

2.3.P.1. DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

The BNT162b2 drug product is supplied as a preservative-free, multi-dose concentrate to be diluted for intramuscular injection, intended for 5 doses. The drug product is a sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer.

Each vial, containing 0.45 mL of the drug product at pH 7.4 is designed to deliver a total of 5 doses after dilution by addition of 1.8 mL of sterile 0.9% sodium chloride solution, with each dose containing 30 µg of RNA in 0.3 mL. There is no manufacturing overage.

The drug product is supplied in a 2 mL glass vial sealed with a bromobutyl rubber stopper and an aluminum seal with flip-off plastic cap.

The composition of the drug product, including amounts per vial and function and quality standard applicable to each component, are given in Table 2.3.P.1-1.

Table 2.3.P.1-1. Composition of BNT162b2 Drug Product, multi-dose vial (225 µg/vial)

Name of Ingredients	Reference to Standard	Function	Concentration (mg/mL)	Amount per vial	Amount per dose
BNT162b2 drug substance	In-house specification	Active ingredient	0.5	225 µg	30 µg
ALC-0315	In-house specification	Functional lipid	7.17	3.23 mg	0.43 mg
ALC-0159	In-house specification	Functional lipid	0.89	0.4 mg	0.05 mg
DSPC	In-house specification	Structural lipid	1.56	0.7 mg	0.09 mg
Cholesterol	Ph. Eur.	Structural lipid	3.1 ^a	1.4 mg	0.2 mg
Sucrose	Ph. Eur.	Cryoprotectant	103 ^a	46 mg	6 mg
Sodium chloride	Ph. Eur.	Buffer component	6	2.7 mg	0.36 mg
Potassium chloride	Ph. Eur.	Buffer component	0.15	0.07 mg	0.01 mg
Dibasic sodium phosphate, dihydrate ^b	Ph. Eur.	Buffer component	1.08	0.49 mg	0.07 mg
Monobasic potassium phosphate ^c	Ph. Eur.	Buffer component	0.15	0.07 mg	0.01 mg
Water for Injection	Ph. Eur.	Solvent/vehicle	q.s.	q.s.	q.s.

a. Values are rounded to maintain the same level of precision as the label claim, with trailing zeros not shown, where applicable. For example, 46 mg sucrose is rounded from 46.35 mg (103 mg/mL).

b. Dibasic sodium phosphate, dihydrate is named as disodium phosphate dihydrate in the Ph. Eur.

c. Monobasic potassium phosphate is named as potassium dihydrogen phosphate in the Ph. Eur.

Abbreviations:

ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)

ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide

DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine



q.s. = quantum satis (as much as may suffice)

2.3.P.2. PHARMACEUTICAL DEVELOPMENT

The formulation and process development and holistic control strategy for BNT162b2 drug product are described in Section 3.2.P.2 Pharmaceutical Development – Introduction . The pharmaceutical development of BNT162b2 utilizes principles described in the ICH Q8 *Pharmaceutical Development* and was based on sound scientific knowledge and prior experience with similar RNA-lipid nanoparticle vaccines, as well as risk assessments and development studies.

A QTPP was established to form the basis for development of BNT162b2. The development of the QTPP considered information from multiple inputs, including the World Health Organization's Target Product Profiles for COVID-19 Vaccines. The QTPP describes the drug product in terms of quality characteristics, listing the intended product quality and performance characteristics to be achieved at the end of the drug substance and drug product manufacturing processes and linking these characteristics to the relevant CQAs. The QTPP for BNT162b2 with associated CQAs (both drug substance and drug product related) is provided in [Table 2.3.P.2-1](#). Quality attributes with associated criticality assessment are discussed in [Section 3.2.P.2.3 Quality Attributes](#).

Table 2.3.P.2-1. BNT162b2 Drug Product Quality Target Product Profile and Quality Attributes

Product Element	Product Quality and Performance Characteristics	Quality Attributes	
Efficacy			
Product Type		Identity of Encoded RNA Sequence	
Indication		In Vitro Expression RNA Integrity 5'-Cap Poly(A) Tail	
Dosage Form		Appearance pH Lipid Identities LNP Size LNP Polydispersity RNA encapsulation RNA Integrity In Vitro Expression	
Drug Product Shelf Life		ALC-0315 Content ALC-0159 Content DSPC Content Cholesterol Content	
Formulation, Ingredients (Drug Product)			
Dosage Strength		RNA Content Container Content for Injections	
Safety			
Primary Package		Appearance (Visible Particulates) Subvisible Particles Bacterial Endotoxins Sterility Container Closure Integrity	
Drug Product Quality Requirements			
Type			
Size			
Tolerability and Clinical Relevance			
Compatibility with Dosing Components		Appearance pH Osmolarity RNA Integrity RNA Content	
Dosing Tolerability		In Vitro Expression Container Closure Integrity Container Content for Injections	
Compatibility with Co-administered Drugs			

Abbreviations: LNP = lipid nanoparticle; ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate); ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide; DSPC = 1,2-Distearoyl-sn-glycero-3-phosphocholine

The 3.2.P.2 Pharmaceutical Development sections describe how the BNT162b2 drug product formulation, presentation, and manufacturing process were developed to ensure the drug

product meets the requirements of the QTPP. CQAs are linked to the product attributes of the QTPP, bridging the QTPP to the control strategy. Because the drug substance is the source of the active component of the drug product, some of the QAs of the drug product are delivered in the drug substance process. The drug product control strategy, presented in [Section 3.2.P.2.3 Control Strategy](#), is built on the assessment of CQAs for drug substance and drug product and considers how they are controlled in both the drug substance and drug product processes.

2.3.P.2.1. Components of the Drug Product

2.3.P.2.1.1. Drug Substance

The RNA component of the drug substance is the only active ingredient in the BNT162b2 drug product. The drug substance is a single-stranded, 5'-capped mRNA produced by in vitro transcription and provided for drug product manufacture as a frozen (-20 ± 5 °C) aqueous solution **CCI** at pH 7.0.

2.3.P.2.1.2. Excipients

The BNT162b2 drug product contains RNA LNPs formulated in phosphate-buffered saline and 300 mM (103 mg/mL) sucrose at target pH 7.4. The buffer components, concentration and rationale for use are presented in Table 2.3.P.2-2.

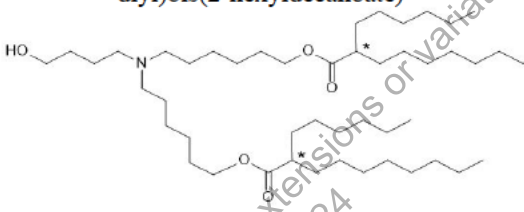
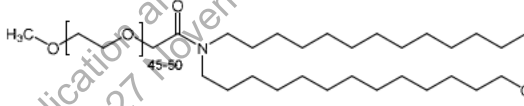
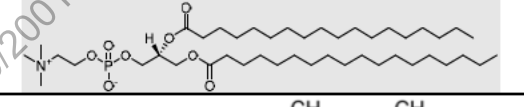
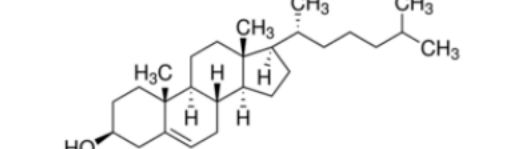
Table 2.3.P.2-2. Buffer Components of BNT162b2 Drug Product

Excipient	Concentration (mg/mL)	Function
Sucrose	103	Sucrose was chosen as a cryoprotectant for frozen storage of the drug product.
Sodium chloride	6	Sodium chloride, potassium chloride, dibasic sodium phosphate dihydrate, monobasic potassium phosphate and WFI, are used to prepare the formulation buffer (PBS). Phosphate based PBS was chosen for its ability to provide adequate buffering capacity at physiological pH.
Potassium chloride	0.15	
Dibasic sodium phosphate, dihydrate	1.08	
Monobasic potassium phosphate	0.15	
Water for Injection	q.s.	

Abbreviations: WFI = Water for Injection; PBS = phosphate-buffered saline

In addition, the BNT162b2 drug product contains four lipid excipients. Each has a functional or structural purpose in the assembly and/or enables stabilization of the LNP component of the drug product. The molecular weight and formula, as well as structure, physical state and storage condition, are shown in [Table 2.3.P.2-3](#) for each of the lipids, followed by a description of the function of each lipid in the assembly and/or stabilization of the RNA LNP.

Table 2.3.P.2-3. Lipid Components of BNT162b2 Drug Product

Lipid	Concentration (mg/mL)	Molecular Weight [Da]	Molecular Formula	Chemical Name (Synonyms) and Structure
ALC-0315 ^a	7.17	766	C ₄₈ H ₉₅ NO ₅	((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) 
ALC-0159 ^b	0.89	~2400-2600	(C ₂ H ₄ O) _n C ₃₁ H ₆₃ N O ₂ n=45-50	2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide 
DSPC ^c	1.56	790	C ₄₄ H ₈₈ NO ₈ P	1,2-Distearoyl- <i>sn</i> -glycero-3-phosphocholine 
Cholesterol ^d	3.1	387	C ₂₇ H ₄₆ O	

a. CAS Number 2036272-55-4

b. CAS Number 1849616-42-7

c. CAS Number 816-94-4

d. CAS Number 57-88-5

Asterisks (*) indicate chiral centers for ALC-0315.

