U.S. FOOD & DRUG ADMINISTRATION

JULY MONTHLY MEETING SUMMARY

Application number:	BLA STN 125742/0
Product name:	COVID-19 mRNA Vaccine (COMIRNATY)
Proposed Indication:	Active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older
Applicant:	BioNTech Manufacturing GmbH
Meeting date & time:	July 15, 2021; 3:30 - 5:00 PM EDT
Committee Chair:	Ramachandra Naik, Ph.D.
Meeting Recorders:	CAPT Michael Smith, Ph.D. and Laura Gottschalk, Ph.D.

1. Background

This meeting was to discuss the original BLA (STN 125742/0) from BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.) for COVID-19 mRNA Vaccine, for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. This is a Rolling BLA submission. The first roll containing eCTD sections 2, 4, and 5 was submitted and received on May 6, 2021. The second and final roll containing eCTD Section 3 (and the rest of Section 1 items) was submitted and received on May 18, 2021.

The purpose of this meeting was to discuss the progress of the review, identify and present any issues, and plan the remainder of the review, including dates for further deliverables and interactions.

Table 1: Review Committee (attendees are listed in bold font)

Review responsibility	Committee Member	Team Leader / Supervisor(s)	Division Director
Chairperson	**Ramachandra Naik**, PhD	BC: **Elizabeth Sutkowski**, PhD	DD: **Loris McVittie**, PhD SA: **Kirk Prutzman**, PhD (acting)
Regulatory Project Managers	**CAPT Mike Smith**, PhD **Laura Gottschalk**, PhD	BC: **Elizabeth Sutkowski**, PhD	DD: **Loris McVittie**, PhD SA: **Kirk Prutzman**, PhD (acting)
Clinical	**Susan Wollersheim**, MD **CAPT Ann Schwartz**, MD	TL: **Lucia Lee**, MD BC: **Maria Allende**, MD	DD: **Doran Fink**, MD, PhD
Product (CMC) DVP Reg coordinator, DVP Product Specialist	**Xiao Wang**, PhD **Anissa Cheung**, MSc	BC: **Keith Peden**, PhD	DD: **Jerry Weir**, PhD DDD: **Robin Levis**, PhD
DS and DP release assays DS and DP release assays DS and DP release assays DS and DP release assays DS and DP release assays LRP and Testing Plan Dev.	**Hsiaoling Wang**, PhD Emnet Yitbarek, PhD **Karla Garcia**, MS Anil Choudhary, PhD, MBA **Esmeralda Alvarado**, PhD **Marie Anderson**, PhD	TL: **Tao Pan**, PhD TL: **Tao Pan**, PhD BC: CDR James Kenney, DSc BC: **Muhammad Shahabuddin**, PhD BC: **Muhammad Shahabuddin**, PhD **Maryna Eichelberger**, PhD	DD: **Maryna Eichelberger**, PhD DDD: N/A

