Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: 125549/0 Meningococcal Group B Vaccine

Drusilla Burns, PhD, Committee Chair, CBER/OVRR/DBPAP
Michael Smith, DVRPA, RPM

Cc: Review Committee Members
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From: Nancy Waites, CMC Facility Reviewer, OCBQ/DMPQ

Through: Carolyn Renshaw, Branch Chief, OCBQ/DMPQ/B1

Subject: Primary Review Memo

Indication: Active immunization to prevent invasive meningococcal disease caused by N. meningitides serogroup B in individuals aged 10 through 25 years.

Applicant: Wyeth Pharmaceuticals Inc. US License # 0003

Facility Sites: ----------(b)(4)----------
Pfizer --(b)(4)-- Pharmaceuticals ----------(b)(4)----------

Primary Review Memo Due Date Goal: 16 Oct 2014

PDUFA Action Due Date: 14 Feb 2015

Recommendation: I recommend approval of this application as long as the other Review Offices do not have any issues. This Primary Review memorandum along with the Addendum Review memo will comprise my complete review of this BLA.

Summary

On 29 May 2014 the FDA received Module 3, part of a rolling BLA, for an original Biologics License Application (BLA) submitted electronically in eCTD. On 16 June 2014 the FDA received the final module to the BLA which started the review clock. The filing memo was completed on 07 July 2014 and concluded the application could be filed per 21 CFR 601.2. I initiated my Primary Review on 05 Jun 2014 and completed my memo on 22 Sep 2014.

Information Request Dates:
On 11 June 2014 a five item information request was e-mailed to Wyeth listing five review related issues. These review issues would not adversely affect the filing of the submission; however the information was needed in order to perform a thorough review.

On 18 Aug 2014 a five item information request was e-mailed to Wyeth.

On 29 Aug 2014 a one item information request was e-mailed to Wyeth. My one item IR was part of a larger IR which covered multiple review offices.

Telecon Dates:
On 12 June 2014 a brief telecon was held with Pfizer to confirm Wyeth understood the review issues and understood the type of information that was needed to be submitted to the application. Reference IR dated 11 Jun 2014, located in the EDR for the discussion between Wyeth and the FDA. The response to the IR will be included in my Primary Review memo since it will not affect my filing decision.

Noteworthy Aspects

The drug substance facility ---(b)(4)--- is a currently approved multi-product manufacturing facility for the manufacture of CDER biotech products that have similar manufacturing platforms as MnB. There are no major differences between the manufacturing platform the facility is currently approved for and the manufacturing processes for the two subfamilies for MnB drug substance.

The drug product facility, ---(b)(4)-------, is currently approved for the manufacture of the licensed drug substance and drug product for ---(b)(4)--- which is a CBER licensed product. The drug product manufacturing process for ---(b)(4)--- is similar to the drug product manufacturing

process for MnB, the subject of this application. The steps for formulation, syringe filling, packaging and inspection are basically the same for both products. No changes have been made to the process.

The packaging and labeling facility ----(b)(4)------is currently approved for the same process for ---(b)(4)---. No changes have been made to the processing steps.

Pfizer is requesting to be allowed to notify the FDA of the introduction of any new products into the drug substance facility ---(b)(4)---in an Annual Report. This request appears to be acceptable based on the cleaning information provided in this application.

Even though this is a Priority Review which would be an eight month review clock under PDUFA V, it was decided that this review will be performed under a compressed timeline and the review will be completed in six months after the receipt of the final BLA module. The review is expected to be completed and all IRs sent by 15 August 2014. Final reviews and Addendum reviews must be approved no later than 16 Nov 2014.