2.3.P.2.2. Drug Product

2.3.P.2.2.1. Formulation Development

The BNT162b2 drug product is manufactured as a preservative-free, sterile, multi-dose concentrate of RNA-containing lipid nanoparticles (LNPs) formulated in phosphate-buffered saline and 300 mM sucrose at pH 7.4 to be diluted for intramuscular (IM) administration. The drug product is filled at 0.45 mL/vial (0.5 mg/mL RNA) into 2-mL glass vials which are stoppered and capped. At the administration site, the vaccine drug product is diluted with 1.8 mL of sterile 0.9% sodium chloride solution to supply 5 doses per vial at 30 µg RNA/dose.

Development of a robust LNP formulation platform, that was ultimately applied to BNT162b2 drug product, was established based on formulation development studies specific

to SARS-CoV-2 spike protein-encoded RNA constructs performed at Acuitas Therapeutics, along with the company's historical knowledge of LNP formulation and process development. Studies described in [Section 3.2.P.2.2 Drug Product](#) were performed with available drug substance and drug product material representing the modRNA platform and included both BNT162b1 and BNT162b2.

Table 2.3.P.2-4 contains a list of the formulation development studies that were conducted during BNT162b2. Further information and descriptions of each study are included in [Section 3.2.P.2.2 Drug Product](#).

Table 2.3.P.2-4. BNT162b2 Formulation Development Studies

Development Study	Study Summary/Outcome
Initial LNP formulation development at Acuitas Therapeutics	Screening studies leading to the selection of the LNP formulation and confirmation of <i>in-vivo</i> activity of the RNA payload.
Formulation of the drug product ^a	Studies support the stability of the drug product formulation to conditions of storage and use.
Drug product – effect of freeze and thaw and frozen storage	Determination of Tg', effect of freeze and thaw on drug product during manufacturing operations and stability upon long term storage.
Excess volume in vial ^a	Rationale for an excess volume in the vial after dilution with 1.8 mL of sterile 0.9% NaCl (saline).
Enhanced analytical characterization	Structure and other physicochemical properties of the BNT162b2 drug product are described.

a. Study performed with BNT162b1 as a surrogate for BNT162b2 based on LNP size, LNP polydispersity and % RNA encapsulation.

2.3.P.2.2.2. Overages

No overage has been added to BNT162b2 drug product.

2.3.P.2.2.3. Physicochemical and Biological Properties

In alignment with ICH Q8, the physicochemical and biological properties of BNT162b2 drug product relevant to the safety, performance and manufacturability of the drug product have been identified and appropriately characterized or controlled.

Please refer to [Section 3.2.P.2.2 Drug Product](#) for further details.

2.3.P.2.3. Manufacturing Process Development

2.3.P.2.3.1. Manufacturing Process Development - Development History

Data for this section is pending and will be updated once the data has been generated, analyzed, and verified.

The drug product has been developed to meet the quality target product profile as described in [Section 3.2.P.2 Introduction](#). The LNP and drug product formulations and processes have remained the same throughout development, except for necessary changes to the scale as development has progressed from initial clinical supplies to commercial manufacture. Based

on evaluation of the results of initial clinical trials, which included multiple RNA constructs, the RNA BNT162b2 construct has been chosen for commercial supply. Development history for the RNA drug substance is discussed in [Section 3.2.S.2.6 Development History and Comparability Assessment](#).

The changes to the manufacturing process have been driven by operational efficiency, and, during facility transfer, driven by fit-to-facility equipment, leading to the proposed commercial process. An overall summary of major process changes made for the LNP fabrication and formulation and filling processes during development is provided in [3.2.P.2.3 Manufacturing Process Development -Development History](#), Table 3.2.P.2.3-1. The indicated process changes are not expected to impact the overall product quality of the resulting drug product lots.

2.3.P.2.3.1.1. Demonstration of Comparability

A comprehensive plan for demonstration of comparability among clinical supplies and commercial product including an assessment of the process designs and comprehensive characterization of the resulting product quality is planned, including Process Design Comparability and Comparability of Product Quality.

2.3.P.2.3.2. Manufacturing Process Development - Quality Attributes

Quality attributes (QAs) of the BNT162b2 drug product (DP) were identified and assessed for criticality. The assessment of QAs relevant to drug substance (DS) is presented within [Section 3.2.S.2.6 Quality Attributes](#), including certain critical quality attributes (CQAs) which are controlled upstream in the DS process and are not further impacted by the DP process.

To focus the criticality assessment on those attributes that are specific to BNT162b2 DP, a subset of attributes that are required aspects of the control strategy were identified. These pre-selected attributes can be found in [Section 3.2.P.2.3 Manufacturing Process Development- Quality Attributes](#) for BNT162b2 DP.

Critical quality attribute (CQAs) for BNT162b2 DP were identified by means of a quality risk and criticality assessment, along with experimentation that determined the extent to which variation in the CQAs had an impact on the quality of the vaccine. The CQAs that may contribute to the ability of the vaccine to elicit the desired immune response or impact safety were further identified through historical knowledge. [Section 3.2.P.2.3 Manufacturing Process Development- Quality Attributes](#) summarizes the DP attributes designated as CQAs as well as the rationale for the criticality assignment.

2.3.P.2.3.3. Manufacturing Process Development - Process Risk Assessment Strategy

Consistent with the expectations for drug development and in alignment with ICH Q8, *Pharmaceutical Development* and ICH Q9, *Quality Risk Management*, a variety of risk assessment tools have been utilized in an iterative process to direct process development and characterization. These have been systematically applied during the course of development and will continue to be used throughout the product life cycle. The approach to BNT162b2

drug product process risk assessment is consistent with the strategy for drug substance described in [Section 3.2.S.2.6 Process Risk Assessment Strategy](#).

Further information is included in [3.2.P.2.3. Manufacturing Process Development - Process Risk Assessment Strategy](#)

2.3.P.2.3.4. Manufacturing Process Development - Process Development and Characterization

Data for this section is pending and will be updated once the data has been generated, analyzed, and verified.

Section [3.2.P.2.3 Manufacturing Process Development -Process Development](#) and Characterization describes the process development and characterization studies performed to understand the effect of process parameters on BNT162b2 product quality attributes.

Process development studies to support the drug product process include studies designed to understand the thawing of the drug substance, mixing of the diluted drug substance and the lipid components in the T-mixer for formation of the lipid nanoparticles (LNP), followed by tangential flow filtration (TFF) for removal of process-related components and formulation of the LNP drug product, followed by sterile filtration, filling, capping and visual inspection. Freezing studies were also performed to support the freezing and storage operations of the final drug product which is stored at the recommended temperature of -90 °C to -60 °C.

2.3.P.2.3.5. Manufacturing Process Development - Lot Genealogy and Usage

Data for this section will be updated once additional data has been generated, analyzed, and verified.

The BNT162b2 and BNT162b1 drug product lots manufactured for nonclinical studies, clinical studies, stability, and development/demonstration purposes are listed in [3.2.P.2.3 Manufacturing Process Development- Lot Genealogy and Usage](#). In addition, the RNA construct, lot number and drug substance batches from which they were derived are listed. The lipids used in the fabrication of BNT162b2 LNPs for one toxicology lot (COVVAC/270320) and the clinical lots are shown in this section. The same BNT162b2 drug product formulation composition has been used throughout nonclinical and clinical studies and will be used for process performance qualification batch production.

2.3.P.2.3.6. Manufacturing Process Development- Control Strategy

Data for this section is pending and will be updated once the data has been generated, analyzed, and verified.

A comprehensive approach to control strategy was taken with the BNT162b2 vaccine manufacturing process to assure sufficient and appropriate controls are in place to minimize any potential risks to the patient. The potential risk to patients is measured through potential harm to the patient from the product (i.e., if critical quality attribute targets are not met). The strategy determines where in the process to install controls to consistently guarantee quality. This control strategy includes not only routine elements of ongoing monitoring and control to

ensure a continuous state of control, but also process validation and process verification through lifecycle management. The control strategy includes non-routine elements where a more intensive assessment is merited in managing intended changes. The control strategy also considers non-critical quality attributes and process performance.

Capturing the elements of control, application of the risk assessment and refinement of the control strategy are iterative processes. The control strategy for the BNT162b2 drug product was developed using a holistic approach considering and assessing several elements of control.

[Section 3.2.P.2.3 Manufacturing Process Development -Control Strategy](#) details the control strategy for BNT162b2 drug product.

2.3.P.2.3.7. Manufacturing Process Development - Analytical Method Evolution

The analytical testing strategy applied to BNT162b2 drug product has evolved throughout the development history as drug product testing sites have changed. These changes to the analytical testing strategy are summarized in [3.2.P.2.3 Manufacturing Process Development - Analytical Method Evolution](#).

Bridging experiments from supportive studies, were conducted for the analytical methods that were changed or replaced. For some methods, both the historic and new methods were tested concurrently, and the data are compared.