Review responsibility	Committee Member	Team Leader / Supervisor(s)	Division Director
Toxicology	Nabil Al-Humadi, PhD	BC: **Martin Green**, PhD	DD: **Doran Fink**, MD, PhD
Statistics: Efficacy data Safety data Non-clinical data	 **Lei Huang**, PhD **Ye Yang**, PhD **Xinyu Tang**, PhD	 BC: **Tsai-Lien Lin**, PhD TL: **Lei Huang**, PhD BC: **Tsai-Lien Lin**, PhD	DD: John Scott, PhD DDD: Shiowjen Lee, PhD
Epidemiology/ Pharmacovigilance	**Deborah Thompson**, MD, MSPH	TL: LCDR Jane Baumblatt, MD BC: **Manette Niu**, MD	DD: Narayan Nair, MD DDD: Meghna Alimchandani, MD
DMPQ Reviewer/Inspector DMPQ Reviewer/Inspector DMPQ Reviewer DMPQ Inspector DMPQ Inspector DMPQ Inspector Lot Release DMPQ RPM	**Kathleen Jones**, PhD **Laura Fontan**, PhD **Gregory Price**, PhD **Zhongren Wu**, PhD **CDR Donald Ertel**, MS **Ekaterina Allen**, PhD **Cheryl Hulme** Iryna Zubkova, PhD	TL: Nicole Li BC: **Lori Peters**, MS TL: **CDR Donald Ertel**, MS BC: Lori Peters, MS BC: Anthony Lorenzo BC: Joseph Quander BC: James Crim	DD: **John Eltermann**, RPh, MS DDD: Carolyn Renshaw
BIMO	**Haecin Chun**, MT(ASCP)SBB, MS	BC: **Dennis Cato**	DD: **Carrie Mampilly**, MPH
APLB Labeling reviewer	**CAPT Oluchi Elekwachi**, PharmD, MPH Dana Jones	BC: **Lisa Stockbridge**, PhD	DD: Robert Sausville
Container Labeling	**Daphne Stewart**	BC: Timothy Nelle, PhD	DD: **Loris McVittie**, PhD
Electronic integrity	CDR David Schwab, MSIS	**Loris McVittie**, PhD	DD: **Loris McVittie**, PhD
CDISC consult	**Brenda Baldwin**, PhD **Kirk Prutzman**, PhD	BC: **Elizabeth Sutkowski**, PhD	DD: **Loris McVittie**, PhD

Other Attendees:
Sudhakar Agnihothram, Nicolette Devore, Varsha Garnepudi, Marion Gruber, Maureen Hess, Douglas Pratt, Philip Krause, David Rouse and Leslie Taylor

Review Timetable (PDUFA Milestones are in blue)

Review Milestone	Target Due Date
Submitted	
Roll 1 Submission:	06-MAY-2021
Roll 2 Submission (final):	18-MAY-2021
Received:	18-MAY-2021
Committee Assignment:	09-JUN-2021
First Committee Meeting:	03-JUN-2021
Filing checklist/reviews complete:	23-JUN-2021
Filing Meeting:	29-JUN-2021
Filing Action:	16-JUL-2021
Deficiencies Identified:	31-JUL-2021
Initial proprietary name review:	16-AUG-2021
Primary Draft Reviews & Reviewer Reports Due (4 days prior to Mid-Cycle meeting):	25-AUG-2021
Mid-Cycle Meeting (Internal):	31-AUG-2021
Mid-Cycle Communication:	13-SEP-2021
Final draft primary reviews with supervisory Concurrence (upload not required):	01-SEP-2021

PLI Inspections completed:	30-JUL-2021
BiMO Inspections completed:	30-JUL-2021
PeRC briefing materials due to PeRC:	27-JUL-2021
PeRC Meeting:	10-AUG-2021
Lot release protocol & testing plan finalized:	15-AUG-2021
Notify OCOD of pending approval:	15-AUG-2021
Draft SBRA	15-AUG-2021
Labeling Comments to Applicant:	15-AUG-2021
Notify Applicant of PMC/PMR:	15-AUG-2021
Final reviews & addenda signed & uploaded:	30-AUG-2021
Targeted Action Due Date (ADD)	**15-SEP-2021**
PDUFA ADD:	**16-JAN-2022**

Table 2: Scheduled Meetings *(new meetings in italics)*

PDUFA Meetings:
• **First Committee Meeting:** June 3, 2021, 4:00PM – 5:30PM
• **Filing Meeting:** June 29, 2021, 2:00PM – 3:30PM
• **Internal Mid-Cycle:** August 31, 2021, 2:00PM – 3:30PM
• **Mid-Cycle Communication:** September 13, 2021, 3:00PM – 4:00PM
Monthly Committee Meetings:
• July 15, 2021, 3:30PM – 5:00PM
• August 9, 2021, 1:30PM – 3:00PM
• September 10, 2021, 12:30PM – 2:00PM
Labeling Meetings:
• August 4, 2021, 3:00PM – 5:00PM
• August 6, 2021, 3:00PM – 5:00PM
• August 11, 2021, 3:00PM – 5:00PM
• August 16, 2021, 11:00AM – 12:30PM (Carton & Container)
• August 18, 2021, 3:30PM – 5:00PM (Carton & Container)
• *August 23, 2021, 4:00PM – 5:30PM*
• *August 25, 2021, 2:30PM – 4:30PM*
• September 2, 2021, 4:00PM – 5:30PM
• September 7, 2021, 2:00PM – 4:00PM
• September 21, 2021, 3:00PM – 5:00PM
Other Meetings:
• June 4, 2021, 12:30 – 1:30 PM (Testing to support licensure; DVP and DBSQC)
• *July 26, 2021, 3:00 – 4:00 PM (Discussion of non-proprietary name)*

