TABLE OF CONTENTS

LIST OF TABLES

090177e19700abfe\Approved\Approved On: 12-May-2021 03:00 (GMT)

FDA-CBER-2021-5683-1149009

ABBREVIATIONS

Abbreviation	Definition
ALC-0159	(2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide)
ALC-0315	((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
A260	Absorbance at 260 nm
ADRM	Animal derived raw material
AOF	Animal origin free
ATM	Animal trial material
ATP	Adenosine triphosphate
BNT	BioNTech
cDNA	Complimentary DNA
CFU	Colony forming units
CI	Confidence Interval
CMC	chemistry, manufacturing, and controls
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
CPP	Critical process parameter
CQA	Critical quality attribute
CTD	Common technical document
CTP	Cytidine triphosphate
DART	developmental and reproductive toxicology (study)
DS	Drug substance
dsRNA	Double stranded RNA
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
(b) (4)	
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked Immunosorbent Assay
EU	Endotoxin unit
FMEA	Failure mode and effect analysis
(b) (4)	
GMP	Good manufacturing practice
GLP	Good Laboratory Practice
(b) (4)	
GTP	Guanosine triphosphate
HEPES	Hydroxyethyl piperazine ethanesulfonic acid
hcDNA	Host cell DNA
hcP	Host cell proteins
HPLC	High performance liquid chromatography
IgG	Immunoglobulin G
(b) (4)	
ICH	International Council for Harmonization
IPC	In-process control
IPT	In-process test
IPT-C	In-process test for control
IPT-M	In-process test for monitoring
IVT	In vitro transcription
LNP	lipid nanoparticle
(b) (4)	
modRNA	nucleoside modified messenger RNA
mRNA	messenger RNA
(b) (4)	
MCB	Master cell bank
NAAT	nucleic acid amplification test
NaCl	Sodium chloride

090177e19700abfe\Approved\Approved On: 12-May-2021 03:00 (GMT)

FDA-CBER-2021-5683-1149010

Abbreviation	Definition
NaOH	Sodium hydroxide
NMR	Nuclear magnetic resonance
nt(s)	Nucleotide(s)
NTPs	Nucleotide triphosphates
NTU	Nephelometric turbidity unit
NOR	Normal operating range
PAR	Proven acceptable range
PV	Process validation
QA	Quality attribute
QC	Quality Control
RPN	Risk priority number
RNA-LNP	RNA lipid nanoparticle
saRNA	self-amplifying messenger RNA
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19
WCB	Working cell bank

090177e19700abfe\Approved\Approved On: 12-May-2021 03:00 (GMT)

FDA-CBER-2021-5683-1149011

2.3. INTRODUCTION

2.3.1. General Information

Pfizer and BioNTech continue to develop a vaccine intended to prevent Coronavirus Disease 2019 (COVID-19) caused by the virus, SARS-CoV-2. The vaccine is based on SARS-CoV-2 spike (S) glycoprotein antigens encoded in RNA and formulated in lipid nanoparticles (LNPs), referred to as COVID-19 Vaccine (BioNTech code number BNT162, Pfizer code number PF-07302048). The goal of the global development program is to rapidly develop and license a vaccine for use in participants ≥12 years of age, followed by a pediatric indication. Initially, four different clinical candidates were considered based on evaluation of emerging preclinical and clinical data. A single vaccine candidate, BNT162b2, was selected to proceed into the Phase 2/3 of Study C4591001 and anticipated licensure at a 30 µg dose level. An Emergency Use Authorization (EUA 27034) for emergency use of the Pfizer-BioNTech COVID-19 Vaccine in individuals > 16 years of age was issued on December 11, 2021, under section 564 of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 360bbb-3).

This nucleoside modified messenger RNA (modRNA), BNT162b2 (RBP020.2) modRNA, encoding P2 S (V9), expresses a prefusion stabilized full-length variant of the SARS-CoV-2 S-glycoprotein. The candidate platform has blunted innate immune sensor activating capacity and thus augmented antigen expression. The RNA-based vaccine is formulated in LNPs.

The vaccine candidate will be released as a concentrated multi-dose liquid formulation stored frozen at -90 to -60 °C in a 2 mL Type 1 glass vial to be thawed and subsequently diluted with sterile 0.9% sodium chloride Solution for Injection, USP (saline diluent), and stored at 2-8 °C until administration. The Applicant intends to commercialize the current formulation and initially plans to provide a single vial which is designed to provide six 30 µg vaccine doses. The multi-dose vial presentation will be preservative-free.

The multi-dose vial is supplied as a white to off-white sterile frozen liquid, packaged in a clear glass 2 mL vial with a bromobutyl rubber stopper, aluminum overseal and flip off cap.

A 1.8 mL volume of saline diluent is added directly to the vaccine concentrate in the multi-dose vial. After dilution, the vials contain a sufficient volume to supply 6 doses, where each 0.3 mL dose contains 30 µg of vaccine for IM injection.

The vaccine will be administered intramuscularly (IM) in the upper arm (deltoid muscle) as a series of two 30 µg doses of the diluted vaccine solution (0.3 mL each) according to the following schedule: a single 0.3 mL dose followed by a second 0.3 mL dose 21 days later (prime/boost regimen).

A summary of the General Information is provided in Table 2.3-1.

