

Table of Contents

Table of Contents	1
3.2.P.8.1 Stability Summary and Conclusion	3
3.2.P.8.1.1 Stability Summary	3
3.2.P.8.1.2 Stability Study Protocols.....	5
3.2.P.8.1.2.1 Study Protocols to Support the Initial Use Period for mRNA-1273 Drug Product.....	5
3.2.P.8.1.2.2 Real-Time Stability Study Protocols for GMP mRNA-1273 Drug Product Lots Manufactured at ModernaTX, Inc. (Norwood, MA)	5
3.2.P.8.1.2.3 Real-Time Stability Study Protocols for GMP mRNA-1273 Drug Product Lots Manufactured at Catalent Pharma Solutions (Bloomington, IN).....	7
3.2.P.8.1.2.4 Freeze/Thaw Stability Study Protocol for mRNA-1273 Drug Product.....	9
3.2.P.8.1.2.5 Bracketing Clinical In-use Stability Study Protocol for mRNA-1273 Drug Product.....	9
3.2.P.8.1.2.6 Clinical In-use Stability Study Protocol to Support Emergency Use Authorization/Commercial Image for mRNA-1273 Drug Product	10
3.2.P.8.1.3 Stability Study Results.....	10
3.2.P.8.1.3.1 Stability Study Results mRNA-1273 Drug Product (Development, Clinical and Process Performance Qualification Lots).....	10
3.2.P.8.1.3.2 Freeze/Thaw Stability Study Results	12
3.2.P.8.1.3.3 Clinical In-Use Stability Study Results	12
3.2.P.8.1.3.3.1 Bracketing Clinical In-Use Stability Study Results.....	12
3.2.P.8.1.3.3.2 Clinical In-Use Stability Study Results to Support Emergency Use Authorization/Commercial Image	13
3.2.P.8.1.4 Conclusions and Use Period Claim.....	14

List of Tables

Table 1:	GMP mRNA-1273 Drug Product Stability Testing Overview	4
Table 2:	Development mRNA-1273 Drug Product Stability Testing Overview	5
Table 3:	Development mRNA-1273 Drug Product Stability Protocols for 0.10 mg/mL mRNA and 0.5 mg/mL mRNA	5
Table 4:	GMP mRNA-1273 Drug Product Stability Protocol for Lots Manufactured at ModernaTX, Inc. (Norwood, MA)	6
Table 5:	GMP mRNA-1273 Drug Product Matrix Stability Protocol for PPQ Lot 6007520005 and PPQ Lot 6007520006	6
Table 6:	GMP mRNA-1273 Drug Product Matrix Stability Protocol for Lot 6007520007	7
Table 7:	GMP mRNA-1273 Drug Product Stability Protocol for PPQ Lot 6007320001 Manufactured at Catalent Pharma Solutions (Bloomington, IN)	8
Table 8:	GMP mRNA-1273 Drug Product Stability Protocol for PPQ Lot 6007320002 and PPQ Lot 6007320003 Manufactured at Catalent Pharma Solutions (Bloomington, IN)	8
Table 9:	Preparation Configurations for the Clinical In-use Stability Studies	9
Table 10:	Preparation Configuration for the Clinical In-use Stability Studies to Support Emergency Use Authorization/Commercial Image	10
Table 11:	mRNA-1273 Drug Product Stability Program Lots	11
Table 12:	Summary of Estimated Degradation Rates by Temperature	14

3.2.P.8.1 Stability Summary and Conclusion

3.2.P.8.1.1 Stability Summary

mRNA-1273 Drug Product (DP) registration stability program was executed according to ICH Q1A (R2), *Stability Testing of new Drug Substances and Products*, and ICH Q5C, *Stability Testing of Biotechnological/Biological Products*. mRNA-1273 DP material stored in the commercial container closure system, defined in Section 3.2.P.7, will be assigned an initial shelf life of 6 months when stored at the recommended long-term storage condition of -15°C to -25°C (-20°C), followed by storage at 2 - 8°C for up to 30 days at the point of care site. On the day of dose administration, the product is allowed an additional in-use time of up to 12 hours at 8 to 25°C.

