacy of therapeutic goods. DRAP recognizes the importance of strengthening local manufacturing capacity for vaccines and other biological products in Pakistan. Progressive localization of biological products manufacturing including vaccines, supported by technology transfer or collaboration with established international manufacturers shall contribute significantly to national health security, availability of essential vaccines & biological drug products and development of domestic technical and manufacturing capabilities.

Following manufacturing arrangements may be adopted to facilitate such localization. These include:

- a. Importation of bulk concentrate (BC) followed by local formulation, filling, labeling & packaging.
- b. Importation of ready-to-fill bulk (RTFB) followed by local filling, labeling & packaging.

Although both of the above arrangements involve the use of an overseas-manufactured biological material, the nature and extent of the subsequent manufacturing operations undertaken in Pakistan may differ, including, further formulation, manufacturing and processing steps to filling, labelling and packaging. Therefore, the associated regulatory data requirements should be appropriately differentiated and commensurate with the nature and extent of manufacturing activities performed in Pakistan.

This guidance provides a regulatory roadmap for applicants and manufacturers proposing to manufacture biological products in Pakistan using imported BC or RTFB. It describes the regulatory expectations relating to the overseas manufacturing site, imported biological material, local manufacturing operations, quality control, process validation, stability, non-clinical and clinical evidence, comparability, bridging, lot release and post-registration lifecycle management.

2. Objectives

The principal objective of this guidance is to establish a regulatory pathway in which manufacturing operations are divided between an overseas manufacturer and a local manufacturer in Pakistan. It further aims to establish a risk-based framework under which existing non-clinical and clinical evidence may be utilized where scientifically justified, while ensuring that appropriate

additional data is generated, where differences in formulation, manufacturing process or product characteristics may affect the quality, safety, immunogenicity or efficacy of the final biological product.

3. Scope

This guidance applies to human therapeutic proteins, monoclonal antibodies, and vaccines for which BC or RTFB is manufactured overseas and subsequently imported into Pakistan for further formulation/filling, labeling, packaging, and release. Plasma-derived medicinal products (PDMPs) and Advanced Therapy Medicinal Products (ATMP) are excluded from the scope of this guidance.

This document should be read in conjunction with the applicable legislation, rules, SROs and DRAP guidelines relating to registration, manufacturing, GMP, lot release, clinical trials, pharmacovigilance and post-registration variations for biological drug products.

4. Definitions

i. Ready to Fill Bulk (RTFB):

Ready to Fill Bulk means Biological Drug which is manufactured at one site in the form of a "Ready-to-fill Bulk" but is transferred to another site for final filling, labeling, packaging and quality control of the finished form. No further formulation or dilution of the Ready-to-fill bulk is allowed in this case of manufacture. The final product is released by the Pakistan's National Control Laboratory for Biologicals under the World Health Organization's Lot Release system of evaluation.

ii. Bulk Concentrate (BC):

Bulk Concentrate means biological drug intermediate that is manufactured at one site but is stored in the form of concentrated bulk of the active ingredient at controlled temperatures. Such Concentrated-Bulk may be transferred to any other site under temperature-controlled conditions for further dilution, stabilization, filling and packaging. The diluted and stabilized bulk requires its own set of quality control test and the final finished form of such Biological Drugs undergo another set of complete quality control tests. The final product is released by the Pakistan's National Control Laboratory for Biologicals under the World Health Organization's Lot Release system of evaluation.

iii. Biological Drug Product:

Biological Drug Product means product that is manufactured, packed by the manufacturer under his responsibility of quality assurance and where applicable is further released by the National Control Authority or the National Control Laboratory of the country of origin under the World Health Organization's Lot Release system of evaluation.

iv. Comparability:

A conclusion that products have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred.

v. Bridging

Bridging means the scientific and/or clinical approach used to establish the applicability of existing non-clinical or clinical evidence to a product that differs in one or more relevant respects from the product used in the original development programme.

vi. Originator Biological Drug

Originator Biological Drug means a biological drug product which has been licensed by the national regulatory authorities on the basis of a full registration dossier; i.e. the approved indication(s) for use were granted on the basis of full quality, efficacy and safety data.

vii. Reference Biotherapeutic product (RBP)

Reference Biotherapeutic product means an originator biological drug product that was licensed on the basis of a full registration dossier. It does not refer to measurement standards such as international, pharmacopoeial, or national standards or reference standards.

