

Peer Reviewers Comments at Day 100

1. This document is sent by:

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2. These Peer Review comments concerns:

Rapporteur's Assessment Report ☒
Co-Rapporteur's Assessment Report ☒

▢ Rapporteur: Filip Josephson filip.josephson@lakemedelsverket.se
▪ Co-Rapporteur: Jean Michel RACE Jean-Michel.RACE@ansm.sante.fr

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and are raised on the following parts of the Assessment Report:

Quality		☒
Non-Clinical		☐
Clinical	☐	☐
RMP		☐
Draft LoQ		☐

Product: COVID-19 mRNA Vaccine BioNTech, BNT162b2, 5'capped mRNA encoding full length SRAS-CoV-2 Spike protein

3. Indication (4.1) - <proposal by the applicant>:

Active vaccination to prevent COVID-19 disease caused by SARS-CoV-2 virus.

4. General comments

This peer review concerns the first rolling review that contains Quality data assessed in the ARs, Overview, new active substance assessments and List of Questions of the Rapporteur (Rapp, SE) and of the Co-Rapporteur (Co-Rapp, FR), in the second rolling review cycle, RR2 (CMC1).

5. Specific Comments

Quality Aspects

A partial CMC package has been submitted for rolling review, where pending sections are clearly indicated in the assessment reports. The evaluation by both Rapporteurs provide a clear review of the presented dossier. The assessment reports and the overviews of both Rapporteurs' allow for secondary assessment without consulting the dossier. The two reports complement each other in many respects and overall provide a comprehensive evaluation of product quality.

The Overviews appropriately summarise the quality assessments, where quality issues are clearly discussed. The LoI is generally properly justified, and there are several questions raised by the rapporteurs which could be merged.

Both Rapporteurs raise major objections, and several other concerns are identified. Both rapporteurs raise a major objection related to comparability between batches used in clinical trials (Process 1) and representative commercial batches (Process 2).

The preliminary assessment of the lipids and the LNPs, as presented by both rapporteurs, is in general supported. In particular, the requests for narrowing specification limits for the lipids and the LNPs, based on available data, are supported. The set of tests and associated analytical methods appear acceptable. It is noted that data from characterisation of the lipids, such as DSC and XRD, are presented, but little or no discussion/interpretation is presented by the applicant. The selection of the amount of each lipid (and allowed ranges) should be justified. For example, it was explained that a cationic lipid to mRNA ratio of around 6.3:1 was found to be suitable, but no details were presented from the development (range investigated, results).

Due to the Applicants plan to update several sections in the quality part of the dossier, no final conclusion can be drawn on the concerned sections until these data are available for assessment. The rapporteurs' overall conclusions are supported.

Non-Clinical Aspects

Clinical Aspects

Risk Management Plan

6. List of Questions

Quality Aspects

The Co-Rapporteur raises several major objections related to GMP status, where the Rapporteur acknowledges that the need for GMP inspections is being addressed by the EMA National competent authority. As a valid EU GMP certificate is an EMA regulatory requirement, the Peer reviewer endorses raising the lack of suitable GMP certifications as a major objection until resolved by the EMA National competent authority. It is recommended that MO 1 and 2 are combined in to one overarching GMP related MO. CoRapp MO3 on MIA and GMP clarifications could be downgraded to an OC and merged with Rapp OC 3.

Rapporteur raises one MO on the comparability of RNA integrity between process 1 and 2, where a significant drop in %RNA integrity is observed in Process 2 batches. This point on the comparability of RNA integrity is raised as an OC by the Co-Rapporteur, where a broader MO on comparability is raised. Raising the comparability of RNA integrity between Process 1 and Process 2 as an MO is supported, and it is suggested that Rapporteurs MO 1 and Co-Rapporteurs MO 4 are merged, as well as several OCs related to comparability be integrated into an overarching comparability MO.

Other concerns:

The following questions are proposed to be merged/harmonised:

Rapp OC4 and Co-Rapp OC5

Rapp OC5 and Co-Rapp OC6

Rapp OC8 and Co-Rapp OC7-OC9

Rapp OC9-OC12 and Co-Rapp OC10/OC12

Rapp OC22 and Co-Rapp OC28/OC29

Co-Rapp OC31 should be reworded to clarify what is requested.

Rapp 37 and Co-Rapp 35 present divergent opinions on the proposed shelf life. Peer reviewer supports Rapps assessment, requesting updated stability reports in order to support the proposed shelf life.

Rapp OC39 and Co-Rapp OC36

Rapp OC42 and Co-Rapp OC45/OC42

Co-Rapp 42, 54 and 48 all relate to the establishment of process parameters.

Rapp OC45 and Co-Rapp OC51

Rapp OC46 and Co-Rapp OC58

Rapp OC47 and Co-Rapp OC59

Rapp OC51 and Co-Rapp OC54, and OC55

Rapp OC53 and Co-Rapp OC61

Rapp OC56 and Co-Rapp OC64

Rapp OC60 (Question on transfer method validation protocol is missing), and Co-Rapp OC63

Rapp OC62 and Co-Rapp OC67

Rapp OC65 and Co-Rapp OC70

Rapp OC70, 72 and Co-Rapp OC75 3. bullet

Divergent opinions:

Rapp OC69 and Co-Rapp OC75 2. bullet. Co-rapporteur's opinion is supported.

Rapp OC48 appears to not be a question, but a typing error.

Non-Clinical Aspects

Clinical Aspects

Risk Management Plan