The shelf life is justified from the composite of data generated from mRNA-1273 Ph 1 (one lot), Phase 2 (three lots), Engineering (two lots) and Phase 3 (six lots), and commercial (three lots) supplies (Section 3.2.P.8.1.3.1). The mRNA-1273 development studies include lots representative of the GMP scales (6 different lots and 11 total arms) (Table 2) manufactured at ModernaTX, Inc. (Norwood, MA). Stability and characterization studies designed to evaluate product stability under freeze/thaw conditions are discussed in Section 3.2.P.8.1.3.2. All lots of mRNA-1273 Drug Product manufactured at ModernaTX, Inc. used the "Scale A" manufacturing process for PPQ, clinical lots and development lots. All lots of mRNA-1273 Drug Product manufactured at Catalent Pharma Solutions used the manufacturing process described in Section 3.2.P.3.3. Stability samples were stored in a container made of the same materials (10R clear Type 1 borosilicate glass vial with rubber serum stopper and an aluminum seal with flip-off cap) as the commercial closure system.

For SM-102-containing mRNA-based vaccines, the mRNA purity, as assessed by reverse-phase high-performance liquid chromatography (RP-HPLC); % RNA encapsulation, as assessed by fluorescence; particle size and polydispersity, assessed by dynamic light scattering (DLS); and lipid impurities, as assessed by ultra-high-performance liquid chromatography with charged aerosol detection (UPLC-CAD) have been demonstrated to be stability-indicating (refer to Section 3.2.P.5.2 for analytical procedures). The stability profiles for all the stability-indicating attributes are being evaluated and monitored, but the primary focus of modeling is for purity, since it is the most shelf-life determining of these attributes. Degradation rates for purity at each temperature of interest are reported in this section.

An overview of the mRNA-1273 Drug Product stability program is provided in Table 1. The available data from these studies are presented in Table 11.

Table 1: GMP mRNA-1273 Drug Product Stability Testing Overview

Lot Number	Usage	Concentration Fill Volume	mRNA-1273 LNP Lot Number	Date of Manufacture	Site of Manufacture	Stability Storage Condition
6007520001	Clinical Supplies and Stability	0.20 mg/mL 5.0 mL	5006820002	28 May 2020	ModernaTX, Inc.	<ul style="list-style-type: none">• -60°C to -90°C• -20°C ± 5°C (Intended Long-term)• 2°C to 8°C (Intended Short-term)• 25°C ± 2°C
6007520002				02 Jun 2020		
6007520003				04 Jun 2020		
6007520004	Moderna PPQ		5006820003	25 Jun 2020		<ul style="list-style-type: none">• -60°C to -90°C• -60°C to -90°C followed by storage at 2°C to 8°C (Intended Short-term)• -20°C ± 5°C (Intended Long-term)• -20°C ± 5°C followed by storage at 2°C to 8°C (Intended Short-term)
6007520005			5006820003	30 Jun 2020		
6007520006			5006820003 and 5006820004	08 Jul 2020		
6007520007	Clinical Supplies and Stability		5006820003 and 5006820005	09 Jul 2020		
6007320001	Catalent PPQ	0.20 mg/mL 6.3 mL	5006820003 and 5006820004	30 Jul 2020	Catalent Pharma Solutions	<ul style="list-style-type: none">• -20°C ± 5°C (Intended Long-term)• -20°C ± 5°C followed by storage at 2°C to 8°C (Intended Short-term)• 25°C ± 2°C
6007320002			5006820006	06 Aug 2020		
6007320003			5006820007	11 Aug 2020		

Abbreviations: PPQ = process performance qualification

Material for the development of mRNA-1273 Lipid Nanoparticle (LNP) (Lot AMPDP-200022) was prepared using a manufacturing process which is representative of the ModernaTX, Inc. GMP mRNA-1273 LNP process as described in Section 3.2.S.2.2 {mRNA-1273 LNP}. Two separate lots of mRNA-1273 Drug Product were prepared with Lot AMPDP-200022 using 20 mM Tris and 87 mg/mL sucrose, pH 7.5 as the formulation buffer, as specified in Section 3.2.P.3.3. One development lot was prepared with a total RNA content of 0.10 mg/mL mRNA (DHM-47519). The other development lot was prepared with a total RNA content of 0.5 mg/mL mRNA (DHM-47516). At the time of manufacture of the development lots, the final total mRNA content for the GMP mRNA-1273 Drug Product had not been finalized. These two different total RNA contents were filled in order to appropriately bracket any proposed total RNA content. The final total RNA content was established as 0.20 mg/mL mRNA. Therefore, the stability of mRNA-1273 Drug Product at dosage strength of 0.10 mg/mL (DHM-47519) and 0.5 mg/mL (DHM-47516) is a suitable bracket to establish the initial long-term (storage between -60°C to -90°C) and short-term (storage between 2°C to 8°C) use periods for mRNA-1273 Drug Product at the intended clinical dose concentration of 0.20 mg/mL mRNA.