Review Milestones

Milestone	**Due Date**
First Committee Meeting	07 Jul 2014
Filing Meeting	31 Jul 2014
Filing Action	15 Aug 2014
Deficiencies Identified	29 Aug 2014
Internal Mid-Cycle Meeting	30 Sep 2014
Mid-Cycle Communication	16 Oct 2014
Late-Cycle Meeting	30 Nov 2014
Action Due Date	14 Feb 2015

Table of Contents

Manufacturing Facilities, Testing Facilities, and Need for Inspection

Manufacturing and Testing Facilities
Facilities and Inspections
The facilities involved in the manufacture and testing of MnB are listed below along with a short description of their manufacturing responsibilities and an indication if an inspection was performed.

Facilities for MnB

Name / Address	Responsibilities	FEI	DUNS	Insp. Y/N/W
Cell Bank				
Wyeth Pharmaceutical Division of Wyeth Holdings Corporation, a subsidiary of Pfizer Inc. -----(b)(4)---- -----(b)(4)----	----------(b)(4)---------- ----------(b)(4)---------- ---------- ----------(b)(4)----------	----(b)(4)----	----(b)(4)----	N
Pfizer ---------- ----------(b)(4)------- ---------- ---------- ----------	-------(b)(4)---------	----(b)(4)----	----(b)(4)----	N
---------- ---------- -----(b)(4)-------- ---- ---------- ---------- ---------- ---------	-------(b)(4)---------	----(b)(4)----	----(b)(4)----	N
Drug Substance				
---------- ---------- -----(b)(4)-------- ---- ---------- ---------- ---------- ---------	----------(b)(4)---------- ---------- ----------(b)(4)-------- ---------- ------(b)(4)--- ----------	----(b)(4)----	----(b)(4)----	Waived
Drug Product				
Pfizer ---------- ---------- ---------- ----(b)(4)-------- ---------- ----------	----------(b)(4)---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ----------	----(b)(4)----	----(b)(4)----	Y 09-13 Jun 2014 TeamBio and Product Office

Wyeth Pharmaceuticals, a subsidiary of Pfizer Inc. ---------- -------(b)(4)-------- ---------- ---------- ----------	----------(b)(4)----------	----(b)(4)----	----(b)(4)----	W
Wyeth Pharmaceutical Division of Wyeth Holdings Corporation, a subsidiary of Pfizer Inc. 401 North Middletown Road Pearl River, NY 10965	----------(b)(4)----------	2410662	054065909	W
---------- -------(b)(4)-------- ---------- ---------- ---------- ---------- ---------- ---------- ----------	----------(b)(4)----------	----(b)(4)----	----(b)(4)----	N

Scope of Review

I have performed a review of this application per CBER SOPP 8401.4: Review Responsibilities for the CMC Section of Biologic License Applications and Supplements. I specifically reviewed the contents for the information that falls under DMPQ responsibility for review.

Items Reviewed

The following sections are included in this BLA. I have provided a summary of information provided in the submission that is under DMPQ purview in this review memorandum. The topics of review follow the sections of the eCTD format.

1. FDA Regional Information (shared review)

1.1 Forms
1.2 Cover Letters
1.4 Reference Section
1.11 Information not covered Under Module 2 to 5
1.12 Other Correspondence (request for categorical exclusion)

2. Common Technical Document Summaries (shared review)

2.3 Quality Overall Summary (shared review)
    2.3 Introduction
2.3.S Drug Substance (shared review)
    2.3.S MnB Subfamily A – --(b)(4)--
    2.3.S MnB Subfamily B – --(b)(4)--
2.3.P Drug Product (shared review)
    2.3.P MnB Vaccine – Liquid – Pfizer --(b)(4)--

2.3.A Appendices
2.3.R Regional Information (shared review)