2.3.P.2.4. Container Closure System

Data for this section is pending and will be updated once the data has been generated, analyzed, and verified.

The container closure systems for the commercial BNT162b2 drug product are described in Section 3.2.P.7 Container Closure System.

The selection of the primary packaging materials for use with BNT162b2 drug product was made based on results of various physicochemical, biological and functional tests of the primary packaging components, as well as the targeted delivery volumes, available components currently qualified for use on the filling line at the manufacturing site for commercial production, sufficient supply capabilities at the component manufacturers and a history of acceptable component performance for parenteral applications. The data provided demonstrate the suitability of the primary packaging components.

The glass vial meets USP <660>, Ph. Eur. 3.2.1, and JP 7.01 compendial requirements for chemical testing for Type I glass containers. The elastomeric stoppers meet USP <381>, Ph. Eur. 3.2.9 and JP 7.03 compendial chemical testing requirements for elastomeric closures. Stopper testing has been performed and results demonstrating compliance is shown in [3.2.P.2.4 Container Closure System](#).

Controlled extraction studies were performed on the product contact bromobutyl rubber stopper material to establish a comprehensive qualitative and quantitative extractable profile. The studies were performed using model solvents that varied in pH and solvent strength.

Leachable studies are being set up to support the labeled shelf life of the BNT162b2 drug product in its commercial container closure system out to 24 months.

2.3.P.2.5. Microbiological Attributes

The BNT162b2 drug product is supplied as a preservative-free, multi-dose concentrate to be diluted for intramuscular injection. The process of manufacturing encompasses the microbial reduction in the process flows by using pre-sterilized raw materials and supplies, HEPA-filtered, classified production areas, and personnel gowning controls. During manufacturing, the formulated bulk is 0.2 µm sterile filtered prior to being aseptically filled into vials. The sterilizing filter is tested for integrity as part of the manufacturing process.

The storage conditions of the final product do not support microbial growth, as the products are stored frozen at -90 °C to -60 °C. The container closure system and its components were selected based on their ability to protect the quality of the product over its shelf life and have been qualified for use.

The BNT162b2 drug product sterility testing is performed in accordance with USP <71>, Ph. Eur. 2.6.1 and JP 4.06. Alternatively, a rapid sterility test may be utilized. BNT162b2 drug product is tested for bacterial endotoxins during release according to USP <85>, Ph. Eur. 2.6.14 and JP 4.01; refer to Section 3.2.P.5.2 Endotoxin.

The BNT162b2 container closure system has been evaluated by both a dye ingress and headspace analysis testing method. These studies have produced acceptable data and verified that the stopper/vial/cap combination maintains integrity when capped with low, high and nominal capper settings. Results shown in [section 3.2.P.2.5 Microbiological Attributes \[Puurs\]](#) provide evidence of container closure integrity for the BNT162b2 drug product container closure system.

2.3.P.2.6. Compatibility

BNT162b2 is supplied as a frozen, sterile, preservative-free multi-dose concentrate for intramuscular injection, and after thawing is a white to off-white suspension free from observable particles which must be diluted prior to administration. The suspension is filled as 0.45 mL per vial containing 0.5 mg/mL BNT162b2. After dilution by the addition of 1.8 mL of sterile 0.9% sodium chloride solution (normal saline) into the drug product vial, the liquid suspension is opalescent, white to off-white and free from observable particles. After dilution, the vial contains 2.25 mL of dosing solution containing 0.1 mg/mL BNT162b2. At least five 0.3 mL doses each containing 30 µg of RNA are withdrawable from the prepared vial.

The studies described in this section have been performed to assess physicochemical stability of the drug product after dilution with saline using common preparation components, as well as to assess for growth potential of microorganisms.

Thawed hold time studies are ongoing as part of the formal stability program to demonstrate that thawed suspensions (undiluted) of BNT162b2 are physicochemically stable at the point of use.

Studies were performed to evaluate the physicochemical stability and compatibility of BNT162b2 diluted with normal saline in the original glass drug product vial and with commercially available administration components that are commonly used during preparation and storage of the dosing solution and/or during injection. The components evaluated were manufactured with different materials of construction provided by different vendors. The conditions evaluated (i.e., hold time, temperature, ambient light exposure) represent typical and/or worst-case conditions during dosage and administration anticipated in the clinical setting.

Please refer to Section [3.2.P.2.6 Compatibility](#) for further details.

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2.3.P.3. MANUFACTURE

2.3.P.3.1. Manufacturer(s)

Table 2.3.P.3-1 lists the sites that have responsibilities in the production of BNT162b2 drug product and their specified functions.

Table 2.3.P.3-1. Sites and Responsibilities for BNT162b2 Drug Product Manufacture

Site	Responsibility
Pfizer Manufacturing Belgium NV Rijksweg 12 Puurs, 2870 Belgium	LNP fabrication and bulk drug product formulation Fill and finish Primary packaging Secondary packaging Release and stability testing (Composition, Adventitious Agents) Batch release by Qualified Person in EEA [European Economic Area]
Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC 1 Burtt Road Andover, MA 01810 United States	Release and stability testing (Composition and Strength, Identity, Potency, Purity, Adventitious Agents)
Pfizer Inc. 875 Chesterfield Parkway West Chesterfield, MO 63017 United States	Release and stability testing (Composition and Strength, Identity, Potency, Purity, Adventitious Agents)
Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin, Dublin 22 Ireland	Release and stability testing (Identity, Composition)
Hospira Zagreb Ltd. ^a Prudnička cesta 60 10291 Prigorje Brdovečko Croatia	Release testing (Sterility)
SGS Lab Simon SA Vieux Chemin du Poète 10 Wavre, 1301 Belgium	Release testing (Sterility)
BioNTech Manufacturing GmbH Kupferbergterrasse 17-19 55116 Mainz German	Batch release by Qualified Person in EEA [European Economic Area]

a. The legal entity name change from Wyeth BioPharma Division of Wyeth Pharmaceuticals was changed at the acquisition by Pfizer in 2009, since then the Wyeth Pharmaceuticals manufacturing site in Andover, Massachusetts belongs to Pfizer's production sites and is embedded in Pfizer's GMP system. Pfizer will be utilized throughout the CTD.

b. Hospira is a wholly owned subsidiary of Pfizer Inc.

2.3.P.3.2. Batch Formula

The target drug product batch size is 139 L CCI Table 3.2.P.3-2 presents the unit formula for one liter of formulated bulk drug product solution, as well as the batch formula for the representative 139 L batch size.

Table 3.2.P.3-2. Batch Formula for BNT162b2 Bulk Drug Product

Name of Ingredients	Reference to Standard	Unit Formula per 1 L (g)	Quantity per 139 L Batch (g)
BNT162b2 drug substance	In-house specification	CCI	
ALC-0315	In-house specification		
ALC-0159	In-house specification		
DSPC	In-house specification		
Cholesterol	Ph. Eur.		
Sucrose	Ph. Eur.		
Sodium chloride	Ph. Eur.		
Potassium chloride	Ph. Eur.		
Dibasic sodium phosphate, dihydrate ^a	Ph. Eur.		
Monobasic potassium phosphate ^b	Ph. Eur.		
Water for Injection	Ph. Eur.		

a. Dibasic sodium phosphate, dihydrate is named as disodium phosphate in the Ph. Eur.

b. Monobasic potassium phosphate is named as potassium dihydrogen phosphate in the Ph. Eur.

Abbreviations:

ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)

ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N'-ditetradecylacetamide

DSPC = 1,2-Distearoyl-sn-glycero-3-phosphocholine

q.s. = quantum satis, meaning as much as is sufficient

2.3.P.3.3. Description of the Manufacturing Process and Process Controls

Overview of Manufacturing Process

The manufacturing process for BNT162b2 drug product includes lipid nanoparticle (LNP) fabrication and bulk drug product formulation followed by fill and finish.

CCI

[Redacted content]

CCI



An overview flow diagram of the BNT162b2 drug product manufacturing process is presented in [Figure 2.3.P.3-1](#). Additional flow diagrams are located in [Section 3.2.P.3.3 LNP Fabrication and Bulk Drug Product Formulation \[Puurs\]](#) and [3.2.P.3.3 Sterile Filtration, Fill, and Finish \[Puurs\]](#).

Figure 2.3.P.3-1. Overview Flow Diagram of the BNT162b2 Drug Product Manufacturing Process



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Figure 2.3.P.3-1. Overview Flow Diagram of the BNT162b2 Drug Product Manufacturing Process



2.3.P.3.4. Controls of Critical Steps and Intermediates

Data for this section is pending and will be updated once the data has been generated, analyzed, and verified.

This section provides a description of the controls of critical steps employed during manufacture of BNT162b2 drug product to ensure that product quality and integrity are maintained. Process parameters and in-process tests that are used to control the process and drug product quality are provided in [Section 3.2.P.3.4 Controls of Critical Steps and Intermediates - In-Process Monitoring and Control - LNP Fabrication and Bulk Drug Product Formulation \[Puurs\]](#) and [3.2.P.3.4 Controls of Critical Steps and Intermediates - In-Process Monitoring and Control - Fill and Finish \[Puurs\]](#)

This section also provides information regarding process step hold times as described in [Section 3.2.P.3.4 Process Step Hold Times – LNP Fabrication and Bulk Drug Product Formulation](#) and [Section 3.2.P.3.4 Process Step Hold Times – Fill and Finish](#).