An overview of development mRNA-1273 Drug Product stability studies is provided in Table 2.

Table 2: Development mRNA-1273 Drug Product Stability Testing Overview

Lot Number	Usage	Concentration Fill Volume	mRNA-1273 LNP Lot Number	Date of Manufacture	Stability Storage Condition
DHM-47519 (Development)	Initial Use Period	0.10 mg/mL 0.6 mL	AMPDP-200022	01 Apr 2020	<ul style="list-style-type: none"> -60°C to -90°C (Intended Long-term) -20°C ± 5°C 2°C to 8°C (Intended Short-term)
DHM-47516 (Development)	Initial Use Period	0.5 mg/mL 0.6 mL	AMPDP-200022	01 Apr 2020	<ul style="list-style-type: none"> -60°C to -90°C (Intended Long-term) -20°C ± 5°C 2°C to 8°C (Intended Short-term)

3.2.P.8.1.2 Stability Study Protocols

3.2.P.8.1.2.1 Study Protocols to Support the Initial Use Period for mRNA-1273 Drug Product

Development mRNA-1273 Drug Product stability samples used to establish the initial use period are tested according to the protocol described in Table 3. Samples stored at the intended condition are evaluated against the acceptance criteria provided in the stability tables.

Table 3: Development mRNA-1273 Drug Product Stability Protocols for 0.10 mg/mL mRNA and 0.5 mg/mL mRNA

Condition	Time Interval (Months)												
	0	1	2	3	4	5	6	9	12	18	24	36	48
-60°C to -90°C													
-20°C ± 5°C													
2°C to 8°C													

A = Appearance, %purity, particle size, polydispersity, %RNA encapsulation

B = RNA content, lipid content, lipid impurities, lipid identity, pH, cell-free translation

C = Bacterial endotoxin, bioburden, particulate matter

D = Osmolality, identity

N/A = Not required per the stability protocol

3.2.P.8.1.2.2 Real-Time Stability Study Protocols for GMP mRNA-1273 Drug Product Lots Manufactured at ModernaTX, Inc. (Norwood, MA)

GMP mRNA-1273 Drug Product stability samples (Lot 6007520001, Lot 6007520002, Lot 6007520003 and PPQ Lot 6007520004) are tested according to the protocols described in Table 4. Samples stored at the intended condition are evaluated against the acceptance criteria in the stability tables.

Table 4: GMP mRNA-1273 Drug Product Stability Protocol for Lots Manufactured at ModernaTX, Inc. (Norwood, MA)

Condition	Months (unless noted)												
	0	24 hr	72 hr	1	2	2.5	3	4	6	9	12	18	24
-60°C to -90°C													
-20°C ± 5°C													
2°C to 8°C													
23°C to 27°C													

A = %RNA encapsulation

B = Appearance, %purity, particle size, polydispersity

C = In-vitro Translation, pH, total RNA content, lipid content and lipid impurities

D = Bacterial endotoxins, particulate matter, sterility

E = Identity, lipid identity, osmolality, container content

N/A = not required per stability protocol

GMP mRNA-1273 Drug Product stability samples from PPQ Lot 6007520005 and PPQ Lot 6007520006 are tested according to the protocols described in Table 5. This protocol has been established to monitor stability for samples stored between -60°C to -90°C followed by storage at 2°C to 8°C with specified intervals for up to three (3) months. Samples stored at the intended condition are evaluated against the acceptance criteria provided in the stability tables.