3.0 Quality
3.2.S Drug Substance (applies to Subfamily A & subfamily B)
    3.2.S MnB Subfamily A – --(b)(4)--
        3.2.S.1 General Information
        3.2.S.1.3 General Properties (shared review)
    3.2.S.2 Manufacture
        3.2.S.2.1 Manufacturer(s)
        3.2.S.2.2 Description of Manufacturing Process and Process Controls (shared review)
        3.2.S.2.3 Control of Materials (shared review)
        3.2.S.2.4 Control of Critical Steps and Intermediates (shared review)
        3.2.S.2.5 Process Validation and/or Evaluation
        3.2.S.2.6 Manufacturing Process Development
    3.2.S.4 Control of Drug Substance
        3.2.S.4.1 Specification (shared review)
        3.2.S.4.4 Batch Analysis (shared review)
        3.2.S.4.5 Justification of Specification (shared review)
    3.2.S.5 Reference Standards or Materials (shared review)
    3.2.S.6 Container Closure System
    3.2.S.7 Stability
        3.2.S.7.1 Stability Summary and Conclusion (shared review)

3.2.P Drug Product
    3.2.P MnB Vaccine – Liquid – Pfizer --(b)(4)--
    3.2.P.1 Description and Composition of the Drug Product (shared review)
    3.2.P.2 Pharmaceutical Development (shared review)
    3.2.P.3 Manufacture
        3.2.P.3.1 Manufacturer(s) (shared review)
        3.2.P.3.3 Description of Manufacturing Process and Process Controls (shared review)
        3.2.P.3.4 Controls of Critical Steps and Intermediates (shared review)
        3.2.P.3.5 Process Validation and / or Evaluation (shared review)
    3.2.P.4 Control of Excipient
    3.2.P.4 AlPO4
        3.2.P.4.1 Specification (shared review)

3.2.P.4.4 Justification for Specifications
3.2.P.4 Compendial
3.2.P.4.1 Specification (shared review)
3.2.P.5 Control of Drug Product
3.2.P.5.1 Specifications (shared review)
3.2.P.5.4 Batch Analysis (shared review)
3.2.P.5.6 Justification of Specifications (shared review)
3.2.P.6 Reference Standards or Materials
3.2.P.7 Container Closure System
3.2.P.8 Stability
3.2.P.8.1 Stability Summary and Conclusion (shared review)

3.2.A Appendices
3.2.A.1 Facilities and Equipment
3.2.A.1 --(b)(4)--
3.2.A.1 Pfizer --(b)(4)--– Liquid – MnB Vaccine

3.2.R Regional Information (shared review)

Amendments Reviewed
None

DMF Reviewed
None. Pfizer submitted LoAs for a number of DMFs; however, I did not review them since sufficient information was included in the BLA for an adequate review.

Topics Deferred to Other Review Divisions
I have deferred review responsibilities to the Product Office or other appropriate office as outlined in SOPP 8401.4.

Review Issues and Resolution

Amendments from the Review
Amendment 5 – response to IR
Amendment 19 – Response to IR
Unassigned Amendment because it has not been submitted at this time. It will be a response to my one item IR.

Review Issues
None

Review and Comment

Module 1.0
1. FDA Regional Information (shared review)

1.1 Forms
I reviewed the 356h and it appeared to be completely filled out and acceptable.

1.2 Cover Letters
I reviewed the cover letter and do not have any comments. No notable requests were made in the cover letter.

1.4 Reference Section
Letters of Authorization for the following DMFs are included in this section:

- DMF --(b)(4)-- - Letter of Authorization - ----------(b)(4)---------
- DMF --(b)(4)-- - Letter of Authorization - --(b)(4)--
- DMF ----(b)(4)----- - Letter of Authorization – (b)(4)
- DMF ----(b)(4)----- - Letter of Authorization - Piston Plunger – -(b)(4)
- DMF ----(b)(4)----- - Letter of Authorization - Syringe Tip Cap – -(b)(4)

Review Note: I did not review the DMFs.

1.**11 Information Not Covered Under Module 2 to 5**

1.11.1Quality Information Amendment
This was a copy of the information discussed prior to the submission of this BLA. The information pertained to manufacturing at --(b)(4)-- and it was used to determine the inspection could be waived.