2. Discussion Topics

2.1 Opening remarks from the Chair and RPMs

- As noted in the email sent to the review team on July 9, 2021, the new targeted action due date (ADD) for the BLA is September 15, 2021.
- Prior to the meeting, the Chair requested that the review committee provide projected dates for the completion of their discipline reviews. Please see Table 3, included at the end of this document, for a list of review activities and projected target completion dates (Appendix).
- The RPMs summarized the IRs and Amendments to the BLA to date (please see details at end of document).

2.2 Review of milestones and internal/projected target dates

- The Filing Letter is targeted to be issued and sent to the Applicant on July 16, 2021.
- A meeting to discuss the non-proprietary product name has been scheduled for July 26, 2021.

2.3 Status update (including any major concerns that have been identified so far) from each member of the review committee

2.3.1 Clinical (Susan Wollersheim and Ann Schwartz):

- The clinical reviewers have been working with the statistical reviewers to determine the preferred terms for AESIs in the VAERS datasets so that they correlate with safety analysis in clinical trials. They are currently ensuring that no IRs will be required for the unblinded periods of the clinical trials. Additionally, IRs regarding efficacy of the vaccine are being drafted regarding the inclusion of data from subjects 12-15 years of age and to provide shell tables to the Applicant for safety and efficacy.

2.3.2 CMC (Xiao Wang):

- The CMC reviewer stated that the review of the drug substance is close to be finished which will then be followed by review of the drug product. There were no specific issues that needed to be discussed with the group during the meeting.

2.3.3 DBSQC (Hsiaoling Wang, Emnet Yitbarek, Karla Garcia, Anil Choudhary, Esmeralda Alvarado and Marie Anderson):

- The DBSQC reviewers provided updates that the reagents and lots for testing were received last week. IRs regarding the lot release protocol templates as well as the number of freeze/thaws allowed for the drug substance will be finalized for sending to the Applicant soon.
- It is not certain at this time that the in-support testing ((b) (4) of DS) will be complete by the target action date since

some of the reagents required for testing have been backordered and the new equipment need to be installed.

2.3.4 Toxicology (Nabil Al-Humadi):

- The toxicology reviewer was unable to attend the meeting, but there were no issues to be discussed regarding the progress of the toxicology review.

2.3.5 Statistics (Lei Huang, Ye Yang and Xinyu Tang):

- The statistical reviewer noted that his review is ongoing and they are targeting completion of the stats review memo at the same time as the completion of the clinical review. To help with the review, two new statistical reviewers have been added to the review committee: Ye Yang will review safety data while Xinyu Tang will be responsible for non-clinical data. Xinyu Tang asked to contact her if any of the discipline reviewers need non-clinical stats support.

2.3.6 Epidemiology/Pharmacovigilance (Deborah Thompson):

- The reviewer noted that a pregnancy registry protocol was submitted to the BLA which she is reviewing to determine if it will be a PMC.

2.3.7 DMPQ (Kathleen Jones, Laura Fontan, Gregory Price, Zhongren Wu, Donald Ertel, Ekaterina Allen, Cheryl Hulme and Iryna Zubkova):

- The DMPQ reviewers are finalizing an IR for the first round of comments to send to the Applicant next week. The Andover inspections will take place from July 19-23 and the Puurs inspections occurred from June 23-July 2. Pending final management review, the waiver for inspections of the Kalamazoo site will be closed next week.
- Until all facilities have been inspected, a firm date for the completion of DMPQ's review cannot be provided.