Table 5: GMP mRNA-1273 Drug Product Matrix Stability Protocol for PPQ Lot 6007520005 and PPQ Lot 6007520006

Condition	Months						
	0	1	2	2.5	3	6	9
-60°C to -90°C (upright)							
-60°C to -90°C followed by 2°C to 8°C (inverted)							

A = Appearance (after thaw from -60°C to -90°C), %RNA encapsulation

B = Appearance (after 2°C to 8°C storage), %purity, particle size, polydispersity

C = In-vitro Translation, pH, total RNA content, lipid content and lipid impurities

D = Bacterial endotoxins, particulate matter, sterility

E = Identity, lipid identity, osmolality, container content

N/A = not required per stability protocol

GMP mRNA-1273 Drug Product stability samples from Lot 6007520007 are tested according to the protocols described in Table 6. This protocol has been established to monitor stability for samples stored between -15°C to -25°C followed by storage at 2°C to 8°C with specified intervals for up to eight (8) weeks. Samples stored at the intended condition are evaluated against the acceptance criteria provided in the stability tables.

Table 6: GMP mRNA-1273 Drug Product Matrix Stability Protocol for Lot 6007520007

Condition	Months (unless noted)											
	0	2 wks	4 wks	1	6 wks	8 wks	3	6	9	12	15	18
-20°C ± 5°C (upright)												
-20°C ± 5°C followed by 2°C to 8°C (inverted)												

A = Appearance, %RNA encapsulation

B = %Purity

C = Particle size, polydispersity, appearance

D = In-vitro Translation, pH, total RNA content, lipid content and lipid impurities

E = Bacterial endotoxins, particulate matter, sterility

F = Identity, container content, lipid identity, osmolality

N/A = not required per stability protocol

3.2.P.8.1.2.3 Real-Time Stability Study Protocols for GMP mRNA-1273 Drug Product Lots Manufactured at Catalent Pharma Solutions (Bloomington, IN)

GMP mRNA-1273 Drug Product stability samples from PPQ Lot 6007320001 manufactured at Catalent Pharma Solutions are tested according to the protocols described in Table 7. GMP mRNA-1273 Drug Product stability samples from PPQ Lot 6007320002 and PPQ Lot 6007320003 manufactured at Catalent Pharma Solutions are tested according to the protocols described in Table 8. Samples stored at the intended condition are evaluated against the acceptance criteria provided in the stability tables. Samples stored at accelerated storage conditions used the acceptance criteria at the intended condition as a reference point to characterize stability trends at the accelerated conditions. This protocol has been established to monitor stability for samples stored between -15°C to -25°C followed by storage at 2°C to 8°C at specified intervals for up to eight (8) weeks.

**Table 7: GMP mRNA-1273 Drug Product Stability Protocol for PPQ Lot 6007320001
Manufactured at Catalent Pharma Solutions (Bloomington, IN)**

Condition	Months (unless noted)													
	0	24 hr	72 hr	2 wks	4 wks	1	6 wks	8 wks	3	6	9	12	18	24
-20°C ± 5°C														
-20°C ± 5°C followed by 2°C to 8°C (inverted)														
23°C to 27°C														

A = Appearance

B = %Purity, particle size, polydispersity

C = In-vitro Translation (Potency), %RNA encapsulation, pH, total RNA content, lipid content and lipid impurities

D = Bacterial endotoxins, particulate matter, container content integrity test

E = Identity, lipid identity, osmolality, sterility

N/A = not required per stability protocol

--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

**Table 8: GMP mRNA-1273 Drug Product Stability Protocol for PPQ Lot 6007320002
and PPQ Lot 6007320003 Manufactured at Catalent Pharma Solutions
(Bloomington, IN)**

Condition	Months (unless noted)													
	0	24 hr	72 hr	2 wks	4 wks	1	6 wks	8 wks	3	6	9	12	18	24
-20°C ± 5°C														
-20°C ± 5°C followed by 2°C to 8°C (inverted)														
23°C to 27°C														

A = Appearance

B = %Purity, particle size, polydispersity

C = In-vitro Translation (Potency), %RNA encapsulation, pH, total RNA content, lipid content and lipid impurities