1.12 Other Correspondence (request for categorical exclusion)

1.12.14 Environmental Analysis

Pfizer requested a categorical exclusion based on 21 CFR 25.31 (c). To the applicant's knowledge, no extraordinary circumstances exist to disallow this exclusion. The active ingredient of the proposed product, *Neisseria meningitidis* Serogroup B Recombinant Lipoprotein (rLP2086, subfamily A and B, *E. coli)* Vaccine, is recognized as a naturally occurring substance.

Review Comment: I reviewed the request for a categorical exclusion and found it to be acceptable.

Module 2 and Module 3

Note: Modules 2 and 3 were reviewed together since Module 2 is a summary of the information provided in Module 3.

2.3 Introduction

2.3.1. General Information

Proprietary Name of Drug Product	Trumenba (proposed)
Non-proprietary or Common Name of Drug Product	*Neisseria meningitidis* Serogroup B Recombinant Lipoprotein (rLP2086; subfamily A and B; *E. coli*) Vaccine
Non-proprietary or Common Name of Drug Substance	*Neisseria meningitidis* Serogroup B Recombinant LP2086 (MnB rLP2086) Subfamily A Protein and *Neisseria meningitidis* Serogroup B Recombinant LP2086 (MnB rLP2086) Subfamily B Protein
Company Name	MnB bivalent rLP2086 Drug Product [vaccine] PF-05212366
Dosage Form(s)	Sterile Liquid Suspension in a Prefilled Syringe
Strength(s)	120 mcg/mL/Subfamily
Route of Administration	Intramuscular injection
Proposed Indication(s)	Prevention of invasive meningococcal disease caused by *Neisseria meningitidis* Serogroup B (MnB) in subjects aged from 10 to 25 years

2.3.S.1. GENERAL INFORMATION and 3.2.S.1 General Information

Review Comment: The information provided in this section does not fall under the purview of DMPQ. The information in this section pertained to nomenclature, structure, and general properties.

2.3.S.2. Manufacture

2.3.S.2.1. Manufacturer(s) and 3.2.S.2.1. Manufacturers

The information provided in this section is contained in the table in Section Manufacturing Facilities, Testing Facilities, and Need for Inspection of this review memorandum. The information is the same for both Subfamily A and Subfamily B.

----------***(b)(4)***----------

---(b)(4)---

----------**(b)(4)**----------

35 pages determined to be not releasable: (b)(4)

----------(b)(4)----------

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----------**(b)(4)**----------

[ ]

----------(b)(4)----------

2.3.P.1. Description and Composition of the Drug Product and 3.2.P.1. Description and Composition of the Drug Product

Description of Dosage Form

MnB bivalent rLP2086 drug product is a sterile liquid suspension composed of rLP2086 subfamily A and B proteins formulated at 120 mcg/mL/subfamily in 10 mM histidine buffer, pH 6.0, --(b)(4)-- sodium chloride (NaCl) with 0.5 mg/mL aluminum as aluminum phosphate (AlPO4). Polysorbate 80 (PS80) is added to drug substance to obtain the ----(b)(4)----------Therefore, PS80 is not added during the drug product formulation but is present in

the final drug product ----(b)(4)---------. The drug product is filled into 1 mL syringes. A single dose of vaccine is 0.5 mL with no preservative.

The composition of MnB bivalent rLP2086 drug product is provided in the table below, with the function and quality standard applicable to each component. The sterile liquid suspension is filled into 1 mL syringes. A single dose of vaccine is 0.5 mL with no preservative.