viii. Biosimilar Biological Drug

Biosimilar biological drug means Similar Biotherapeutic Product (SBP) which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

ix. Shipping/ Transport Validation

A documented and scientifically justified programme demonstrating that the packaging system, shipping configuration and transportation arrangements used for the transfer of BC/RTFB from the supplying manufacturer to the receiving site are capable of consistently maintaining the specified temperature, storage and other prescribed transportation conditions and protecting the integrity and quality of the BC/RTFB throughout the validated transportation route and duration. The validation shall consider applicable environmental and logistical conditions, including seasonal temperature variations, transportation duration, handling, loading and unloading, and reasonably foreseeable delays or temperature excursions.

x. Hold Time Studies

A documented study establishing the maximum allowable period for which a biological material, intermediate or bulk product may be held under specified and controlled conditions at a particular stage of the manufacturing process without adversely affecting its predefined quality attributes

xi. Vaccines

A biological preparation that elicits or improves immunity to a particular disease. A vaccine contains an antigen or antigenic material capable of inducing a specific immune response and may also contain other components, such as adjuvants, preservatives, stabilizers or other excipients, as applicable.

xii. Monoclonal Antibody (mAb)

A monoclonal antibody is an immunoglobulin, derived from a monoclonal cell line, having a defined specificity for a particular antigen or ligand. Its biological or immunological activity is primarily mediated through specific binding to its target and may additionally depend on Fc-mediated or other effector functions.

5. Regulatory Principles

The overseas manufacturer supplying the Bulk Concentrate or Ready-to-Fill Bulk (BC or RTFB) should hold a valid manufacturing authorization from the competent regulatory authority of the country of origin for the manufacture of the relevant biological drug. Documentary evidence of the manufacturing authorization, licence or equivalent regulatory approval shall be submitted as part of the registration application.

The finished biological product of the BC or RTFB supplier shall be registered, approved or otherwise authorized by the competent regulatory authority in the country of origin and is available for commercial sale in that country. Documentary evidence of registration, free sale and Certificate of Pharmaceutical Product (CoPP) shall be submitted as a part of the registration application.

The finished biological product of the BC or RTFB supplier shall preferably be a reference/innovator/WHO Prequalified product. In case finished biological product of the BC or RTFB supplier is non-reference product, the same shall be developed in comparison to innovator/originator/reference biological product and finished biological product should have at least one year of post-marketing experience in the country of origin or other jurisdictions with an established regulatory framework, supported by an adequate level of cumulative exposure, before registration in Pakistan.

6. Regulatory Documents

The following document shall be submitted by the applicant which is issued by the regulatory authority of country of origin from where the bulk concentrate shall be imported for local formulation and subsequent filling & packaging.

- i. Certificate of Pharmaceutical Product (CoPP) issued by the regulatory authority of the country of origin of the finished product of the bulk concentrate supplier, confirming that the biological product manufactured from the said bulk concentrate is duly licensed/registered and authorized for sale in the respective market. The said certificate shall be duly legalized or apostilled, as applicable, in accordance with the requirements prescribed by the Government of Pakistan for the acceptance of foreign public documents. However, where the product registration status and the relevant information contained in the certificate can be independently verified online through the official database or website

of the regulatory authority concerned, legalization or apostillation of the certificate may not be required.

- ii. Where online verification is relied upon in lieu of legalization or apostillation, the applicant shall provide the official web link and sufficient details, including the product name, registration/authorization number, manufacturer/supplier name, and any other relevant information necessary to enable the Authority to independently verify the registration status and authorization for sale of the biological product.
- iii. Where the finished biological drug product manufactured using the BC or RTFB supplied by the supplier is registered and/or authorized for marketing in any jurisdiction other than the country of origin, the applicant shall provide the requisite regulatory information/documents specified under points (i) and (ii) above, issued by the relevant regulatory authority of such jurisdiction
- iv. GMP certificate of BC or RTFB supplier issued by concerned regulatory authority.
- v. Shipping and transportation validation data shall demonstrate maintenance of prescribed storage and transportation conditions for the BC or RTFB between manufacturing sites.

The above documents shall become part of Module I of Form -5F (CTD).