D = Bacterial endotoxins, particulate matter, container content integrity test

E = Identity, lipid identity, osmolality, sterility

N/A = not required per stability protocol

--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

3.2.P.8.1.2.4 Freeze/Thaw Stability Study Protocol for mRNA-1273 Drug Product

Stability studies in support of mRNA-1273 Drug Product freeze-thaw cycling were performed using representative mRNA-1273 Drug Product. Two separate lots of mRNA-1273 Drug Product were formulated from Lot AMPDP-200022. One development lot was prepared with a total RNA content of 0.10 mg/mL mRNA (DHM-47522). The other development lot was prepared with a total RNA content of 0.5 mg/mL mRNA (DHM-47518). Similarly, as the studies to establish the initial use period, mRNA-1273 Drug Product lots at dosage strength of 0.10 mg/mL mRNA (DHM-47522) and 0.5 mg/mL mRNA (DHM-47518) were utilized to bracket for freeze-thaw cycling studies. Vials were frozen between -60°C to -90°C, held in frozen state for at least overnight, thawed at room temperature, and held at room temperature for at least 30 minutes. Lots were also thawed at 5°C for at least 30 minutes. The freeze-thaw cycling was repeated up to five times. Samples were tested for appearance, %purity, %RNA encapsulation, particle size and polydispersity after samples were subjected to one freeze-thaw cycle (cycle A), three freeze-thaw cycles (cycle B) and five freeze-thaw cycles (cycle C).

3.2.P.8.1.2.5 Bracketing Clinical In-use Stability Study Protocol for mRNA-1273 Drug Product

Clinical in-use stability studies were performed to mimic handling of mRNA-1273 Drug Product at the clinical sites, using representative materials, representative test articles and the appropriate dose preparation procedure for clinical use. Two lots of mRNA-1273 Drug Product (representative multi-dose vials with 6.5 mL fill volume) were used for the study (Table 9). These two lots were manufactured under cGMP conditions were used for bracketing the intended clinical dose concentrations to demonstrate compatibility of administration materials (polypropylene and polycarbonate syringes and stainless-steel needles) with mRNA-1273 Drug Product. Similar to the studies to establish the initial use period, mRNA-1273 Drug Product lots at dosage strength of 0.10 mg/mL mRNA (Lot 6006820001) and 0.5 mg/mL mRNA (Lot 6006920001) were utilized to bracket the clinical in-use studies. mRNA-1273 Drug Product was not diluted for this study.

Table 9: Preparation Configurations for the Clinical In-use Stability Studies

Lot No.	Dose, µg	Dose Concentration (mg/mL)	Dose volume (mL)
6006820001	50	0.10 (neat)	0.5
6006920001	250	0.5 (neat)	0.5

3.2.P.8.1.2.6 Clinical In-use Stability Study Protocol to Support Emergency Use Authorization/Commercial Image for mRNA-1273 Drug Product

Clinical in-use stability studies were performed to mimic the handling of the commercial image of mRNA-1273 Drug Product at the clinical sites, using representative materials, representative test articles and the appropriate dose preparation procedure for clinical use. GMP Lot 6007520007 was used for the study as described in Table 10 and manufactured under cGMP conditions. These clinical in-use studies were conducted using the intended commercial dose concentration to demonstrate compatibility of administration materials (polypropylene and polycarbonate syringes and stainless-steel needles) with mRNA-1273 Drug Product. mRNA-1273 Drug Product was not diluted for this study.

Table 10: Preparation Configuration for the Clinical In-use Stability Studies to Support Emergency Use Authorization/Commercial Image

Lot No.	Dose, µg	Dose Concentration (mg/mL)	Dose volume (mL)
6007520007	100	0.20 (neat)	0.5

3.2.P.8.1.3 Stability Study Results

3.2.P.8.1.3.1 Stability Study Results mRNA-1273 Drug Product (Development, Clinical and Process Performance Qualification Lots)

A summary of the development, clinical and Process Performance (PPQ) mRNA-1273 Drug Product lots in the stability program is provided in Table 11. Data availability from these studies are noted in the table and included in Section 3.2.P.8.3. Samples stored at the recommended and alternate storage conditions, met the acceptance criteria as presented in Section 3.2.P.5.1.