Composition of MnB bivalent rLP2086 Drug Product

Ingredient	Grade/Quality Standard	Concentration	Function	Amount/Dose
MnB rLP2086 subfamily A[a]	Company Specification	120 mcg/mL	Active Ingredient	0.06 mg
MnB rLP2086 subfamily B[a]	Company Specification	120 mcg/mL	Active Ingredient	0.06 mg
Sodium chloride	---(b)(4)--------	---(b)(4)--------	---(b)(4)--------	---(b)(4)--------
Histidine	---(b)(4)--------.	10 mM	pH control	0.78 mg
Polysorbate 80[a] (PS80)	---(b)(4)--------	0.035 mg/ml	---(b)(4)--------	0.018 mg
Aluminum phosphate	Company Specification	0.50 mg aluminum/mL	---(b)(4)--------	0.25 mg
Water for injection	---(b)(4)--------	---(b)(4)--------	Diluent	---(b)(4)--------

a. Polysorbate 80 (PS80) is part of drug substance.

No excipients of human or animal origin and no novel excipients are used.

2.3.P.2. Pharmaceutical Development and 3.2.P.2. Pharmaceutical Development

3.2.P.2.1. Pharmaceutical Development - Introduction to the Quality Target Product Profile

Review Comment: I included the information in this section only to demonstrate that Pfizer assessed the desired product profile prior to start of development work. This is similar to Design Controls of the 21 CFR 820s. Pfizer's target product profile appears to be acceptable. I do not have any comments.

A target product profile (TPP) which lists the proposed product concept and essential elements was composed for MnB bivalent rLP2086 drug product prior to start of development. The TPP indicates that the product must be safe, tolerable, and efficacious. The TPP also indicates that the dose is fixed and administered in a physician's office. The proposed indication is for active immunization to prevent invasive meningococcal disease (IMD) caused by *N. meningitidis* serogroup B in individuals aged 10 through 25 years. The vaccine is to be administered as a 3-dose series at months 0, 2, and 6. The vaccine is administered by intramuscular injection.

The Quality Target Product Profile (QTPP) describes the drug product (DP) in terms of quality characteristics. The QTPP is the driver for development of the drug product. As a guide to development, the QTPP lists the intended product quality and performance characteristics to be achieved at the end of the drug product manufacturing process. The QTPP for MnB bivalent rLP2086 drug product is provided in the table below.

MnB Bivalent rLP2086 Drug Product Quality Target Product Profile

Product Attribute	**MnB Bivalent rLP2086 Drug Product Target Profile**
Product Type	*Neisseria meningitidis* Serogroup B Bivalent Recombinant Lipoprotein (rLP2086; subfamily A and B; *E. coli*) Vaccine
Indication	Prevention of invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* serogroup B (MnB) in subjects aged from 10 to 25 years
Route of Administration	Intramuscular Injection
Dosage Form	Sterile Liquid Suspension in a Pre-filled Syringe
Dosage Strength	120 mcg/ml/Subfamily
Dose Schedule	3 dose schedule of 0, 2 and 6 months
Total Protein/Syringe	120 mcg
Formulation	MnB rLP2086 subfamily A and B proteins formulated at 120 mcg/mL/subfamily in 10 mM histidine buffer, pH 6.0, -(b)(4) sodium chloride (NaCl), 0.0035 mg/mL Polysorbate 80 (PS80) with 0.5 mg/mL aluminum as Aluminum Phosphate (AlPO4)
Drug Product Shelf Life	-(b)(4)- at 2-8°C
Drug Product Quality Requirements	Meets pharmacopeial requirements for parenteral dosage form as well as product-specific requirements.
Biocompatibility	Acceptable tolerability upon injection to TDaP-containing adolescent vaccine
Compatibility of the Drug Substance and Drug Product Manufacturing Processes	Drug Substance stable to ----------(b)(4)----------
Compatibility with Delivery Systems	Not applicable
Compatibility with Co-administered Drugs OR Concomitant Use	No drugs are co-administered with MnB rLP2086 Vaccine**.** Immune response of recommended vaccines is non-inferior when administered concomitantly with MnB
Primary Packaging	
Type	Pre-filled Syringe
Materials	Syringe ----(b)(4)----------Glass with plastic Luer Lok adapter, rubber stopper and a synthetic -----(b)(4)-------- rubber tip cap with a plastic rigid tip cap cover
Size	1 mL syringe

3.2.P.2.2 Drug Product Critical Quality Attributes

3.2.P.2.2.2. Summary of Quality Attribute Criticality Assignment Rationale

A critical quality attribute (CQA) is physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. For MnB bivalent rLP2086 drug product, these critical quality attributes are ----------(b)(4)----------.

