

IND Number 19745
Sequence No. 0066

November 9, 2020

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Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
Document Control Center
10903 New Hampshire Avenue
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Submission Type: Information Amendment – Chemistry, Manufacturing and Control

Dear Dr. Gruber:

Reference is made to Investigational New Drug Application (IND# 19745) for mRNA-1273, a messenger RNA (mRNA)-based active immunization to induce protective immunity against acute respiratory disease associated with the SARS-COV-2 virus (Sequence No. 0001, April 27, 2020).

The purpose of this submission is to provide manufacturing, comparability assessment on GMP lots (Scale B), and Process Performance Qualification (PPQ) protocols for the (b) (4) of CX-024414 mRNA manufacturing, (b) (4), and (b) (4) of mRNA-1273 LNP manufacturing processes at ModernaTX, Inc.'s Norwood, MA facility. Additionally, in response to "Comment C" as per electronic communication received October 6, 2020, from (b) (6) Reviewer, (b) (6) (refer to Information Amendment - CMC Sequence No. 0039, September 28, 2020), information for the four lipid reference standards has been provided (CTD Section 3.2.S.5 {SM-102 LNP}).

The revised Module 3 CTD sections, as described in the following table, are being submitted including the final Certificates of Analysis for six additional GMP lots, CX-024414 Lot 4007420001 and Lot 4007420002, (b) (4) and mRNA-1273 LNP Lot 5007320002 and Lot 5007320004:

CTD Section		Changes
3.2.S.2.1 {CX-024414}	Manufacturer(s)	<ul style="list-style-type: none"> Addition of (b) (4) of CX-024414 manufacturing process to ModernaTX, Inc.'s responsibility
3.2.S.2.2 {CX-024414}	Description of Manufacturing Process and Process Controls	<ul style="list-style-type: none"> Addition of (b) (4) of CX-024414 manufacturing process and process controls Addition of Item Numbers
3.2.S.2.3 {CX-024414}	Control of Materials	<ul style="list-style-type: none"> Addition of (b) (4) CX-024414 manufacturing process Addition of vendor name and location for (b) (4) used for CX-024414 manufacturing Addition of the use of Lonza manufactured

CTD Section		Changes
		<p>buffers for CX-024414 processing at ModernaTX, Inc. and alternatively the use of ModernaTX, Inc. manufactured buffers for use for Lonza CX-024414 manufacturing</p> <ul style="list-style-type: none"> • Addition of vendor and location for enzymes used for CX-024414 manufacturing • Addition of (b) (4) • Addition of vendor specifications and release testing for additional supply option for (b) (4) • (b) (4) • Throughout section: changed “Non-critical” to “Not Critical”
3.2.S.2.4 {CX-024414}	Control of Critical Steps and Intermediates	<ul style="list-style-type: none"> • Removed definitions of “Non Critical In Process Controls” and “Non Critical Process Parameters” • Addition of microbial controls for (b) (4) • (b) (4) of CX-024414
3.2.S.2.5 {CX-024414}	Process Validation and/or Evaluation	<ul style="list-style-type: none"> • Addition of reference to (b) (4) of CX-024414 Process Performance Qualification (PPQ) report • Inclusion of (b) (4) of CX-024414 PPQ report
3.2.S.2.6 {CX-024414}	Manufacturing Process Development	<ul style="list-style-type: none"> • Addition of lot detail for Scale B (b) (4) GMP lots • Addition of CX-024414 process characterization detail • Addition of CX-024414 comparability assessment detail for Scale B GMP lots • Addition of Comparability Protocol attachment
3.2.S.3.1 {CX-024414}	Elucidation of Structure and Other Characteristics	<ul style="list-style-type: none"> • Provided additional detail in (b) (4) • (b) (4) response section (3.2.S.3.1.1.8) • Addition of functional properties section (3.2.S.3.1.3) which includes (b) (4) • (b) (4) • (b) (4) • Addition of impurities characterization section (3.2.S.3.1.4) which includes (b) (4) • (b) (4)
3.2.S.3.2 {CX-024414}	Impurities	<ul style="list-style-type: none"> • Addition of detail on product-related and process-related impurities for CX-024414 • Addition of literature references as attachments
3.2.S.4.4 {CX-024414}	Batch Analysis	<ul style="list-style-type: none"> • Added batch analysis data for GMP CX-024414 Lot 4007420001 and Lot 4007420002 (Table 2). • Provided Certificate of Analysis for GMP CX-024414 Lot 4007420001 and Lot 4007420002.
3.2.S.4.5 {CX-024414}	Justification of Specifications	<ul style="list-style-type: none"> • Addition of reference to new functional properties section for purity and product-related RP-HPLC QCA determinations
3.2.S.6 {CX-024414}	Container Closure System	<ul style="list-style-type: none"> • Addition of information (b) (4) as an alternative container closure system for use with CX-024414 • Addition of technical drawings, certificates of analysis in support of container closure system
3.2.S.7.1 {CX-024414}	Stability Summary and Conclusions	<ul style="list-style-type: none"> • Updated stability summary and conclusion for Development CX-024414, (b) (4) (Table 4)