7. Quality Requirements

The applicant shall submit comprehensive quality documentation as delineated in the DRAP's guidance document for registration of biological drugs for human use.

a. Drug Substance

A complete information on its description, source, manufacturing site(s), manufacturing process and process controls, critical manufacturing steps, process development and validation, product characterization, specifications, analytical procedures and their validation status, batch analysis, reference standards, container-closure system, storage and transportation conditions, hold-time requirements and stability data for BC or RTFB. The relevant information should be provided under relevant CTD structure, CTD section 3.2.S.2 (Manufacture), 3.2.S.3 (Characterisation),

3.2.S.4 (Control of Drug Substance), 3.2.S.5 (Reference Standards or Materials), 3.2.S.6 (Container Closure System) and 3.2.S.7 (Stability), as applicable.

b. Drug Product of BC/RTF Supplier

A comprehensive technical dossier containing sufficient product and process knowledge shall be submitted. The information shall include the qualitative and quantitative composition; specifications of the bulk concentrate and excipients; manufacturing and formulation processes; critical quality attributes (CQAs); critical process parameters (CPPs); critical material attributes (CMAs); process-development and scale-up information; in-process controls; finished-product specifications; analytical methods and their validation status; container-closure information; stability data; hold-time requirements; storage and transportation conditions; process-validation information; and relevant product and process risk assessments. Such information should correspond, as applicable, to CTD sections for product part. The said information shall provide sufficient technical and scientific knowledge to enable the receiving manufacturer in Pakistan to develop and optimize the formulation and manufacturing process and to demonstrate that the process is adequately defined, controlled, validated, and supported by appropriate development and risk-management data.

The dossier shall also include comprehensive comparability data generated on the finished product manufactured by the BC/RTFB supplier against the innovator/reference biological product. The data shall demonstrate that the BC/RTFB supplier's finished product is comparable to the innovator/reference biological product with respect to relevant quality attributes and biological activity.

Appropriate studies shall be provided to demonstrate and justify the proposed storage and transportation conditions for BC and RTFB. For BC, where applicable, such studies shall establish the maximum allowable time periods for thawing, dilution, formulation, mixing, filtration and filling. For RTFB, studies shall establish the maximum allowable holding period prior to filling.

c. Drug Product (Locally Manufactured)

Where the dossier provided by the (BC/RTFB) supplier for its product adequately demonstrates established product and process knowledge, the receiving manufacturer may rely on such information and shall not be required to unnecessarily repeat development studies that have already been adequately performed, scientifically justified and appropriately documented by the supplier.

However, the receiving manufacturer shall demonstrate that the formulation (in case of BC) and manufacturing process are suitable for implementation at its own site and that differences in facilities, equipment, utilities, materials, personnel, process parameters or analytical systems do not adversely affect product quality. The need for, and extent of, additional development, verification, validation, comparability or other studies shall therefore be determined through a documented quality-risk assessment, with the resulting justification and supporting data incorporated, as appropriate, into CTD sections 3.2.P.2, 3.2.P.3, 3.2.P.5 and 3.2.P.8.

A complete CTD Module 3.2.P dossier shall be submitted by the local manufacturer. The dossier shall include 3.2.P.1 (Description and Composition of the Drug Product), 3.2.P.2 (Pharmaceutical Development), 3.2.P.3 (Manufacture), 3.2.P.4 (Control of Excipients), 3.2.P.5 (Control of Drug Product), 3.2.P.6 (Reference Standards or Materials), 3.2.P.7 (Container Closure System) and 3.2.P.8 (Stability), as applicable. The applicant shall provide the proposed batch formula and manufacturing process for commercial-scale production, together with appropriate process validation or process verification data with validation batches representative of proposed manufacturing process and equipments. Particular emphasis shall be placed on BC/RTF receipt and storage, formulation (where applicable), mixing or homogenization, filtration, filling, stoppering or sealing, environmental controls, aseptic processing, media fills or aseptic process simulations where applicable, hold times, cleaning validation and container-closure integrity. These aspects shall be appropriately addressed in CTD sections 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.5 and 3.2.P.7. The stability Programme shall adequately support the proposed shelf life, storage conditions, transportation requirements and any specified holding periods for the locally formulated/ filled and packaged product and shall be presented under CTD section 3.2.P.8, including 3.2.P.8.1 (Stability Summary and Conclusion), 3.2.P.8.2 (Post-approval Stability Protocol and Stability Commitment) and 3.2.P.8.3 (Stability Data), as applicable.

The applicant shall demonstrate that the local formulation and filling operations consistently maintain the identity, purity, potency, safety and other relevant CQAs of the finished biological product.