Table 3.2.P.2-2 “Quality Attribute Criticality Designation and Rationale”, located in the submission, summarizes the quality attributes as well as the rationale for the criticality

assignment for MnB bivalent rLP2086 drug product. Detailed rationale is outlined in the submission.

The drug product control strategy is built on the understanding of critical and other quality attributes for drug substance and drug product and considers how they are controlled or monitored throughout the manufacture of both the drug substance and drug product. The control strategy for the drug substance is provided in the submission in Section 3.2.S.2.6 Control Strategy [Subfamily A] and Section 3.2.S.2.6 Control Strategy [Subfamily B]. Some of the critical quality attributes are controlled upstream in the drug substance process and are not further impacted by the drug product process. Process capability, robustness and process controls were taken into consideration for establishing the overall control strategy for drug product, as summarized in the submission in Section 3.2.P.2.3 Control Strategy Summary.

3.2.P.2.3. Quality Attribute Criticality Assignment Rationale-Critical Quality Attributes

Review Comment: The testing included ----------(b)(4)----------, and Purity. I did not review any of this testing since it does not fall under the purview of DMPQ review responsibilities.

3.2.P.2.4. Quality Attribute Criticality Assignment Rationale – Other Quality Attributes

Review Comment: The testing included Aluminum Concentration, Identity, --(b)(4)-- Potency, ----------(b)(4)----------. I did not review any of this testing since it does not fall under the purview of DMPQ review responsibilities.

2.3.P.2.3.2. Critical Process Parameters and Critical Quality Attributes and 3.2.P.2.3 Critical Process Parameters

A critical process parameter (CPP) is a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. A risk-based methodology was used to determine the CPPs for formulation and filling. Process parameters that could potentially have an impact on CQAs and have acceptable ranges associated with are listed below in Table 3.2.P.2.3-1.

Table 3.2.P.2.3-1. Process Parameters that have a Potential Impact on CQAs

Process Parameter	Potentially Impacted CQAs[a]	NOR	PAR	Supporting data in submission
----------(b)(4)-----				

2 pages determined to be not releasable: (b)(4)

[(b)(4)]

Based on referenced data (Table 3.2.P.2.3-1) it was shown that none of the above-listed process parameters result in failure of product quality at the edges of NOR and PAR, and were therefore deemed non-critical.

In addition, a risk assessment was also performed on process parameters based on Failure Mode Effect and Cause Analysis (FMECA) principles for evaluating the potential impact of each operating parameter on product quality attributes, process consistency and operational reliability. A rating was given to each parameter for each of the three categories: Severity (SEV), probability (PRO) and detection (DET). A risk priority number (RPN) was calculated for each parameter by multiplying the rating values for severity, probability and detection (RPN = SEV x PRO x DET). Process parameters with high RPN scores are presented in Table 3.2.P.2.3-2.

Table 3.2.P.2.3-2. Process Parameters with a High RPN Score

[(b)(4)]

Since the classification of process parameters is guided by a data driven process, parameters may be reclassified based on additional process knowledge gained through periodic review of process performance or additional development and clinical experience.

2.3.P.2.3. Manufacturing Process Development and 3.2.P.2.3. Development History
2.3.P.2.3.1. Development History
The product produced throughout clinical development and process validation was representative of the product planned for commercial distribution.

Development studies were performed to establish normal operating ranges (NOR) and proven acceptable ranges (PAR) for each of the unit operations used to formulate and fill MnB bivalent..