Table 11: mRNA-1273 Drug Product Stability Program Lots

Lot	Purpose	Manufacturing Location	Date of Manufacturing	Lot Size	Conditions		Available Data	Section 3.2.P.8.3 Data Table
					Temperature	Study Duration		
6007320003	PPQ	Catalent Biologics, LLC	11 Aug 2020	10,000 vials	-20 ± 5°C	24 mo	Initial	N/A
					5 ± 3°C ^(a)	8 w	Initial	N/A
					25 ± 2°C	72 h	72 h	N/A
6007320002	PPQ	Catalent Biologics, LLC	06 Aug 2020	10,000 vials	-20 ± 5°C	24 mo	Initial	N/A
					5 ± 3°C ^(a)	8 w	Initial	N/A
					25 ± 2°C	72 h	72 h	N/A
6007320001	PPQ	Catalent Biologics, LLC	30 Jul 2020	10,000 vials	-20 ± 5°C	24 mo	Initial	N/A
					5 ± 3°C ^(b)	8 w	Initial	N/A
					25 ± 2°C	72 h	72 h	N/A
6007520006	PPQ	ModernaTX, Inc.	08 Jul 2020	3000 vials	-60 to -90°C	9 mo	2 mo	Table 25
					5 ± 3°C ^(c)	3 mo	1 mo	Table 26
6007520005	PPQ	ModernaTX, Inc.	30 Jun 2020	3000 vials	-60 to -90°C	9 mo	2 mo	Table 23
					5 ± 3°C ^(c)	3 mo	1 mo	Table 24
6007520004	PPQ	ModernaTX, Inc.	25 Jun 2020	3000 vials	-60 to -90°C	24 mo	2 mo	Table 19
					-20 ± 5°C	12 mo	2 mo	Table 20
					5 ± 3°C	6 mo	2.5 mo	Table 21
					25 ± 2°C	72 h	72 h	Table 22
6007520003	Clinical	ModernaTX, Inc.	04 Jun 2020	3000 vials	-60 to -90°C	24 mo	3 mo	Table 15
					-20 ± 5°C	12 mo	3 mo	Table 16
					5 ± 3°C	6 mo	3 mo	Table 17
					25 ± 2°C	72 h	72 h	Table 18
6007520002	Clinical	ModernaTX, Inc.	02 Jun 2020	3000 vials	-60 to -90°C	24 mo	3 mo	Table 11
					-20 ± 5°C	12 mo	3 mo	Table 12
					5 ± 3°C	6 mo	3 mo	Table 13
					25 ± 2°C	72 h	72 h	Table 14
6007520001	Clinical	ModernaTX, Inc.	28 May 2020	3000 vials	-60 to -90°C	24 mo	3 mo	Table 7
					-20 ± 5°C	12 mo	3 mo	Table 8
					5 ± 3°C	6 mo	3 mo	Table 9
					25 ± 2°C	72 h	72 h	Table 10
AMPDP-200022 (sub-lot DHM 47519)	Development	ModernaTX, Inc.	01 Apr 2020	2.2g	-60 to -90°C	48 mo	6 mo	Table 1
					-20 ± 5°C	48 mo	6 mo	Table 2
					5 ± 3°C	3 mo	5 mo	Table 3
AMPDP-200022 (sub-lot DHM 47516)	Development	ModernaTX, Inc.	01 Apr 2020	2.2g	-60 to -90°C	48 mo	3 mo	Table 4
					-20 ± 5°C	48 mo	3 mo	Table 5
					5 ± 3°C	3 mo	3 mo	Table 6

Abbreviations: N/A = not applicable; PPQ = process performance qualification

a) Stability is evaluated throughout 8 weeks at the accelerated storage condition of 5 ± 3°C, which occurs after 1 and 3 months of storage at -20°C.

b) Stability is evaluated throughout 8 weeks at the accelerated storage condition of 5 ± 3°C, which occurs after 1, 3, and 24 months of storage at -20°C.

c) Stability is evaluated throughout 3 months at the accelerated storage condition of 5 ± 3°C, which occurs after 1, 3, and 9 months of storage at -60 to -90°C.

3.2.P.8.1.3.2 Freeze/Thaw Stability Study Results

Freeze-thaw stability studies were performed using representative mRNA-1273 Drug Product lots at 0.10 mg/mL mRNA (Lot DHM-47522) and 0.5 mg/mL mRNA (Lot DHM-47518). mRNA-1273 Drug Product samples were subjected to a series of five freezing and thawing cycles and assessed for appearance, % RNA encapsulation, mRNA purity by RP-HPLC, mean particle size and polydispersity index.

