Briefing Materials for CMC Meeting on 26th November

The purpose of the meeting is to provide an update on quality aspects of the COVID19 mRNA vaccine program including revised drug product manufacturing plans, changes to specification criteria, description and data in support of an increase in batch size , and a summary of the process validation strategy. This updated and new information is being provided in the upcoming CMC submission. We are prepared to discuss any other quality topics in this meeting to support the MAA, potential approval and roll out of of vaccine doses for administration in 2020/21.

Update of Drug Product (DP) specifications

The 2nd CMC Roll will include updated DP specifications for the appearance of visible particulates and RNA integrity.

Appearance of visible particulates

Product-related visible particles have been observed in drug product lots. Therefore, the DP specification for appearance of visible particulates has changed from “Essentially free from visible particulates” to “May contain white to off-white opaque, amorphous particles”.

Characterization by FTIR indicates that these particles contain lipids and are thus intrinsic to the product. Complete justification and characterization are described in Section 3.2.P.2.2 Drug Product, subsection 3.2.P.2.2.3.5 Appearance and Characterization of Intrinsic Particles. In brief, The toxicity has been characterized in nonclinical repeat-dose toxicity studies (Study Numbers 38166 and 20GR142), and their presence as visible particulates (versus sub-visible LNPs) would not be associated with any unique chemical toxicological concern.

In the attachment, the current Draft Section 3.2.P.2.2 is provided to facilitate early review of the information that will be provided in the 2nd CMC Roll. Further discussion of visible particulates will be included within the reply to FDA questions, which will be provided to EMA on 26th November to facilitate early review.

RNA integrity

Capillary gel electrophoresis is routinely used to evaluate the RNA integrity of the BNT162b2 drug product at release and during stability. The acceptance criterion lower limit for drug product RNA integrity had previously been set to align with the drug substance acceptance criterion of ≥ 50% intact RNA. In order to provide further assurance of 50% intact RNA at point of dosing, an acceptance criterion of ≥ 55% at release with an allowance of 5% decrease across stability is proposed. As additional supply nodes are introduced and manufacturing experience is gained, acceptance criteria will be evaluated and revised, as appropriate to assure consistent quality.

In addition, a so-called late migrating species (LMS) has been observed in capillary gel electrophoresis that migrates after the main mRNA peak. The LMS has been observed in drug product batches but is not present in the corresponding final RNA drug substance batches. Characterization results from an evaluation by multiple techniques demonstrate the LMS is intact RNA. The results of characterization evaluations has been included in Section 3.2.P.2.2 Pharmaceutical Development in the subsection titled Enhanced Analytical Characterization.

In the attachment, the current Draft Section 3.2.P.2.2 is provided to facilitate early review of the information that will be provided in the 2nd CMC Roll. Additional characterization data and justification will be included within the reply to FDA questions, which will be provided to EMA on 26th November to facilitate early review.

Updated DP process validation strategy and manufacturing plan

The Process Validation Plan for the 1st Phase of process validation is provided in the attachment. The first phase describes a holistic process validation approach that includes manufacture of one batch from each global supply node. In a later phase, the full validation of all supply nodes will be completed.

The phased approach ensures preliminary process validation data is available from each individual supply node as soon as possible to provide confirmatory manufacturing consistency for the conditional MA in the EU, the EUA in the US, and initial regulatory applications in other regions.

The first phase will provide data for a total of five PPQ lots manufactured in parallel in calender week 48. The timing of manufacturing campaigns is presented in detail in the attached Manufacturing Plan. One DP lot will be manufactured at Pfizer Manufacturing Belgium NV (FC2 filling line, 139 L scale, process as defined for the Puurs site in the 1st CMC Roll of the MAA), whereas four lots will be manufactured at other nodes of the global supply chain. Comparability assessment is planned for all PPQ lots.

A comparison of the process of each supply node is provided in the Supply Node Tables Document in the attachment. The process of supply nodes #4 and #5 (i.e., Pfizer Kalamazoo, USA, filling lines 8 and 18) are considered comparable to the EU supply node #1 (FC2 filling line, Pfizer Manufacturing Belgium NV) and thus representative of the DP process 139 L as defined in the MAA. The supply nodes #2 and #3 are considered supportive.

A preliminary timeline for full validation (i.e. 2nd phase of PPQ) of the DP process at Pfizer Manufacturing Belgium NV (Puurs) is presented in the attached Manufacturing Plan. Full validation is intended as matrix approach including a total of seven PPQ lots addressing different DS supply sites (Andover vs BioNTech/Rentschler), different fill lines (FC2 vs VC2) and different scales (139 L vs 278 L).

Additional filling line

At the DP manufacturing site in Puurs an additional filling line (VC2) is introduced for BNT162b2 drug product and is described in the respective sections in the MAA. The second filling line is added to BNT162b2 production as a measure to ensure supply from Puurs site.

Validation of the VC2 filling line is planned to be addressed in the 2nd phase of process validation, as described above.

Batch size increase for DP process

A batch size increase for DP process is intended to provide sufficient EU supplies for administration prior to the submission of variations for post-approval addition of further DP manufacturing sites.

Two tangential flow filtration (TFF) unit operations are run in parallel during the DP process (Step 5 in Section 3.2.P.3.3) to increase the batch size from 139 L to 278 L. The batch size in Section 3.2.P.3.2 are changed from 139 L to the 139-278 L range.

This change is supported by data from one completed engineering lot and a first GMP lot scheduled to be completed this week. Process validation of the 278 L range is planned to be addressed in the 2nd phase of process validation, as described above.

List of Attachments

Annex 1: Draft Section 3.2.P.2.2 Drug Product

Annex 2: Process Validation Plan for Covid-19 Vaccine Drug Product – Phase I

Annex 3: Draft Supply Node Tables Document

Annex 4: Updated manufacturing plan with tentative timelines