CTD Section		Changes
		<ul style="list-style-type: none"> Added stability summary and conclusion for GMP Lot 4007220004 (Table 12 and Table 13) Added stability summary and conclusion for GMP Lot 4007220005 (Table 14 and Table 15)
3.2.S.7.3 {CX-024414}	Stability Data	<ul style="list-style-type: none"> Added T = 6 month stability data for Development CX-024414, (b) (4) (Table 1). (b) (4)

(b) (4)

CTD Section	Changes
(b) (4)	
3.2.S.2.2 {mRNA-1273 LNP}	Description of Manufacturing Process and Process Controls <ul style="list-style-type: none"> • Addition of (b) (4) of mRNA-1273 LNP manufacturing process and process controls • Addition of Item Numbers • Revision of diluted mRNA hold duration from (b) (4)
3.2.S.2.3 {mRNA-1273 LNP}	Control of Materials <ul style="list-style-type: none"> • Addition of single-use consumables for (b) (4) mRNA-1273 LNP manufacturing process • Addition of raw materials for alternate preparations of mRNA dilution buffer • Addition of (b) (4) to table of compendial raw materials • Addition of (b) (4) mRNA-1273 LNP manufacturing process
3.2.S.2.4 {mRNA-1273 LNP}	Control of Critical Steps and Intermediates <ul style="list-style-type: none"> • Removed definitions of “Non Critical In Process Controls” and “Non Critical Process Parameters” • Updated WFI specifications (Table 3)
3.2.S.2.5 {mRNA-1273 LNP}	Process Validation and/or Evaluation <ul style="list-style-type: none"> • Addition of reference to (b) (4) of mRNA-1273 LNP Process Performance Qualification (PPQ) report • Inclusion of (b) (4) of mRNA-1273 LNP PPQ report
3.2.S.2.6 {mRNA-1273 LNP}	Manufacturing Process Development <ul style="list-style-type: none"> • Addition of lot detail for (b) (4) GMP lots • Addition of mRNA-1273 LNP comparability assessment detail for (b) (4) GMP lots
3.2.S.3.2 {mRNA-1273 LNP}	Impurities <ul style="list-style-type: none"> • Addition of detail on product-related and process-related impurities for mRNA-1273 LNP • Addition of literature references as attachments
3.2.S.4.1 {mRNA-1273 LNP}	Specification <ul style="list-style-type: none"> • Revision of specification for Lipid Impurities to introduce acceptance criteria for individual and total impurities.
3.2.S.4.4 {mRNA-1273 LNP}	Batch Analysis <ul style="list-style-type: none"> • Added differences between (b) (4) • Added batch analysis data for mRNA-1273 LNP GMP Lot 5007320002 and Lot 5007320004 (Table 2). • Provided Certificate of Analysis for mRNA-1273 LNP GMP Lot 5007320002 and Lot 5007320004 (Table 2).
3.2.S.4.5 {mRNA-1273 LNP}	Justification of Specifications <ul style="list-style-type: none"> • Addition of reference to new functional properties section for purity and product-related RP-HPLC QCA determinations
3.2.S.5 {mRNA-1273 LNP}	Reference Standard <ul style="list-style-type: none"> • Revised to clarify location of information for reference standard or materials for determination of Total RNA content, % purity and Lipid identification, content and impurity
3.2.S.6 {mRNA-1273 LNP}	Container Closure System <ul style="list-style-type: none"> • Addition of information to support (b) (4) option • Addition of technical drawings, certificates of analysis in support of container closure system
3.2.S.7.1 {mRNA-1273 LNP}	Stability Summary and Conclusions <ul style="list-style-type: none"> • Updated Table 1 for available long-term stability data • Updated stability protocol of Development

CTD Section		Changes
		<p>mRNA-1273, (b) (4)</p> <ul style="list-style-type: none"> Updated stability summary and conclusions for Development (b) (4) Updated stability summary and conclusions for GMP Lot 5006820002 (added Table 6 and Table 7) Added stability summary and conclusions for GMP Lot 5006820005 (Table 8 and Table 9) Added stability summary and conclusions for GMP Lot 5006820006 (Table 10 and Table 11)
3.2.S.7.3 {mRNA-1273 LNP}	Stability Data	(b) (4)
3.3.	Literature References	<ul style="list-style-type: none"> Addition of applicable literature references

If FDA has any questions, please do not hesitate to contact me directly at (b) (6) or at (b) (6)@modernatx.com.

This eCTD submission has been prepared by PPD Development, Inc. in full compliance with ICH and FDA guidance. The eCTD has been verified and confirmed to be virus and spyware free. PPD utilizes Palo Alto Traps v4.2.2. All technical questions should be directed to (b) (6) at PPD (b) (6) or email at (b) (6).



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Yours Sincerely,

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