In-process tests for control (IPT-Cs) and in-process tests for monitoring (IPT-Ms) are used throughout the process to ensure consistent manufacturing. The test methods for IPT-Cs and IPT-Ms are described in [Section 3.2.P.3.4 In-Process Test Methods](#).

2.3.P.3.5. Process Validation and/or Evaluation

2.3.P.3.5.1. Process Validation and or Evaluation - Manufacturing Process [Puurs]

Data for this section is pending and will be updated once the data has been generated, analyzed, and verified.

The objective of the process validation program will be to demonstrate that the BNT162b2 drug product manufacturing process consistently produces drug product lots of acceptable quality. The validation will include an appropriate number of consecutive process performance qualification (PPQ) lots (also called process validation (PV) lots), to be manufactured at commercial scale to validate the drug substance (DS) thaw [redacted], transfer and dilution of DS, preparation of organic phase (lipids), lipid nanoparticle (LNP) formation and stabilization, buffer exchange and concentration, filtration, concentration adjustment and addition of cryoprotectant, sterile filtration, aseptic filling, stoppering and capping, visual inspection, labeling, freezing, secondary packaging, and shipping of the drug product vials.

2.3.P.3.5.2. Process Validation and or Evaluation - Hold Times [Puurs]

Data for this section is pending and will be updated once the data has been generated, analyzed, and verified.

Maximum process hold times will be justified through developmental activities and additional qualification studies incorporated into the process validation runs. The routine in-process hold times for the BNT162b2 drug product manufacturing process will be confirmed during process validation lots.

All buffers and solutions held ≥ 24 hours will have microbial testing performed during all drug product process validation lots.

All in-process testing for the hold challenge batches will be required to meet the pre-determined acceptance criteria with results consistent across process validation batches as well as with commercial drug product acceptance criteria.

2.3.P.3.5.3. Process Validation and or Evaluation - Validation of Aseptic Filling Procedure by Media Fills [Puurs]

Aseptic simulations (media fills) have been performed to demonstrate that the aseptic manufacturing steps of the BNT162b2 drug product process at Puurs, Belgium, on the Focus Cell 2 (FC2) filling line will be performed aseptically.

Media fills are performed in accordance with aseptic processing guidelines and are periodically required as part of routine requalification of the facility. Media fills are performed after implementation of any significant facility, equipment, process or personnel flow changes in the aseptic fill area or upon introduction of new container closure systems that vary significantly from existing, qualified processes.

2.3.P.3.5.4. Process Validation and or Evaluation - Shipping Validation

Data for this section is pending and will be updated once the data has been generated, analyzed, and verified.

This section summarizes the qualification of the shipping process for transport of BNT162b2 drug product by passive thermal shipping containers for air and road shipments in

commercial images maintaining temperature conditions of -90 to -60 °C from the drug product manufacturing and packaging site in Puurs, Belgium, to dosing sites in EU.

The overall qualification strategy considered both thermal and mechanical aspects of shipping in passive thermal shippers, supported by operational qualification (OQ) and performance qualification (PQ) testing.

Results of thermal qualification and mechanical performance studies have met specified acceptance criteria and support shipments of BNT162b2 drug product by dry-ice based thermal shipping containers when shipped from Puurs, Belgium, to dosing facilities in the EU either directly or via qualified distribution centers.

In addition to the thermal qualification activities for the passive thermal shippers, a simulated distribution study is being conducted to assess drug product and package integrity impact of concurrently applied transport hazards. This study will simulate exposure to worst-case concurrently applied transport hazards with durations replicating a global commercial shipping route that exceeds the anticipated real time shipping requirements.

2.3.P.3.5.5. Process Validation and or Evaluation - Verification of In-Process Test Methods

Data for this section is pending and will be updated once the data has been generated, analyzed, and verified.

2.3.P.4. CONTROL OF EXCIPIENTS

2.3.P.4.1. Control of Excipients (Compendial)

2.3.P.4.1.1. Specifications (Compendial)

The compendial excipients used in the manufacture of BNT162b2 drug product and their quality standards are provided in Table 2.3.P.4-1.

Table 2.3.P.4-1. Specifications for Compendial Excipients

Excipient	Reference to Standard
Cholesterol	Ph. Eur. ^a
Sucrose	Ph. Eur.
Sodium chloride	Ph. Eur.
Potassium chloride	Ph. Eur.
Dibasic sodium phosphate, dihydrate	Ph. Eur.
Monobasic potassium phosphate	Ph. Eur.
Water for Injection	Ph. Eur.

a. Refer to Table 3.2.P.4.1-2 for details.

2.3.P.4.1.2. Analytical Procedures (Compendial)

The compendial excipients are tested in accordance with the current compendia.

2.3.P.4.1.3. Validation of Analytical Procedures (Compendial)

No specific validation is required for compendial methods employed for the testing of compendial excipients.

The GC-FID analytical procedure is qualified as a quantitative procedure for the determination of residual solvents in Cholesterol and includes assessments of system suitability, specificity, linearity, range, limit of detection, limit of quantitation and accuracy.

The qualification results are provided in [Section 3.2.P.4.3 Validation of Analytical Procedures \(Compendial\)](#).

2.3.P.4.1.4. Justification of Specifications (Compendial)

The compendial excipients meet the requirements of the current compendia. No further justification of the compendial specifications is therefore deemed necessary.

Cholesterol is tested against the Ph.Eur. monograph for Cholesterol (0993) with minor differences and some additional tests. For further details, please refer to [Section 3.2.P.4.4 Justification of Specifications \(Compendial\)](#).

2.3.P.4.2. Control of Excipients (Non Compendial)

2.3.P.4.2.1. Specifications (Non-Compendial Excipients)

ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), ALC-0315 ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), and DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine) are non-compendial excipients used in the manufacture of BNT162b2 drug product.

2.3.P.4.2.1.1. Non-Compendial, Novel Excipients - ALC-0159 and ALC-0315

The acceptance criteria for the tests that are performed by or on behalf of the the drug product manufacturing site for the non-compendial excipients ALC-0159 and ALC-0315, prior to their use in the manufacture of the lipid nanoparticle (LNP) drug product, are provided in Table 2.3.P.4-2 and Table 2.3.P.4-3.

Table 2.3.P.4-2. Specification for ALC-0159^a

Quality Attribute	Analytical Procedure	Acceptance Criteria
Appearance	Visual examination	White powder which contains no foreign matter
Identity	Infrared spectroscopy	IR spectrum of the sample corresponds to the reference spectrum
Microbial contamination	Ph. Eur. 2.6.12	TAMC NMT CCI

a. In order to release a batch for use in the manufacture of LNP drug product, results from the supplier are also required for the following tests. For details regarding the specification and methods for these tests performed at the supplier, refer to Section 3.2.A.3.4 Control of Excipients [ALC-0159]. The drug product manufacturer intends to implement these tests as part of incoming materials testing following qualification of the methods.

1. Assay
2. Impurities
3. Residual solvents

Abbreviations: IR = infrared; NMT = not more than; LNP = lipid nanoparticle; TAMC = Total aerobic microbial count; Ph. Eur. = European Pharmacopeia.

Table 2.3.P.4-3. Specification for ALC-0315^a

Quality Attribute	Analytical Procedure	Acceptance Criteria
Appearance	Visual examination	Colorless to pale yellow oil which contains no foreign matter
Identity	Infrared spectroscopy	IR spectrum of the sample corresponds to that of the reference spectrum
Microbial Contamination	Ph. Eur. 2.6.12	TAMC CCI

a. In order to release a batch for use in the manufacture of LNP drug product, results from the supplier are also required for the following tests. For details regarding the specification and methods for these tests performed at the supplier, refer to Section 3.2.A.3.4 Control of Excipients [ALC-0315]. The drug product manufacturer intends to implement these tests as part of incoming materials testing following qualification of the methods.

1. Assay
2. Impurities
3. Residual solvents

Abbreviations: IR = infrared; NMT = not more than; LNP = lipid nanoparticle; TAMC = Total aerobic microbial count; Ph. Eur. = European Pharmacopeia

2.3.P.4.2.1.2. Non-Compendial, Non-Novel Excipient - DSPC

DSPC is a non-compendial, non-novel excipient. The specification for DSPC is provided in Table 2.3.P.4-4.