12 pages determined to be not releasable: (b)(4)

---(b)(4)---

[**(b)(4)**]

---(b)(4)---

[**(b)(4)**]

Review Comment: ---
---(b)(4)---

3.2.P.2.3.5. Drug Product Storage and Shipping

3.2.P.2.3.5.1. DP Storage

DP syringes are stored at 2-8°C in the tip horizontal orientation. Stability data on MnB bivalent rLP2086 vaccine syringes in tip up orientations is provided in the submission in Section 3.2.P.8.3 Stability Data. Tip up orientation is considered "worst case" from product quality standpoint due to product contact with the syringe barrel as well as the stopper.

3.2.P.2.3.5.2. DP Shipping

The effect of shipping on product quality was evaluated by carrying out a worst case simulated shipping study as described below. In addition, shipping validation studies on the drug product

syringes were performed as discussed in this review memorandum in Section 3.2.P.3.5 "Qualification of Packaging and Shipping – Pfizer, --(b)(4)--".

3.2.P.2.3.5.2.1. Simulated Shipping Study

---(b)(4)---

3.2.P.2.3.5.2.2. Plunger Movement during Shipping

---(b)(4)---

---(b)(4)---

Review Comment: The simulated shipping study is acceptable. I do not have any questions or comments.

2.3.P.2.4 Comparability and 3.2.P.2.3 Comparability

Review Comment: I performed a high-level review of the information in this section since it mostly fell under the review responsibility of the Product Office. The information provided demonstrated that the MnB bivalent rLP2086 drug product manufactured at the commercial scale at the ------(b)(4)---------- manufacturing site is comparable to the drug product manufactured at the Pfizer ----------(b)(4)---------- manufacturing site. The manufacturing process, equipment, fill mechanism, in-process tests and release specifications are similar between the two sites. The same syringe container closure was used at both sites.

2.3.P.2.8. Microbiological Attributes and 3.2.P.2.5. Microbiological Attributes

The container closure integrity testing was performed by ----------(b)(4)----------. The results obtained demonstrated container/closure integrity under these worst-case conditions. The container closure system integrity testing was performed on 1 mL ----------(b)(4)---------- Luer-Lok® syringes with ----(b)(4)--- tip caps and plastic rigid tip cap (PRTC) overseals. Syringes are sealed with ----(b)(4)--- stoppers.

3.2.P.2.5.1. Microbial Challenge Testing

The microbial challenge testing was performed using ----------(b)(4)----------

Review Comment: Not enough information is provided in the application to determine the acceptability of the CCIT. See comment below for IR questions.

----------(b)(4)----------

----------(b)(4)----------

----------(b)(4)----------

Review Comment: Not enough information was included in the application to determine the acceptability of the CCIT procedure and validation. The following questions were included in an Information Request that was sent to Pfizer on 11 Jun 2014:

1. Please submit the method validation studies for your container closure integrity test (CCIT) performed on the final product syringes. This would include a description of the positive and negative controls used, sensitivity of the ---(b)(4)--- test, description of test parameters, etc.

2. Please submit testing validation for the CCIT performed on the filled syringes.

3. Pfizer proposes to use CCIT testing in lieu of sterility testing during stability. Please indicate if the ---(b)(4)--- test was validated using product filled syringes. If product filled syringes were not used for method validation, please provide a comparison between what was used to validate the test method and the product filled syringe. Lastly, please provide your rationale for the equivalence between the two.

2.3.P.3 Manufacture and 3.2.P.3. Manufacture Drug Product

2.3.P.3.1. Manufacturer(s) and 3.2.P.3.1. Manufacturer(s)

The ----(b)(4)---- drug product vaccine for commercial distribution is formulated and filled at Pfizer in ----(b)(4)----------. Final product testing is performed at Pfizer, --(b)(4)---, with the exception of (b)(4)- potency testing which is performed at ----------(b)(4)------. Final labeling and packaging is performed at Pfizer in -----(b)(4)----. The table in section "Manufacturing Facilities, Testing Facilities, and Need for Inspection" at the beginning of this review memorandum lists the responsible manufacturers and testing laboratories for Aluminum Phosphate (AlPO4) and MnB bivalent rLP2086 drug product.

