2. DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS [{DRUG SUBSTANCE NAME}, {MANUFACTURER}]

The description of the drug substance manufacturing process represents the applicant's regulatory commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls. For example:

For NCE:

A flow diagram of the synthetic processes should be provided that includes molecular formulas, weights, yield ranges, chemical structures of starting materials, intermediates, reagents, and drug substance reflecting stereochemistry, and that identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment, and operating conditions (eg, temperature, pressure, pH, time).

Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in 3.2.S.2.5.

For Biotech:

Information should be provided on the manufacturing process, which typically starts with vials of the cell bank and includes cell culture, harvests, purification and modification reactions, filling, storage, and shipping conditions.

Batches and scale definition

An explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates, and batch size or scale should be provided.

Cell culture and harvest

A flow diagram should be provided that illustrates the manufacturing route from the original inoculum (eg, cells contained in one or more vials of the working cell bank) up to the last harvesting operation. The diagram should include all steps (ie, unit operations) and intermediates. Relevant information for each stage, such as population doubling levels, cell concentration, volumes, pH, cultivation times, holding times, and temperature should be included. Critical steps and critical intermediates for which specifications are established (as mentioned in 3.2.S.2.4) should be identified.

A description of each process step in the flow diagram should be provided. Information should be included, for example, on scale; culture media and other additives (provide details in 2.3.S); major equipment (provide details in Appendix 3.2.A.1); and process controls, including in-process tests and operational parameters, process steps, equipment, and intermediates with acceptance criteria (provide details in 3.2.S.2.4). Information on procedures used to transfer

material between steps, equipment, areas, and buildings, as appropriate, and on shipping and storage conditions should be provided. (Provide details on shipping and storage in 3.2.S.2.4.)

Purification and modification reactions

A flow diagram should be provided that illustrates the purification steps (ie, unit operations) from the crude harvests up to the step preceding filling of the drug substance. All steps and intermediates and relevant information for each stage (eg, volumes, pH, critical processing time, holding times, temperatures and elution profiles, selection of fraction, and storage of intermediate, if applicable) should be included. Critical steps for which specifications are established as mentioned in 3.2.S.2.4 should be identified.

A description of each process step (as identified in the flow diagram) should be provided. The description should include information on, for example, scale, buffers, and other reagents (provide details in 3.2.S.2.3), major equipment (provide details in Appendix 3.2.A.1), and materials. For materials such as membranes and chromatography resins, information for conditions of use and reuse also should be provided. (Provide equipment details in Appendix 3.2.A.1; provide validation studies for the reuse and regeneration of columns and membranes in 3.2.S.2.5) The description should include process controls (including in-process tests and operational parameters) with acceptance criteria for process steps, equipment, and intermediates. (Provide details in 3.2.S.2.4.)

Reprocessing procedures with criteria for the reprocessing of any intermediate or the drug substance should be described. (Provide details in 3.2.S.2.5.)

Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and on shipping and storage conditions should be provided (provide details on shipping and storage in 3.2.S.2.4).

Filling, storage and transportation (shipping)

A description of the filling procedure for the drug substance, process controls (including in-process tests and operational parameters), and acceptance criteria should be provided (provide details in 3.2.S.2.4). The container closure systems used for storage of the drug substance (3.2.S.6.) and storage and shipping conditions for the drug substance should be described.

Reference ICH guidances Q5A, Q5B, and Q6B.