Table 2.3.P.4-4. Specification for DSPC

Quality Attribute	Analytical Procedure	Acceptance Criteria
Appearance ^a	Visual examination	White solid which contains no foreign matter
Identity ^a	Infrared spectroscopy	IR spectrum of the sample corresponds to the reference spectrum
Assay	HPLC	CC1
Specified Impurities	HPLC	CC1
Unspecified impurities	HPLC	CC1 each
Total Impurities	HPLC	CC1
Residual solvents	GC FID	CC1
Microbial Contamination ^a	Ph. Eur. 2.6.12	CC1

a. Test performed by or on behalf of the drug product manufacturer to confirm the result on vendor CoA
Abbreviations: NMT = not more than; GC FID = gas chromatography flame ionization detection; HPLC = High performance liquid chromatography; IR = Infrared; TAMC = Total aerobic microbial count

2.3.P.4.2.2. Analytical Procedures (Non-Compendial)

Analytical procedures for non-compendial methods and performed by the drug product manufacturing site for the non-compendial, novel excipients ALC-0159 and ALC-0315 are described in [Section 3.2.P.4.2 Analytical Procedures \(Non-Compendial\)](#). Details regarding the methods for the additional tests performed at the supplier are provided in [Section 3.2.A.3.4.2 Analytical Procedures \[ALC-0159\]](#) and [Section 3.2.A.3.4.2 Analytical Procedures \[ALC-0315\]](#).

Analytical procedures for non-compendial methods for the non-compendial, non-novel excipient DSPC are described in this section.

2.3.P.4.2.3. Validation of Analytical Procedures (Non-Compendial)

Non-compendial analytical procedures used to test ALC-0159 and ALC-0315 are verified as summarized in [3.2.P.4.3 Validation of Analytical Procedures – Non-Compendial](#).

Method verification or qualification information for the analytical methods used to test and release DSPC is presented in [3.2.P.4.3 Validation of Analytical Procedures – Non-Compendial](#).

2.3.P.4.2.4. Justification of Specifications (Non-Compendial)

The justification of specifications for the tests performed by the manufacturer of the LNP DP site for ALC-0159 is provided in Table 2.3.P.4-5.

Table 2.3.P.4-5. Justification of Specification for ALC-0159

Attribute	Acceptance Criteria	Justification of Specification
Appearance	White powder which contains no foreign matter	The material is a white powder and should not have foreign matters.
Identity	IR spectrum of the sample corresponds to the reference spectrum of the standard	A match of IR spectra of the sample and the standard confirms the identity of the sample.
Microbial Contamination	TAMC NMT CCI	The limit for microbiological contamination is based on the general limits defined in Ph. Eur. 5.1.4 for non-sterile substances for pharmaceutical use.

Abbreviations: IR = infrared; NMT = not more than; TAMC = Total aerobic microbial count.

The justification of specifications for the tests performed by the manufacturer of the LNP DP site for ALC-0315 is provided in Table 2.3.P.4-6.

Table 2.3.P.4-6. Justification of Specification for ALC-0315

Attribute	Acceptance Criteria	Justification of Specification
Appearance	Colorless to pale yellow oil which contains no foreign matter	The material is a colorless to pale yellow oil and should not have foreign matters.
Identity	IR spectrum of the sample corresponds to the reference spectrum of the standard	A match of IR spectra of the sample and the standard confirms the identity of the sample.
Microbial Contamination	TAMC NMT CCI or NMT CCI	The limit for microbiological contamination is based on the general limits defined in Ph. Eur. 5.1.4 for non-sterile substances for pharmaceutical use.

Abbreviations: IR = infrared; NMT = not more than; TAMC = Total aerobic microbial count

Details regarding the justification of specifications for the additional tests performed at the supplier are provided in [Section 3.2.A.3 Excipients \[ALC-0315\]](#) and [Section 3.2.A.3 Excipients \[ALC-0159\]](#).

2.3.P.4.2.4.1. Non-Compendial, Non-Novel Excipient - DSPC

The justification of specifications for DSPC is provided in Table 2.3.P.4-7.

Table 2.3.P.4-7. Justification of Specification for DSPC

Attribute	Acceptance Criteria	Justification of Specification
Appearance	White solid which contains no foreign matter	The material is a white solid and should not have foreign matters.
Identity	IR spectrum of the sample corresponds to the reference spectrum of the standard	A match of IR spectra of the sample and the standard confirms the identity of the sample.
Assay	CCI [REDACTED]	Assay value within the limits of CCI [REDACTED] is acceptable for an excipient. The limits will be reassessed when data for more batches are available.
Specified Impurities	CCI [REDACTED]	An acceptance criterion for CCI [REDACTED] for each specified impurity equates to a maximum of 1 microgram of an individual impurity in a single dose of the vaccine. This level poses minimal risk from a safety perspective as it is well below the qualification threshold of CCI [REDACTED] in ICH Q3A and well below the M7 limit for an individual mutagenic impurity of CCI [REDACTED] based on a less than lifetime exposure of ≤ 1 month treatment duration of the BNT162b2 drug product.
Unspecified Impurities	CCI [REDACTED] each	An acceptance criterion for CCI [REDACTED] for an individual unspecified impurity equates to a maximum of CCI [REDACTED] of an individual impurity in a single dose of the vaccine. This level poses minimal risk from a safety perspective as it is well below the identification threshold of CCI [REDACTED] ICH Q3A and well below the M7 limit for an individual mutagenic impurity of CCI [REDACTED] based on a less than lifetime exposure of ≤ 1 month treatment duration of the BNT162b2 drug product. Furthermore, the unprecedented speed of development for the BNT162b2 drug product in the context of a global pandemic led to limited manufacturing experience for ALC-0315. In this context, setting specifications based on batch data is not appropriate and could lead to supply issues. The proposed limit guarantees the safety of the patient whilst also ensuring that supplies are available to meet the challenging global demand for this product.

Table 2.3.P.4-7. Justification of Specification for DSPC

Attribute	Acceptance Criteria	Justification of Specification
Total Impurities	CCI	An acceptance criterion of CCI equates to a maximum of CCI in a single dose of the vaccine. The total impurities limit is appropriate based on the limit for individual specified and unspecified impurities. Furthermore, the unprecedented speed of development for the BNT162b2 drug product in the context of a global pandemic led to limited manufacturing experience for ALC-0315. In this context, setting specifications based on batch data is not appropriate and could lead to supply issues. The proposed limit guarantees the safety of the patient whilst also ensuring that supplies are available to meet the challenging global demand for this product.
Residual Solvents		CCI According to ICH guideline Q3C Impurities: Guideline for Residual Solvents, the Option 1 limit is CCI. The specification limits of CCI comply with the Q3C Option 1 limit.
Microbial Contamination		The limit for microbiological contamination is based on the general limits defined in Ph. Eur. 5.1.4 for non-sterile substances for pharmaceutical use.

Abbreviations: IR = infrared; NMT = not more than; TAMC = Total aerobic microbial count; International Council for Harmonisation

2.3.P.5. CONTROL OF DRUG PRODUCT

2.3.P.5.1. Specifications

The release and stability testing specifications for BNT162b2 drug product are provided in Table 2.3.P.5-1.

Table 2.3.P.5-1. BNT162b2 Drug Product Specifications

Quality Attribute	Analytical Procedure ^a	Acceptance Criteria
Composition and Strength		
Appearance	Appearance (Visual)	White to off-white suspension
Appearance (Visible Particulates)	Appearance (Particles) ^b	Essentially free from visible particulates
Subvisible Particles	Subvisible Particulate Matter ^{b, c}	Particles CCI
		Particles CCI
pH	Potentiometry ^b	CCI
Osmolality	Osmometry ^{b, d, e}	CCI
LNP Size	Dynamic Light Scattering (DLS)	CCI
LNP Polydispersity	Dynamic Light Scattering (DLS)	CCI
RNA Encapsulation	Fluorescence assay	CCI
RNA content	Fluorescence assay	CCI
ALC-0315 content	HPLC-CAD	CCI
ALC-0159 content	HPLC-CAD	CCI
DSPC content	HPLC-CAD	CCI
Cholesterol content	HPLC-CAD	CCI
Container content for injections	Volume of injections in containers ^{e, f}	Not less than the sum of the nominal volumes of doses
Identity		
Lipid identities	HPLC-CAD ^e	Retention times consistent with references (ALC-0315, ALC-0159, Cholesterol, DSPC)
Identity of encoded RNA sequence	RT-PCR ^e	Identity confirmed
Potency		
In Vitro Expression	Cell-based flow cytometry	CCI
Purity		
RNA Integrity	Capillary Gel Electrophoresis	CCI
Adventitious Agents		
Bacterial Endotoxin	Endotoxin (LAL) ^b	CCI
Sterility	Sterility ^b	No Growth Detected
Container Closure Integrity	Dye incursion ^g	Pass

a. All assays performed on stability unless otherwise noted.

b. Compendial

c. USP<787> (obscuration method), and aligned with upcoming (Jan 2021) revision of Ph. Eur. 2.9.19

d. USP<785>; also in accordance with Ph Eur. 2.2.35, with minor difference in instrument calibration

e. Assay not performed on stability.

f. Procedure is aligned with Test for Extractable Volume of Parenteral Preparations.

g. Tested at release and on stability for stability batches only

Abbreviations: LNP = Lipid nanoparticles; CAD = charged aerosol detector; RT-PCR = reverse transcription polymerase chain reaction; FACS = fluorescence activated cell sorter; ddPCR = droplet digital PCR; qPCR = quantitative PCR; dsRNA = double stranded RNA; LAL = Limulus amoebocyte lysate; EU = endotoxin unit

2.3.P.5.2. Analytical Procedures

Analytical procedures that are common to BNT162b2 drug substance and BNT162b2 drug product are presented in Table 2.3.P.5-2, and the corresponding methods are detailed in [Section 3.2.S.4.2 Analytical Procedures](#). The analytical procedures that are specific to BNT162b2 drug product are listed in Table 2.3.P.5-3 and are detailed in this section.