For Lot DHM-47522 (0.10 mg/mL mRNA), for five cycles of storage between -60°C to -90°C and thaws at room temperature, there was a [REDACTED] in %purity at Cycle 5 [REDACTED] compared to the T = 0 data [REDACTED]. Product-related Impurities Group 1, Group 2, and Group 3 at Cycle 5 were [REDACTED] compared to T = 0 data [REDACTED]. There was [REDACTED] in particle size as measured by Dynamic Light Scattering at Cycle 5 [REDACTED] compared to the T = 0 data [REDACTED]. These data are presented in Table 19, Section 3.2.P.8.3.

For Lot DHM-47522 (0.10 mg/mL mRNA), for five cycles of storage between -60°C to -90°C and thaws between 2°C to 8°C, there was [REDACTED] in %purity at Cycle 5 [REDACTED] compared to the T = 0 data [REDACTED]. Product-related Impurities Group 1, Group 2, and Group 3 at Cycle 5 were [REDACTED] compared to T = 0 data [REDACTED]. There was [REDACTED] in particle size as measured by Dynamic Light Scattering at Cycle 5 [REDACTED] compared to the T = 0 data [REDACTED]. These data are presented in Table 20, Section 3.2.P.8.3.

For Lot DHM-47518 (0.5 mg/mL mRNA), for five cycles of storage between -60°C to -90°C and thaws at room temperature, there was a [REDACTED] in %purity at Cycle 5 [REDACTED] compared to the T = 0 data [REDACTED]. Product-related Impurities Group 1, Group 2, and Group 3 at Cycle 5 were [REDACTED] compared to T = 0 data [REDACTED]. There was a [REDACTED] in particle size as measured by Dynamic Light Scattering at Cycle 5 [REDACTED] compared to the T = 0 data [REDACTED]. These data are presented in Table 21, Section 3.2.P.8.3.

For Lot DHM-47518 (0.5 mg/mL mRNA), for five cycles of storage between -60°C to -90°C and thaws between 2°C to 8°C, there was [REDACTED] in %purity at Cycle 5 [REDACTED] compared to the T = 0 data [REDACTED]. Product-related Impurities Group 1, Group 2, and Group 3 at Cycle 5 were [REDACTED] compared to T = 0 data [REDACTED]. There was a [REDACTED] in particle size as measured by Dynamic Light Scattering at Cycle 5 [REDACTED] compared to the T = 0 data [REDACTED]. These data are presented in Table 22, Section 3.2.P.8.3.

These studies support five freeze/thaw cycles for bracketing dosage strengths of 0.10 mg/mL to 0.5 mg/mL mRNA for mRNA-1273 Drug Product.

3.2.P.8.1.3.3 Clinical In-Use Stability Study Results

3.2.P.8.1.3.3.1 Bracketing Clinical In-Use Stability Study Results

Bracketing clinical in-use stability studies for mRNA-1273 Drug Product were conducted using Lot 6006820001 and Lot 6006920001 and materials of contact planned for clinical

3.2.P.8.1 Stability Summary and Conclusion

dosing (polypropylene and polycarbonate syringes, stainless steel needles) to determine material compatibility and in-use stability. mRNA-1273 Drug Product under evaluation is a multi-dose vial. The study was designed to enable direct removal of product solution from vial and holding in syringes. The product solution was held in the vial at room temperature for either 1 hour or 7 hours after thaw. Dosing syringes were prepared from the vial after 1 hour and then again after 7 hours upon completion of a 1 hour thaw at room temperature. The syringes were then held for 0, 8, and 24 hours at room temperature and refrigerated conditions, and assayed for RNA content by AEX-HPLC, % purity by RP-HPLC, lipid content by UPLC-CAD, % RNA encapsulation, and mean particle size and polydispersity by DLS. Attributes of mRNA-1273 Drug Product stayed within specification when held in a vial for 6 hours at room temperature, followed by storage in a syringe for 8 hours, at either 0.5 mg/mL or 0.10 mg/mL. Clinical in-use stability was demonstrated for bracketing dosage strengths of 0.10 mg/mL to 0.5 mg/mL mRNA for up to 6 hours in the vial followed by 8 hours in the syringe at either ambient temperature or at storage between 2°C to 8°C. These data are provided in Table 23, Section 3.2.P.8.3 to Table 28, Section 3.2.P.8.3.

