3.2.S.2.4. MANUFACTURING PROCESS

3.2.S.2.4.1. Introduction

This section provides a description of the controls of critical process steps employed during manufacture of BNT162b2 drug substance to ensure that product quality is maintained. Process parameters and tests that are used to control the process and drug substance quality are provided in this section.

Process parameters discussed in this section include all critical process parameters (CPPs). In addition to CPPs, the risk assessment process is also used to identify relevant non-CPPs that have an impact on quality attributes. As described in Section 3.2.S.2.6 Process Development and Characterization, CPPs were conservatively defined after the Cause and Effect (C&E) risk assessment by evaluating the parameters which had a strong functional relationship to a quality attribute (high C&E scores). These relationships were supported by established scientific rationale, platform knowledge or confirmed data available from the process characterization studies. For this program, no non-CPPs having an impact on quality attributes were identified.

Assessment of the methodology for the determination of CPPs is provided in Section 3.2.S.2.6 Process Risk Assessment Strategy. The ICH guidelines define a critical process parameter as "*A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.*"

The ICH guidelines define critical quality attribute (CQA) as "*a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. The assignment of criticality to a quality attribute is based upon the potential of the quality attribute to impact patient safety or efficacy*." CQAs are distinguished from QA by an iterative process of quality risk management and experimentation that assesses the extent to which their variation can have an impact on the quality of the drug product.

For assessment of the drug substance manufacturing process, the assignment of parameter criticality was expanded for all applicable quality attributes.

In-process test for control (IPT-C) and in-process test for monitoring (IPT-M) are used throughout the process to ensure consistent manufacturing. IPT-Cs are in-process tests used to control a quality attribute within a specified range so that it meets the desired DS/DP quality. The IPT-Cs have an associated acceptance criterion. These IPT-Cs are tabulated in this section with their associated acceptance criterion and described in Section 3.2.S.2.4 In-Process Test Methods [Andover] and Section 3.2.S.2.4 In-Process Test Methods [BNT Mainz and Rentschler].

IPT-Ms are in-process tests used to monitor a quality attribute to either ensure that it is consistent with respect to previous process history or for forward processing. The monitoring tests may have action limits. These IPT-Ms are described in Section 3.2.S.2.4 In-Process Test Methods [Andover] and Section 3.2.S.2.4 In-Process Test Methods [BNT Mainz and Rentschler].

These in-process controls (process parameters and in-process tests) are used to ensure control of the individual process steps, process consistency and product quality. If the results of these controls are outside of the acceptable ranges/acceptance criteria, an evaluation of the deviation is performed and the material could subsequently be dispositioned for further manufacture, based on the investigation conclusion.

3.2.S.2.4.2. Manufacturing Process Controls

As described above, Table 3.2.S.2.4-1 provides a list of in-process controls (critical process parameters and IPT-Cs) with their acceptable ranges/acceptance criteria for the drug substance manufacturing process.

Table 3.2.S.2.4-1. Process Controls

Unit Operation	Process Control	Acceptable Range/ Acceptance Criteria	Category
In vitro transcription	4.2 1st ind		
DNase I digestion	4.2 1st ind		
Proteinase K digestion	4.2 1st ind		
Ultrafiltration/ diafiltration	4.2 1st ind		

a. 4.2 1st ind

b. 4.2 1st ind