2.3.8 BiMO (Haecin Chun):

- The BIMO reviewers had no issues to share with the review committee. BIMO inspections were previously conducted for Protocol C4590001. Due to the COVID-19 pandemic restrictions, no foreign study sites were selected. On-site inspections were conducted for a total of nine (9) domestic study sites and the final classification of all nine inspections were No Action Indicated (NAI). No significant information was gathered from the inspections that would preclude approval of the BLA.
- BIMO noted that the data integrity component of these nine inspections was missing. However, since no study conduct issues were identified during inspections, BIMO does not believe that the lack of the data integrity component is a concern.
- BIMO wanted to make the team aware of the previous BIMO inspection history of Dr. Michael Levin (Study Site# 1036), who had participated in

the study of Protocol C4590001. His study site was inspected last November for a Moderna COVID-19 Vaccine clinical trial. At the end of the inspection, a form 483 was issued. CBER classified it as OAI (Official Action Indicated) and an untitled letter was issued to Dr. Levin.

2.3.9 APLB (Oluchi Elekwachi):

- The APLB reviewer reminded the review committee that priority name review for the submission was completed and comments are being drafted. If additional safety changes are made, APLB will make an addendum.

2.3.10 Container Labeling (Daphne Stewart):

- The reviewer noted that no major issued have been identified and minor IRs will be sent out for the labels later.

2.4 Additional Discussion Item: Post-authorization Effectiveness Data

- No post-authorization effectiveness data were submitted to the BLA. However, there have been numerous studies published to date on the real-world evidence (RWE) from the post-authorization use of Pfizer-BioNTech COVID-19 Vaccine. The review team and managers discussed the best way to include the RWE data into the clinical review memo, if at all.
- The clinical reviewer and others noted that RWE would be difficult to capture in the review memo due to the high volume of data that is being published; any information included in the memo would be quickly outdated. As a compromise, a summary could be included in the review memo stating whether RWE data affect the conclusions from our review and whether they are or are not contradictory to what was observed in the clinical trials for effectiveness.

3. Information Requests:

1. 05/18/2021: Three questions regarding datasets (Response in 125742/0.3)

2. 05/20/2021: Four facilities questions and a request for a t-con on 5/25/21 or 5/26/21 to discuss production schedule and the shutdown activities planned for the Puurs, Belgium site (Response in 125742/0.4)

3. 06/08/2021: Three clinical questions regarding datasets and the PI (Response in 125742/0.6)

4. 06/09/2021: Clinical IR requesting dates for PREA deferred studies (Response in 125742/0.7)

5. 06/25/2021: DBSQC IR regarding the lot release protocol (LRP) template and samples and reagents (Response in 125742/0.10)

6. 06/25/2021: Clinical IR regarding the document titled “bnt162-01-intrim3-report-body” (Response in 125742/0.9)

7. 06/29/2021: Clinical IR RE latest date of randomization for participants included in the reactogenicity subset for Study C4591001. (Response in 125742/0.8)

8. 07/02/2021: 18 question from DVP on product related issues and categorical exclusion for an environmental assessment. (Awaiting response)

9. 07/06/2021: Clinical IR RE the document titled “c4591001-interim-mth6-report-body.pdf.” (Awaiting response)

10. 07/09/2021: IR RE the validation of the RNA Integrity by capillary gel electrophoresis method. (Awaiting response)

11. 07/13/2021: OBE IR to add myocarditis and pericarditis to the PVP. (Awaiting response)

12. 07/13/2011: DVP IR regarding exception or alternative to the requirement that products in multiple-dose vials include a preservative (Awaiting response)

4. Amendments:

1. 05/18/2021: Second roll and final piece of the BLA, the review clock has started. This amendment was not submitted in response to an IR.

2. 05/19/2021: Request for Proprietary Name Review. This amendment was not submitted in response to an IR.