3.2.P.8.1.3.3.2 Clinical In-Use Stability Study Results to Support Emergency Use Authorization/Commercial Image

Clinical in-use stability studies for mRNA-1273 Drug Product were conducted using Lot 6007520007 and materials of contact planned for clinical dosing (polypropylene and polycarbonate syringes, stainless steel needles) to determine material compatibility and in-use stability. mRNA-1273 Drug Product under evaluation is a multi-dose vial. The study was designed to enable direct removal of product solution from vial and holding in syringes. The product solution was held in the vial at room temperature for either 1 hour or 7 hours after thaw. Dosing syringes were prepared from the vial after 1 hour and then again after 7 hours upon completion of a 1-hour thaw at room temperature. The syringes were then held for 0, 4, 8, and 12 hours at room temperature and refrigerated conditions, and assayed for % purity by RP-HPLC, % RNA encapsulation, in-vitro translation (potency), and mean particle size and polydispersity by DLS. Attributes of mRNA-1273 Drug Product stayed within acceptance criteria when held in a vial for up to 7 hours at room temperature after first puncture, followed by storage in a syringe for up to 12 hours.

Clinical in-use stability was demonstrated for dosage strengths of 0.20 mg/mL for 6 hours after first puncture in the vial followed by 8 hours in the syringe at either ambient temperature or at storage between 2°C to 8°C. These data are provided in Table 29, Section 3.2.P.8.3 to Table 31, Section 3.2.P.8.3.

3.2.P.8.1.4 Conclusions and Use Period Claim

A statistical model aligned with the WHO 2006 guidance document, Guidelines on Stability Evaluation of Vaccines, is being applied for setting mRNA-1273 Drug Product (DP) minimum release limits and shelf life expiry periods.

To generate robust statistical models for the mRNA-1273 purity degradation rates and estimates of variance, purity data from development and GMP stability studies were combined. The analysis (reference DPAD-00880) includes assessment of poolability of lots for common slope at each study temperature. Stability data, at time of data lock (Oct22, 2020), were generated out to 6 months for frozen and 2 - 8°C conditions. The models will be updated on an interim basis as additional data become available.

The mRNA purity (determined using an ion pairing reverse phase HPLC method) is the primary stability shelf-life determining product attribute.

Degradation rates for purity of mRNA-1273 Drug Product (DP) were estimated for five different storage temperatures using the stability study results available as of October 22, 2020. The loss rates are significantly different from zero for all study temperatures except at -40°C and the loss rates increase for higher temperatures. The rates along with their 95% confidence intervals are summarized in Table 12.

Table 12: Summary of Estimated Degradation Rates by Temperature

Temperature	Estimated Degradation Rate, % purity per month	Lower 95% CI for Degradation Rate	Upper 95% CI for Degradation Rate
-70°C			
-40°C			
-20°C			
5°C			
	Estimated Degradation Rate, % purity per hour	Lower 95% CI for Degradation Rate	Upper 95% CI for Degradation Rate
25°C			

The stability study data was also used to estimate the variation for the purity assay, with GCV = [REDACTED] overall based on data pooled for all temperatures combined.

The minimum purity at the end of shelf life will be supported at 50% by applying the internal MRL to support 6 months of long term storage at -15 to 25°C, followed by up to 30 days of storage at 2 - 8°C at the point of care site.

The degradation rates and associated variance estimates were used to calculate minimum release limits (MRL) for purity. The MRL is higher than the end of shelf life release limit for the product and accommodates the estimated loss during times at temperatures specified and the uncertainty due to estimating loss rates.

3.2.P.8.1 Stability Summary and Conclusion

Based on the statistical model with available stability data, the shelf life for a minimum purity of 50% can be extended to 6 months for long term storage at -15 to -25°C, followed by storage at 2 - 8°C for up to 30 days at the point of care site. On the day of dose administration, the product is allowed an additional in-use time of up to 12 hours at 8 to 25°C. The calculations for shelf life assessment will be updated as additional stability timepoints are completed.

Based on the clinical in-use dosage stability data for GMP Lot 6007520007 (0.20 mg/mL), mRNA-1273 Drug Product was demonstrated stable when held for 6 hours after first puncture in the dosing vial followed by 8 hours in the dosing syringe, at either ambient temperature or at 2°C to 8°C.