Table 2.3.P.5-2. Analytical Procedures Common to BNT162b2 Drug Substance and BNT162b2 Drug Product

Analytical Procedure	Quality Attribute
Potentiometry	pH
RT-PCR	Identity of Encoded RNA Sequence
Capillary Gel Electrophoresis	RNA Integrity
Endotoxin	Bacterial Endotoxin

Abbreviations: RT-PCR = reverse transcription polymerase chain reaction

Table 2.3.P.5-3. Analytical Procedures for BNT162b2 Drug Product Only

Analytical Procedure	Quality Attribute
Appearance	Appearance and Visible Particulates
Subvisible Particulate Matter	Subvisible Particles
Osmometry	Osmolality
Dynamic Light Scattering	LNP Size and Polydispersity
Fluorescence Assay	RNA Content
HPLC-CAD	Lipid Content and Identity
Volume of Injections in Containers	Container Content for Injections
Cell-based Flow Cytometry	In Vitro Expression
Sterility	Sterility
Dye Incursion	Container Closure Integrity

Abbreviations: HPLC-CAD = high performance liquid chromatography-charged aerosol detection, LNP = lipid nanoparticle

2.3.P.5.3. Validation of Analytical Procedures

Validation of analytical procedures was performed to ensure the composition, strength, identity, potency, purity, and safety of BNT162b2 drug product. All non-compendial and compendial analytical procedures were confirmed suitable for their intended use.

Analytical procedures were validated against the parameters presented in ICH Q2(R1), Validation of Analytical Procedures: Text and Methodology, for the respective methodology categories. Quantitative analytical procedures were validated for precision, accuracy, specificity, linearity, range, and robustness. Quantitative procedures used to determine the content of minor constituents were further validated for quantitation limit (QL) and/or detection limit (DL). The identity analytical procedures were evaluated for specificity and robustness. Compendial procedures were verified for use in accordance with the applicable pharmacopeias.

Summaries of the non-compendial validations performed for BNT162b2 drug product release and stability analytical procedures are provided in [Section 3.2.P.5.3 Validation of Analytical Procedures](#).

2.3.P.5.4. Batch Analyses

BNT162b2 drug product lots used for toxicology studies, clinical trials, emergency supply, and stability are summarized in Table 2.3.P.5-4. The analytical testing strategy applied to BNT162b2 drug product has evolved throughout the development history. All results met the acceptance criteria at the time of release.

Table 2.3.P.5-4. Summary of BNT162b2 Drug Product Lots

DP Lot Number ^a	Date of Manufacture	Drug Substance Batch(es)	Purpose of Material
COVVAC/270320	27-MAR-2020	RNA-RF200321-06	Nonclinical toxicology, Stability
BCV40420-A	30-APR-2020	R427-P020.2-DS	Clinical, Stability
BCV40620-A	24-JUN-2020	R438-P020.2-DS	Clinical, Stability
BCV40620-B	25-JUN-2020	R438-P020.2-DS	Clinical
BCV40620-C	26-JUN-2020	R438-P020.2-DS	Clinical
BCV40620-D	29-JUN-2020	R438-P020.2-DS	Clinical
BCV40620-E	30-JUN-2020	R438-P020.2-DS	Nonclinical, Stability
BCV40720-A	23-JUL-2020	R443-P020.2-DS	Clinical, Stability
BCV40720-B	24-JUL-2020	R443-P020.2-DS	Clinical
BCV40720-C	25-JUL-2020	R443-P020.2-DS	Clinical, Stability
ED3938 ^c	16-JUL-2020	R443-P020.2-DS	Clinical inventory, Stability
EE3813 ^d	29-JUL-2020	R445-P020.2-DS	Clinical, Stability
EE8492	05-AUG-2020	20Y513C101	Emergency supply ^b , Stability
EE8493	05-AUG-2020	20Y513C101	Emergency supply ^b , Clinical inventory, Stability

a. See Section 3.2.P.2.3 Lot Genealogy for drug product manufacturing site and scale, and drug substance manufacturing site.

b. Emergency supply designation applies to U.S. market.

c. This lot number is equivalent to BCV40720-P.

d. This lot number is equivalent to BCV40820-P.

Please refer to section [3.2.P.5.4. Batch Analyses](#) for further details.

2.3.P.5.5. Characterization of Impurities

Data for this section is pending and will be updated once the data has been generated, analyzed, and verified.

The impurity profile of the BNT162b2 drug product is based primarily on the impurity profile of the materials used for its manufacture.

The lipid impurities are controlled through the acceptance criteria used for their manufacture.

Impurities from the sucrose, phosphate and chloride salts used in the final drug product formulation are controlled through testing and specifications ensuring compliance to relevant compendial monographs.

There are four identified drug product manufacturing process-related impurities as shown in Table 2.3.P.5-5.

Table 2.3.P.5-5. Potential BNT162b2 Drug Product Process Related Impurities

CCI

Residual ethanol and citrate are introduced during the drug product manufacturing process and HEPES (N (2Hydroxyethyl) piperazineN ' (2 ethanesulfonic acid)) and EDTA (ethylenediaminetetraacetic acid) enter the process as components of the drug substance excipient buffer.

Please refer to [Section 3.2.P.5.5. Characterization of Impurities](#) for further details.

2.3.P.5.6. Justification of Specifications

The specification for BNT162b2 drug product is based on an understanding of the control strategy and CQAs for the drug product. The attributes tested and associated acceptance criteria ensure the consistency of drug product and linkage to clinical experience. This preliminary specification was established to ensure the quality, purity, potency/biological activity and safety of the commercial drug product at release and during storage. The specification was informed by:

- Development experience (manufacture and analytical) with BNT162b2 drug product;
- Total BNT162b2 manufacturing experience, including drug product lots used in development, nonclinical and clinical studies;
- The ongoing release and stability data for drug product.
- Relevant BNT162b2 drug product development data and modRNA platform knowledge.

2.3.P.5.6.1. Specification Setting Strategy

A comprehensive panel of analytical procedures was implemented along with corresponding acceptance criteria to monitor and control BNT162b2 drug product quality at release and during shelf life.

Appropriate analytical procedures were established to monitor and assess BNT162b2 drug product as detailed in Section 3.2.P.5.2 Analytical Procedures and Section 3.2.S.4.3 Validation of Analytical Procedures. With the exception of osmometry (osmolality), volume of injections in containers (container content for injections), HPLC-CAD (lipid identities), and RT-PCR (identity of encoded RNA sequence) assays, which are conducted at drug product release only, all other procedures are conducted at release and during stability studies for drug product.

The approach to setting acceptance criteria for each quality attribute in the BNT162b2 drug product specification included understanding gained from:

- Data obtained for drug product lots used as nonclinical toxicology and clinical trial supplies.
- The relevant long-term stability data that were obtained for the BNT162b2 drug product at recommended storage conditions of -90 °C to -60 °C.
- Experience with the analytical procedure and knowledge of the method capabilities.
- The regulatory expectations for RNA-based products, where appropriate.
- Relevant BNT162b2 development data, including understanding of an impact to potency, safety and immunogenicity of the quality attribute evaluated, available literature, as well as the institutional experience with other mRNA products.

Testing results for each of the quality attributes obtained for drug product lots used as clinical trial supplies served as the basis for clinical justification of the specifications.

Because limited stability data are yet available for representative BNT162b2 drug product at the recommended storage condition of -90 to -60 °C, the acceptance criteria used for stability during shelf life will be the same as the acceptance criteria used for lot release. Finally, the Sponsor also acknowledges that limited data from drug product manufacture at the commercial scale using the commercial process is available at this time to inform the determination of acceptance criteria. When an adequate number of batches have been manufactured, the specification and all associated acceptance criteria will be reassessed.

Thus, the acceptance criteria in the drug product specification reflect the current understanding of criticality of quality attributes, their impact on product performance, and the quality of the product used in clinical trials to ensure consistent manufacture of drug product.

The lots included in the establishment of the commercial specification are presented in [3.2.P.5.6. Justification of Specifications](#).

Descriptions of the analytical methodology used to set the BNT162b2 drug product specifications are contained in the respective analytical procedure sections, Section 3.2.P.5.2. Analytical Procedures.

Method evolution and changes, with bridging information as appropriate, are described in detail [Section 3.2.P.2.3 Analytical Method Evolution](#).

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2.3.P.6. REFERENCE STANDARDS OR MATERIALS

A summary of the drug product reference materials is presented in Table 2.3.P.6-1. The drug product clinical reference material (CRM) has been prepared for use as a reference material for the release and stability testing of drug product and this material may also be used as assay control material for release and stability testing of clinical and process validation materials, as well as initial commercial supply. Additionally, the drug substance reference material detailed in [Section 3.2.S.5.1 Reference Standards or Materials](#) and lipids being purchased from Avanti are also used as a reference material for the release and stability testing of drug product.