3. 05/19/2021: Response to May 18, 2021, IR RE three dataset questions.

4. 05/24/2021: Response to DMPQ’s May 20, 2021, IR RE four facilities questions and a request for a t-con on 5/25/21 or 5/26/21 to discuss production schedules and the shutdown activities planned for the Puurs, Belgium site.

5. 05/24/2021: COVID-19 case strain sequencing data. This amendment was not submitted in response to an IR.

6. 06/16/2021: Response to June 8, 2021, clinical IR on three clinical questions regarding datasets and the PI.

7. 06/17/2021: Response to June 9, 2021, clinical IR requesting dates for PREA deferred studies.

8. 07/02/2021: Response to June 29, 2021, clinical IR RE latest date of randomization for participants included in the reactogenicity subset for Study C4591001.

9. 07/02/2021: Response to June 25, 2021, clinical IR regarding IR regarding the document titled “bnt162-01-interim3-report-body”

10. 07/09/2021: Response to DBSQC’s 6/25/21 IR regarding the lot release protocol (LRP) template and samples & reagents.

5. Post-meeting Updates:

- The Filing Notification Letter was sent to the Applicant on July 16, 2021.
- The IRs discussed by DBSQC were emailed to the Applicant on July 16, 2021.
- Pfizer submitted STN 125742/0.13 on July 19, 2021, waiving their rights to mid- and late-cycle review meetings.

Appendix

Table 3. Review Activities and Target Completion Dates

Task title/description/milestone	Target completion date (Week of…)
BLA submission Roll 1 submission Roll 2 submission (final	 May 6, 2021 May 18, 2021
Received	May 18, 2021
Committee assignment	May 19, 2021
First Committee Meeting	June 3, 2021
Discussion of testing of DS and DP to support licensure (DVP and DBSQC)	June 4, 2021
Filing review complete	June 23, 2021
Request for lot release protocol template, reagents and samples for testing	June 25, 2021
Filing Meeting	June 29, 2021
Proprietary Name Review complete	July 2, 2021
Reagents and samples received	July 9, 2021
Filing Action	July 15, 2021
VRBPAC meeting	No plan to hold an advisory committee meeting
Pre-licensure facilities inspections complete	July 23, 2021
PeRC briefing materials due	July 27, 2021
Post-authorization safety/Epidemiology/ Pharmacovigilance Plan review memo complete	August 5, 2021
PeRC meeting	August 10, 2021
First set of comments on Package Insert	August 11, 2021
Notification of PMC/PMR	August 13, 2021
Obtain Lot Release Clearance	August 16, 2021

Obtain Compliance check	August 16, 2021
Determine non-proprietary name	August 16, 2021
APLB review memo complete	August 20, 2021
Comments on carton and container labels	August 20, 2021
Establishment Inspection Reports complete	August 27, 2021
Establish product expiry date	August 30, 2021
Nonclinical review memo complete	August 30, 2021
DMPQ memo complete (reviewer)	August 30, 2021
Waiver for FDA-designated suffix to proper name	August 30, 2021
Lot release protocol and testing plan finalized	August 30, 2021
CMC review memo complete (reviewer)	August 30, 2021
Clinical review memo complete (reviewer)	August 30, 2021
Statistical review memo complete (reviewer)	August 30, 2021
BIMO review memo complete	August 31, 2021
Mid-Cycle Meeting, Internal (scheduled)	August 31, 2021
DBSQC review memo complete	September 3, 2021
Carton and container labels done	September 3, 2021
Labeling review complete	September 10, 2021
Mid-Cycle Communication (scheduled)	September 13, 2021 (may be canceled)
DMPQ memo complete (supervisory review)	September 13, 2021
CMC review memo complete (supervisory review)	September 13, 2021
Statistical review memo complete (supervisory review)	September 14, 2021
Clinical review memo complete (supervisory review)	September 15, 2021
SBRA complete (Chair draft: August 30, 2021)	September 15, 2021
Target Action Due Date	**September 15, 2021**
DS and DP testing complete (DBSQC)	After the ADD