

2.4 NONCLINICAL OVERVIEW

Justification for the Absence of an Update to the Nonclinical Overview

November 2023

LIST OF ABBREVIATIONS

Abbreviation	Term
CMC	Chemistry Manufacturing and Controls
MAH	Marketing Application Holder
NCO	Nonclinical Overview
PPQ	Process Performance Qualification

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1. INTRODUCTION

Reference is made to Pfizer/BioNTech's line extension submission filed in November 2023 to seek marketing authorization for Comirnaty Omicron XBB.1.5 3 microgram/3 dose concentrate for dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified) multidose vial with a yellow cap.

Rationale is provided in Section 2 below justifying why an updated NCO will not be submitted with the line extension submission.

2. JUSTIFICATION FOR OMISSION OF THE NON-CLINICAL OVERVIEW FROM THE LINE EXTENSION APPLICATION

The MAH believes that a NCO for Comirnaty Omicron XBB.1.5 3 microgram/3 dose (concentrate for dispersion for injection) multidose vial (yellow cap) is not required with this line extension submission based on the following rationale. The formulation and associated manufacturing process is the same as the registered 10 microgram/1 dose (concentrate for dispersion for injection) single dose vial (light blue cap), with the exception of cap color (See Section 2.1). There is no change in the clinical administration route (intramuscular) or posology. There are no safety concerns specific to the formulation, manufacturing process or posology that would warrant additional measures compared to those already in place for the current registered product (concentrate for dispersion for injection pharmaceutical form). The benefit-risk profile of the vaccine remains favorable and unchanged. Therefore, there were no new nonclinical studies conducted to support the change in concentration or dosing volume and thus the NCO has not been updated.

2.1. CMC/MANUFACTURING

The following modifications have been made to Comirnaty Omicron XBB.1.5 3 microgram/3 dose (concentrate for dispersion for injection) multidose vial (yellow cap) that differentiates it from the currently registered 3 microgram/10 dose (concentrate for dispersion for injection) multidose vial (maroon cap):

1. The concentration of the Comirnaty Omicron XBB.1.5 3 microgram/3 dose (concentrate for dispersion for injection) multidose vial is 0.033 mg/mL RNA while the current registered 3 microgram/10 dose (concentrate for dispersion for injection) multidose vial concentration is 0.1 mg/mL RNA.
2. The multidose vials for Comirnaty Omicron XBB.1.5 3 microgram/3 dose (concentrate for dispersion for injection) product will contain 3 doses of 0.3 mL while the current registered 3 microgram/10 dose (concentrate for dispersion for injection) multidose vial contains 10 doses of 0.2 mL after dilution.
3. The Comirnaty Omicron XBB.1.5 3 microgram/3 dose (concentrate for dispersion for injection) drug product will have an injection volume of 0.3 mL while the current registered 3 microgram/10 dose (concentrate for dispersion for injection) multidose vial has an injection volume of 0.2 mL.

4. The Comirnaty Omicron XBB.1.5 3 microgram/3 dose (concentrate for dispersion for injection) drug product will have a yellow cap while the currently registered 3 microgram/10 dose (concentrate for dispersion for injection) multidose vial has a maroon cap.

From a manufacturing process and equipment perspective, the 3 microgram/3 dose (concentrate for dispersion for injection) drug product is equivalent to the registered 10 microgram/1 dose (dispersion for injection), with the exception of cap color. Additionally, there are no changes to specifications from the registered 10 microgram/1 dose (dispersion for injection) relative to the 3 microgram/3 dose (concentrate for dispersion for injection) vials. Process validation of the registered 10 microgram/1 dose (dispersion for injection) vial was successfully completed and consisted of three PPQ lots demonstrating that the manufacturing process consistently produces drug product lots of acceptable quality, thereby supporting manufacture of the 3 microgram/3 dose (concentrate for dispersion for injection) drug product.

The amount of RNA and amount of each lipid component per dose remain constant between the pediatric 0.1 mg/mL (3 microgram)/ 10 dose (concentrate for dispersion for injection) and 0.033 mg/mL (3 microgram)/ 3 dose (concentrate for dispersion for injection) vials. However the sucrose and Tris buffer components in the 0.033 mg/mL (3 microgram)/3 dose (concentrate for dispersion for injection) vials are higher in concentration than the sucrose and Tris buffer components in the 0.1 mg/mL (3 microgram)/10 dose (concentrate for dispersion for injection) vials; the difference in the amount per dose results from differences in container content, dilution prior to administration, and injection volume of each presentation. Sucrose and Tris buffer components do not exceed levels applied in presentations for adults (15/15 micrograms/dose). See [Table 1](#) for drug product composition amount per dose comparisons for the 3 microgram/10 dose (concentrate for dispersion for injection) and the 3 microgram/3 dose (concentrate for dispersion for injection) presentations.

Table 1. Drug Product Compositions

Presentation	Composition at Filling ^a	Fill Vol (mL)	Dilution Vol (mL) ^b	Composition at Point of Use	Amount per dose
Tris/Sucrose Formulation 3 µg MDV (Dilution required, 10 dose vial)	0.1 mg/mL mRNA, 10 mM Tris (pH 7.4), 300 mM sucrose	0.4	2.2	CCI [REDACTED]	3 µg RNA 0.04 mg ALC-0315 0.005 mg ALC-0159 0.01 mg DSPC 0.02 mg Cholesterol 3.2 mg Sucrose 0.006 mg Tris base (tromethamine) 0.04 mg Tris HCl 1.52 mg NaCl ^c
Tris/Sucrose Formulation 3 µg MDV (Dilution required, 3 dose vial)	0.033 mg/mL mRNA, 10 mM Tris (pH 7.4), 300 mM sucrose	0.48	1.1	CCI [REDACTED]	3 µg RNA 0.04 mg ALC-0315 0.005 mg ALC-0159 0.01 mg DSPC 0.02 mg Cholesterol 9.4 mg Sucrose 0.02 mg Tris base (tromethamine) 0.12 mg Tris HCl 1.88 mg NaCl ^c

a. Partial composition shown to highlight differences between the products. Lipid composition is proportional to RNA amount.

b. Dilution performed with 0.9% sodium chloride.

c. Sodium Chloride (NaCl) is from normal saline diluent (0.9%).

MDV = Multi-dose vial

Primary and PPQ stability studies are ongoing, available stability data for the 0.033 mg/mL (3 microgram)/3 dose (concentrate for dispersion for injection) at long term and accelerated storage conditions indicate a similar stability profile to the approved presentations and support the proposed shelf life of 18 months.

Document Approval Record

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COVID-19 Vaccine M2.4 NCO Justification for Absence of Update to Nonclinical Overview for EU LE Submission Nov 2023 Yellow Caps

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PPD