Table 2.3.P.6-1. Summary of Reference Materials

Reference Material Designation	Parental Drug Substance Lot	Reference Material Establishment Date	Types of Material Released/Evaluated	
Drug Product Reference Material				
Clinical Reference Material (CRM) lot number PF-07302048-RM	EE8493	September 2020	Clinical Supplies Process Validation Initial Commercial Supplies	DP
Primary Reference Material	TBD	Planned for 2021	Working Reference Material	NA
Working Reference Material	TBD	Planned for 2021	Commercial Supplies	DP
ALC-0315 Reference Material (Used in HPLC-CAD Method)				
CRM lot number TBD ^a	Purchased from Avanti	TBD	Clinical Supplies Process Validation Initial Commercial Supplies	DP
ALC-0159 Reference Material (Used in HPLC-CAD Method)				
CRM lot number TBD ^a	Purchased from Avanti	TBD	Clinical Supplies Process Validation Initial Commercial Supplies	DP
DSPC Reference Material (Used in HPLC-CAD Method)				
CRM lot number TBD ^a	Purchased from Avanti	TBD	Clinical Supplies Process Validation Initial Commercial Supplies	DP
Cholesterol Reference Material (Used in HPLC-CAD Method)				
CRM lot number TBD ^a	Purchased from Avanti	TBD	Clinical Supplies Process Validation Initial Commercial Supplies	DP

a. Initial reference material being used to test commercial materials. Previous lipid materials sourced from Avanti have been used to release lots prior to commercial supplies.
NA = Not Applicable TBD = To be determined

2.3.P.7. CONTAINER CLOSURE SYSTEM

The primary container closure system for the BNT162b2 vaccine consists of the vial components listed in Table 2.3.P.7-1. Listed component dimensions are subject to standard industry tolerances.

Table 2.3.P.7-1. List of Components in Container Closure System

Component	Description
Vial	2 mL Type I borosilicate glass vial, 13 mm finish
Vial Stopper	13 mm vial stopper composed of gray CCI elastomer (bromobutyl rubber) coated with CCI
Vial Seal	13 mm aluminum vial seal with tamper-evident polypropylene flip off cap
a. CCI lubricant complies with USP/National Formulary (NF) requirements for CCI, Ph. Eur. requirements for CCI, Ph. Eur. requirements for CCI Used as a Lubricant CCI CCI for CCI	

2.3.P.7.1. Primary Container Closure System

2.3.P.7.1.1. Vial

CCI
The vial meets USP <660>, Ph. Eur. 3.2.1 and JP 7.01 requirements for Type I glass containers.

2.3.P.7.1.2. Vial Stopper

CCI
The vial stopper meets the requirements of USP <381>, Ph. Eur. 3.2.9, and JP 7.03. Vial stoppers are sterilized by steam.

2.3.P.7.1.3. Vial Seal

CCI
CCI

2.3.P.7.2. Secondary Packaging Components

Drug product vials are placed into corrugated boxes with lids.

2.3.P.8. STABILITY

2.3.P.8.1. Stability Summary and Conclusion

2.3.P.8.1.1. Shelf Life at Recommended Storage Temperature

The initial commercial shelf life of the BNT162b2 drug product is 6 months when stored at the intended storage condition of -90 to -60 °C. The initial shelf life is based on the currently available data from stability studies utilizing material from two emergency supply lots, one clinical lot and one non-clinical lot of drug product. Additionally, supportive stability studies are also being presented for two clinical BNT162b1 lots.

Drug product stability lots have been enrolled in stability programs and are being monitored in accordance with the approved protocols. All testing to date has been performed using analytical methodology and phase appropriate specifications in place at time of testing. The analytical procedures used in the stability programs were developed to monitor the composition, strength, purity, safety and general quality attributes of the drug product.

A summary of all drug product lots on stability studies and current available stability data are shown in [Table 2.3.P.8-1](#). At this time, stability studies are on-going, or are scheduled to be initiated after manufacture of the drug product lot.

Table 2.3.P.8-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
PPQ3: Lot Number TBD (Pfizer, Puurs)	TBD	Stability, Clinical, Commercial, Process performance qualification	Long Term	-90 to -60 °C	0 months	To be initiated
			Accelerated	-60 to -30 °C	0 months	To be initiated
			Accelerated	-20 ± 5 °C	0 months	To be initiated
			Accelerated	5 ± 3 °C	0 months	To be initiated
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	0 months	To be initiated
			Thermal Stress	30 ± 2 °C/ 65 ± 5 % RH	0 months	To be initiated
PPQ2: Lot Number TBD (Pfizer Puurs)	TBD	Stability, Clinical, Commercial, Process performance qualification	Long Term	-90 to -60 °C	0 months	To be initiated
			Accelerated	-60 to -30 °C	0 months	To be initiated
			Accelerated	-20 ± 5 °C	0 months	To be initiated
			Accelerated	5 ± 3 °C	0 months	To be initiated
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	0 months	To be initiated
			Thermal Stress	30 ± 2 °C/ 65 ± 5 % RH	0 months	To be initiated
PPQ1: Lot Number TBD (Pfizer Puurs)	TBD	Stability, Clinical, Commercial, Process performance qualification	Long Term	-90 to -60 °C	0 months	To be initiated
			Accelerated	-60 to -30 °C	0 months	To be initiated
			Accelerated	-20 ± 5 °C	0 months	To be initiated
			Accelerated	5 ± 3 °C	0 months	To be initiated
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	0 months	To be initiated
			Thermal Stress	30 ± 2 °C/ 65 ± 5 % RH	0 months	To be initiated

Table 2.3.P.8-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
EE8493 (Polymun Scientific/Pfizer, Puurs)	September 2020	Stability, Emergency Supply ^a , Clinical inventory	Long Term	-90 to -60 °C	Release	On-going
			Accelerated	-60 to -30 °C	Release	On-going
			Accelerated	-20 ± 5 °C	Release	On-going
			Accelerated	5 ± 3 °C	Release	On-going
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	Release	On-going
			Thermal Stress	30 ± 2 °C/ 65 ± 5 % RH	Release	On-going
EE8492 (Polymun Scientific/Pfizer, Puurs)	September 2020	Stability, Emergency Supply ^a	Long Term	-90 to -60 °C	Release	On-going
			Accelerated	-20 ± 5 °C	Release	On-going
			Accelerated	5 ± 3 °C	Release	On-going
GMP1: Lot Number TBD (Pfizer, Puurs)	TBD	Stability, Clinical	Long Term	-90 to -60 °C	0 months	To be initiated
			Accelerated	-60 to -30 °C	0 months	To be initiated
			Accelerated	-20 ± 5 °C	0 months	To be initiated
			Accelerated	5 ± 3 °C	0 months	To be initiated
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	0 months	To be initiated
			Thermal Stress	30 ± 2 °C/ 65 ± 5 % RH	0 months	To be initiated
BCV40420-A (Polymun Scientific)	May 2020	Stability, Clinical	Long Term	-70 ± 10 °C	4 months	On-going
			Accelerated	-40 ± 5 °C	4 months	On-going
			Accelerated	5 ± 3 °C	4 months	On-going
			Thermal Stress	25 ± 2 °C	4 months	Complete
CoVVAC/270320 (Polymun Scientific)	March 2020	Stability, non-clinical toxicology	Long Term	-70 ± 10 °C	3 months	On-going
			Accelerated	-40 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	On-going

Table 2.3.P.8-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
Supportive Stability (BNT162b1)						
BCV10420-A (Polymun Scientific)	April 2020	Supportive Stability, Clinical	Long Term	-70 ± 10 °C	3 months	On-going
BCV10320-A (Polymun Scientific)	April 2020	Supportive Stability, Clinical	Long Term	-70 ± 10 °C	3 months	On-going
			Accelerated	-40 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	On-going
			Thermal Stress	25 ± 2 °C	3 months	Complete

a. Emergency supply designation applies to US market.
TBD = To be Determined, RH = Relative Humidity

2.3.P.8.1.1.1. Protocol for Testing at the Long Term Condition (-90 to -60°C)

Vials from drug product lots were stored at the recommended storage condition of -90 to -60 °C. Testing is currently being performed on emergency supply lots according to the protocol indicated in Table 3.2.P.8.1-2. The initial clinical lot and a minimum of three process validation lots will also be placed on formal stability according to the protocol indicated in Table 2.3.P.8-2.

Additionally, testing at -70 ± 10 °C is being performed on one clinical lot, one non-clinical lot and two supportive BNT162b1 lots according to the protocol indicated in [Table 2.3.P.8-3](#).