The formulation of the locally manufactured product shall be justified against the formulation of the corresponding finished product of BC/RTFB supplier. The rationale for the formulation and any differences from the reference formulation shall be addressed primarily under CTD section 3.2.P.2

(Pharmaceutical Development). Any differences between the formulation used at the receiving site and that of the reference formulation shall be scientifically justified and supported by appropriate quality, stability, nonclinical and/or clinical data, as applicable. Comparative analytical and studies shall be performed to establish that the locally formulated and filled product remains comparable to the product for which the clinical safety and efficacy data are being relied upon. Relevant comparative data shall be presented under 3.2.P.5 and, where appropriate, supported by information in Module 4 and Module 5.

The applicant shall provide evidence of appropriate testing of each imported BC/RTFB lot prior to manufacturing including testing by the designated National Control Laboratory where applicable.

8. Non-Clinical

The applicant shall provide available original nonclinical data generated by the BC/RTFB manufacturer for its finished product, including relevant pharmacology, immunogenicity, toxicity, local tolerance and other applicable studies for a locally formulated/ filled biological product manufactured using a licensed imported BC/RTFB. The applicant shall demonstrate that the locally formulated/ filled product is sufficiently comparable to the product represented in the original nonclinical studies.

Additional nonclinical studies shall particularly be required where there is a significant change in antigen quantity, adjuvant type or concentration (in case of vaccines), preservative concentration, excipients, formulation, route of administration or manufacturing process, or where comparative quality data do not adequately establish comparability with the finished biological product on which the existing safety data are based. The applicant should provide scientific justification where existing nonclinical data are being relied upon instead of repeating the complete nonclinical development programme.

Where the imported BC/RTFB is new, inadequately characterized, not previously licensed, or is not sufficiently supported by an established nonclinical and clinical development programme, an appropriate nonclinical package shall be submitted. Such data should include relevant pharmacological and immunogenicity studies, toxicological evaluation and local tolerance studies, as appropriate to the nature of the biological product. The extent of additional nonclinical studies should be determined on a risk-based basis, taking into consideration the nature of the vaccine,

previous human experience, the extent of manufacturing or formulation changes and the availability of reliable safety and immunogenicity information.

9. Clinical Requirements

Where the imported BC/RTFB is derived from a licensed/registered product with established clinical experience, the applicant shall provide the available clinical evidence supporting the safety, immunogenicity and, where applicable, efficacy/effectiveness. This should include relevant clinical development data, immunogenicity studies, safety data, dosing schedules, target population information and available post-marketing clinical experience. The applicant shall establish a scientific bridge between the product evaluated in the original clinical studies and the product proposed for registration in Pakistan. Such bridging should primarily be supported by comparative quality and analytical data demonstrating that the imported bulk and locally formulated/filled finished product have comparable critical quality attributes.

Where the locally formulated and filled product is essentially the same formulation as the clinically evaluated biological product, and adequate analytical, biological and manufacturing comparability has been demonstrated, repetition of the complete clinical development programme may not ordinarily be necessary. However, the DRAP may require a comparative clinical immunogenicity and/or safety study where the available quality data is insufficient to establish comparability, where formulation or manufacturing changes could potentially influence immune response or safety or efficacy, or where the product is intended for a population, dose, schedule or indication different from that supported by the existing clinical evidence.

Where the imported BC/RTFB is not an established licensed product, lacks adequate clinical experience, or is materially different from the product for which clinical data is submitted, the applicant shall provide an appropriate clinical development programme. Depending on the nature and development status of the product, this may include Phase I, II and/or III studies addressing safety, tolerability, immunogenicity and efficacy/effectiveness. The clinical programme should be appropriate to the product type, target population, indication, dosing/vaccination schedule and intended use in Pakistan.

10. Post-Marketing Safety and Pharmacovigilance

The applicant shall submit available post-marketing safety and pharmacovigilance data for the imported BC/RTFB finished product, particularly where the finished biological product is already licensed and marketed in the country of origin or other jurisdictions. The submission should include cumulative safety data, where applicable Adverse Event Following Immunization (AEFI) information, serious adverse events, identified safety signals, recalls or withdrawals, regulatory actions, relevant Product Safety Update Report (PSUR) reports, risk-management measures and any significant safety-related variations. The applicant shall also provide a pharmacovigilance system and risk-management plan appropriate for the applied biological product, including arrangements for collection, assessment and reporting of adverse events. The duration and extent of post-marketing safety data should be considered on a risk-based basis, taking into account the duration of marketing, number of doses administered, extent of international use, target population and availability of established safety information; however, for an established vaccine or other biological product, a meaningful cumulative post-marketing safety history should normally be expected rather than an arbitrary minimum duration alone.

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