090177e19700abfe\Approved\Approved On: 12-May-2021 03:00 (GMT)

FDA-CBER-2021-5683-1149012

Table 2.3-1. General Information

Item	
Proprietary Name of Drug Product	To be determined
Non-proprietary or Common Name of Drug Product	COVID-19 Vaccine
Compound Name	BioNTech code number BNT162b2
Dosage Form(s)	Liquid Concentrated Formulation in a 2 mL vial
Strength(s)	225 µg/vial
Route of Administration	Intramuscular injection

2.3.2. Module 3 Layout

Module 3 of the dossier is structured with:

- one drug substance (DS) section,
- one drug product (DP) section,
- five A.1 Facilities and Equipment sections,
- three A.2 Adventitious Agents Safety Evaluation sections,
- two A.3 Excipients sections to describe two novel lipid excipients, and
- one R Regional section.

A specific document is provided to describe the plasmid (3.2.S.2.3 Control of Materials - Source, History and Generation of Plasmids).

2.3.3. Control Strategy

A control strategy has been designed to ensure that a product of required quality will be consistently produced. Elements of the control strategy as defined in ICH Q10 may include the parameters and attributes related to the drug substance and drug product, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

The approach to developing a control strategy for the vaccine manufacturing process (b) (4)

(b) (4) The control strategies are described in further detail Sections 3.2.S.2.6 Control Strategy and Section 3.2.P.2.3 Control Strategy.

(b) (4)

090177e19700abfe\Approved\Approved On: 12-May-2021 03:00 (GMT)

FDA-CBER-2021-5683-1149013

(b) (4)

2.3.3.1. Selection of Critical Quality Attributes

The assignment of criticality to a quality attribute is based upon the potential of the quality attribute to impact safety or efficacy. Critical quality attributes (CQAs) are distinguished from quality attributes (QAs) by an iterative process of quality risk management and experimentation that is assessed to the extent to which their variation has an impact on the quality of the product. Additional information is provided in Section 3.2.S.2.6 Quality Attributes and Section 3.2.P.2.3 Quality Attributes.

2.3.3.2. Process Risk Assessment Approach and Parameter Designation

A structured quality risk management program is utilized for all new products, which includes Cause and Effect Matrices (C&E) and Failure Modes and Effects Analysis (FMEA).

The Cause and Effects (C&E) risk assessment was used to assess each process parameter for potential impact on quality attributes. Critical process parameters (CPPs) were conservatively defined after the C&E risk assessment by evaluating the parameters which had a strong functional relationship to a quality attribute as supported by data available from the process characterization studies, established scientific rationale or platform knowledge.

For the PPQ (process validation) campaigns, all CPPs will be included to confirm consistent process performance. Parameter criticality and associated range and settings may be reassessed throughout the product's lifecycle.

(b) (4)

In addition to evaluation of process parameters, for both drug substance and drug product, in process tests for control (IPT-C) and in process tests for monitoring (IPT-M) are used to ensure a consistent manufacturing process. In process tests for control (IPT-C) are in-process tests used to control a QA/CQA to within a specified value so that it meets desired DS/DP quality. The IPT-Cs have an associated acceptance criterion. IPT-Ms are in-process tests used to measure a QA/CQA to either ensure that it is consistent with respect to previous process history or for forward processing. The monitoring tests may have action limits.

Refer to Section 3.2.S.2.6 Manufacturing Process Development and Section 3.2.P.2.3 Manufacturing Process Development for additional information.

090177e19700abfe\Approved\Approved On: 12-May-2021 03:00 (GMT)

FDA-CBER-2021-5683-1149014

2.3.3.3. Presentation of Control Strategy in the Drug Substance Sections

Provided in Table 2.3-2 is a schematic which summarizes where control information is presented in the drug substance sections of Module 3. Studied and evaluated parameters are discussed in Section 3.2.S.2.6 Process Development and Characterization.

090177e19700abfe\Approved\Approved On: 12-May-2021 03:00 (GMT)

FDA-CBER-2021-5683-1149015

Table 2.3-2. Module 3 Drug Substance Control Strategy Information

	Category	3.2.S.2.6 Manufacturing Process Development	3.2.S.2.2 Description of Manufacturing Process and Process Controls	3.2.S.2.4 Control of Critical Steps and Intermediates	3.2.S.2.5 Process Validation and/or Evaluation
(b) (4)					

090177e19700abfe\Approved\Approved On: 12-May-2021 03:00 (GMT)

FDA-CBER-2021-5683-1149016

2.3.3.4. Presentation of Control Strategy in the Drug Product Sections

Provided in Table 2.3-3 is a schematic which summarizes where control information is presented in the drug product sections of Module 3. Studied and evaluated parameters are discussed in Section 3.2.P.2.3 Process Development and Characterization.

090177e19700abfe\Approved\Approved On: 12-May-2021 03:00 (GMT)

FDA-CBER-2021-5683-1149017

Table 2.3-3. Module 3 Control Strategy Information for Drug Product

	Category	3.2.P.2.3 Manufacturing Process Development	3.2.P.3.3 Description of Manufacturing Process and Process Controls	3.2.P.3.4 Control of Critical Steps and Intermediates	3.2.P.3.5 Process Validation and/or Evaluation
(b) (4)					

090177e19700abfe\Approved\Approved On: 12-May-2021 03:00 (GMT)

FDA-CBER-2021-5683-1149018