Table 2.3.P.8-2. Protocol for BNT162b2 at the Long Term Condition of -90 to -60°C

Analytical Procedure	Test Interval ^a
Appearance (Visible)	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Appearance (Visible Particulates)	
Potentiometry	
Dynamic Light Scattering (LNP Size)	
Dynamic Light Scattering (LNP Polydispersity)	
Fluorescence Assay (RNA Encapsulation)	
Fluorescence Assay (RNA Content)	
HPLC-CAD (ALC-0315 Content)	
HPLC-CAD (ALC-0519 Content)	
HPLC-CAD (DSPC Content)	
HPLC-CAD (Cholesterol Content)	
Cell-based FACS (In vitro expression)	
Capillary Gel Electrophoresis (RNA Integrity)	
Subvisible Particles	0, 6M, 12M, 18M, 24M
Container Closure Integrity Test	0, 12M, 24M
Endotoxin	0, 12M, 24M
Sterility	0, 12M, 24M

a. Testing not performed at the 1W, 2W or 2M timepoint for emergency supply lot EE8493
W = Week, M = Month, LNP = Lipid Nanoparticle

Table 2.3.P.8-3. Protocol for BNT162b2 Early Clinical, Non-clinical and Supportive Stability DS at the Long Term Condition of $-70 \pm 10^\circ\text{C}$

Analytical Procedure	Test Interval (months) ^{abc}
Appearance (Visible & Visible Particles)	0, 1, 3, 6, 9, 12, 18, 24
LNP Size	
LNP Polydispersity	
RNA Encapsulation	
RNA Content	
ALC-0315 Content	
ALC-0519 Content	
DSPC Content	
Cholesterol Content	
RNA Integrity	
Subvisible Particles	
pH	0, 12, 24
Sterility ^d	0, 24

a. For BNT162b2 lot BCV40420-A, a 4 month time point was added and tested

b. For BNT162b1 lot BCV10420-A, only testing on 0, 3, 6 and 12 months is being performed. Sterility is being performed on 12M end point rather than 24M for this lot

c. For BNT162b2 lot CoVVAC/270320, a 2 week and 2 month time point were tested. Study ends at 6 month time point.

d. Sterility testing not performed on non-clinical lot CoVVAC/270320.

2.3.P.8.1.1.2. Protocol of Testing at the Accelerated Condition

To study the effects of temporary excursions above the recommended storage temperature, drug product is being stored under the accelerated conditions of -60 to -30°C , -40°C , $-20 \pm 5^\circ\text{C}$ and $5 \pm 3^\circ\text{C}$. Protocols are detailed in section [Section 3.2.P.8.1 Stability Summary and Conclusions](#).

2.3.P.8.1.1.3. Protocol for Testing at the Thermal Stress Conditions

To study the effects of temporary excursions above the recommended storage temperature, drug product is being stored under thermal stress conditions at $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{ RH}$ and $30 \pm 2^\circ\text{C}/65\% \pm 5 \text{ RH}$ and tested per the protocols indicated in Section 3.2.P.8.1 Stability Summary and Conclusions.

2.3.P.8.1.2. Summary of Stability Data

2.3.P.8.1.2.1. Summary of Stability Data at the Long Term Storage Condition (-90 to -60°C)

Results from stability studies on BNT162b2 DP stored at the long term condition of $-70 \pm 10^\circ\text{C}$ are currently available for one clinical lot, one non-clinical lot and two supportive clinical lots of BNT162b1 material and results are provided in [Section 3.2.P.8.3 Long-Term](#).

Up to 4 months of data are currently available for the lots manufactured by Polymun Scientific. All data remained within the clinical acceptance criteria in place at the time of testing through the four month time point for lot BCV40420-A and the three month time point for lots CoVVAC/270320, BCV10420-A and BCV10320-A. Overall, the data indicate

that there have been no significant changes in terms of quality, purity, or strength for the drug product.

Additionally, two lots of emergency supply have been placed on formal stability at the long term condition of -90 to -60 °C, with release data available at this time. Stability data will be provided in the future as it becomes available.

2.3.P.8.1.3. Summary of Stability Data at the Accelerated Storage Condition

Results from stability studies on BNT162b2 DP stored at the accelerated condition of -40 ± 5 °C are presented for one clinical lot, one non-clinical lot and one supportive BNT162b1 clinical lot in [Section 3.2.P.8.3 Accelerated](#).

Up to 4 months of data are currently available for lots manufactured by Polymun Scientific. All data remained within the clinical acceptance criteria in place at the time of testing through the four month time point for lot BCV40420-A and the three month time point for lots CoVVAC/270320 and BCV10320-A. The -40 ± 5 °C accelerated condition provides additional supportive data for the long-term storage under recommended condition and supports temporary temperature excursions from the recommended storage condition for up to four months.

Additionally, one lot of emergency supply has been placed on formal stability at the long term condition of -60 to -30 °C, and both lots of emergency supply have been placed on formal stability at the -20 ± 5 °C condition, with release data available at this time. Stability data will be provided in the future as it becomes available.

Results from stability studies on BNT162b2 DP stored at the accelerated condition of 5 ± 3 °C are presented for one clinical lot, one non-clinical lot and one supportive BNT162b1 clinical lot in [Section 3.2.P.8.3 Accelerated](#).

Up to 4 months of data are currently available for lots manufactured by Polymun Scientific. All data remained within the clinical acceptance criteria in place at the time of testing through the two month time point. LNP polydispersity was out of specification at the 3 and 4 month time points for clinical drug product lot BCV40420-A. Additionally, the 3 month time point for clinical drug product lot BCV40420-A was also out of specification for RNA integrity. Changes can be expected at accelerated stability conditions and does not impact the overall stability strategy for this material. The 5 °C accelerated condition provides additional supportive data for the long-term storage under recommended condition and supports temporary temperature excursions from the recommended storage condition for up to one month.

Additionally, two lots of emergency supply have been placed on formal stability at the accelerated condition of 5 ± 3 °C with release data available at this time. Stability data will be provided in the future as it becomes available.

2.3.P.8.1.4. Summary of Stability Data at the Thermal Stress Storage Conditions

To support short term temperature excursions, drug product was exposed to the thermal stress condition of 25 ± 2 °C. Results for one clinical lot and one supportive BNT162b1 clinical lot are presented in [Section 3.2.P.8.3 Thermal – Stress and Cycling](#). There is currently up to four months of available data.

Up to 4 months of data are currently available for lots manufactured by Polymun Scientific. All data remained within the clinical acceptance criteria in place at the time of testing through the one month time point. At the 2 month time point and beyond, drug product lot BCV40420-A was out of specification for RNA integrity. Changes can be expected at stressed stability conditions and does not impact the overall stability strategy for this material.

Additionally, one lot of emergency supply has been placed on formal stability at both the stressed conditions of 25 °C/60% RH and 30 °C/65% RH with release data available at this time. Stability data will be provided in the future as it becomes available.

2.3.P.8.1.5. Summary of Stability Data at the Thermal Cycling Storage Conditions

A minimum of one process validation drug product lot will be subjected to thermal cycling studies at a future date. These studies have not yet been initiated.

2.3.P.8.1.6. Summary of Photostability Stability in Drug Product Vials

A minimum of one process validation drug product lot will be subjected to the ICH photostability condition (option 2) at a future date. This study has not yet been initiated.

2.3.P.8.1.7. Shelf Life and Conclusions

The initial shelf life for the BNT162b2 DP is 6 months when stored at the recommended temperature of -90 to -60 °C.

The initial shelf life is based on:

- Up to 4 months of current available stability data on one lot of clinical drug product
- Up to 3 months of current available stability data on one lot of non-clinical drug product
- Up to 3 months of current available stability data on two clinical lots of BNT162b1 drug product
- Comprehensive comparability assessments performed during development.
- Understanding of the mRNA platform to support the initial shelf life

The shelf life will be extended beyond the 6 month initial shelf life using real time stability data on a minimum of 3 batches of commercially representative material.

Additional drug product lots representative of the commercial process may be placed on stability in the future. Protocols and data will be submitted in the future and used as additional support of the drug product shelf life.

2.3.P.8.2. Post Approval Stability Protocol and Stability Commitment

The commercial shelf life of the drug product will be established based on the ICH stability studies that are being carried out per protocols detailed in [Section 3.2.P.8.1 Stability Summary and Conclusions](#).

Post-approval, a minimum of one lot of BNT162b2 drug product will be enrolled in the commercial stability program at the long term storage condition of -90 to -60 °C each year that drug product is manufactured. The protocol is provided in Table 2.3.P.8-4 for the long term storage conditions of -90 to -60°C.

Table 2.3.P.8-4. Post-Approval Commercial Stability Protocol for Drug Product Stored at -90 to -60 °C

Analytical Procedure/ Quality Attribute		Test Intervals (Months) ^a
Appearance (Visible)		0, 6, 12, 18, 24
Appearance (Visible Particulates)		
pH		
Subvisible Particulate Matter		
Dynamic Light Scattering (DLS)	LNP Size	
	LNP Polydispersity	
Fluorescence Assay	RNA Encapsulation	
	RNA Content	
HPLC-CAD	ALC-0315 Content	
	ALC-0159 Content	
	DSPC Content	
	Cholesterol Content	
Cell-based Flow Cytometry	In Vitro Expression	
Capillary Gel Electrophoresis	RNA Integrity	
Container Closure Integrity Test		Annually through end of shelf life
Sterility		0, End of shelf life
Endotoxin		

a. Additional test intervals may be included for the purpose of extending expiry.

Abbreviations: LNP = Lipid Nanoparticle

2.3.P.8.3. Stability Data

Stability data for long term conditions, accelerated condition, thermal stress and photostability studies are provided in Section 3.2.P.8.3.Stability Data.