2.3.P.3.2. Batch Formula and 3.2.P.3.2. Batch Formula

A batch formula for a representative -(b)(4)- batch of MnB bivalent rLP2086 (also described as a -(b)(4)- batch) is provided in the table located in this review memorandum in Section 2.3.P.1-1 "Description and Composition of Drug Product".

6 pages determined to be not releasable: (b)(4)

Abbreviation: NMT = Not More Than

2.3.P.3.3.6. Packaging and Shipping from Pfizer, --(b)(4)-- and 3.2.P.3.3. Packaging and Shipping from Pfizer, --(b)(4)--

MnB bivalent rLP2086 syringes are bulk packaged at Pfizer, --(b)(4)--, shipped to Pfizer, (b)(4) for labeling and final secondary packaging, and then shipped to distribution centers for commercial distribution from Pfizer, (b)(4). All shipments of MnB bivalent rLP2086 syringes are monitored for temperature during shipment to ensure that the temperature remains within the established shipping temperature range of ----------(b)(4)----------.

3.2.P.3.3.1. Bulk Packaging

The bulk packaging of unlabeled MnB bivalent rLP2086 syringes at Pfizer, --(b)(4)-- occurs following inspection. The packaging operation includes confirmation of quantity, labeling the tubs, packaging the tubs into boxes such that syringes are in horizontal position and labeling the boxes. The boxes are placed onto pallets and stored in temperature-controlled areas.

3.2.P.3.3.2. Shipping of Unlabeled Syringes from Pfizer, --(b)(4)-- to Pfizer, (b)(4)

All shipments of MnB bivalent rLP2086 syringes are monitored for temperature during shipment to ensure that the temperature remains within the established shipping temperature range of ----------(b)(4)---------- Unlabeled syringes are shipped from Pfizer, --(b)(4)-- to Pfizer, (b)(4) using qualified ----------(b)(4)---------- are packed within established minimum and maximum product loads. Temperature monitoring devices are applied and activated. The product is transported via ----------(b)(4)----------. Temperatures during transport are verified and the syringes are stored in designated 2 – 8°C storage areas until final labeling and packaging for distribution.

3.2.P.3.3.3. Packaging and Shipping Process Controls

Packaging and shipping of unlabeled syringes to final packaging site are operated under the following process controls:

Process Parameters for Packaging and Shipping of Unlabeled Syringes to Final packaging site

Parameter	Acceptable Range
Shipping Temperature (°C)	--(b)(4)--
----------(b)(4)----------	--(b)(4)--

----------(b)(4)----------

2.3.P.3.3.7. Labeling, Packaging and Shipping from Pfizer, (b)(4) and 3.2.P.3.3. Labeling, Packaging and Shipping from Pfizer, (b)(4)

3.2.P.3.3.1. Labeling and Packaging

The labelling and packaging of MnB bivalent rLP2086 vaccine syringes for commercial distribution is performed on a fully automated packaging line. The line has an integrated

inspection system, which electronically verifies printed variable data and printed component resource numbers, and which performs checks for complete syringe assembly.

The labelling and packaging operations include the following sequential steps: ----------
---
----------(b)(4)----------

Pallets of MnB bivalent rLP2086 syringes are stored in designated storage areas at 2 - 8 degrees C pending shipment for commercial distribution. The packaged drug product is tested for Identity prior to shipment.

3.2.P.3.3.2. Shipping of Syringes for Commercial Distribution

MnB bivalent rLP2086 final product syringes are shipped in the horizontal orientation by qualified insulated shipping systems to distribution centers for commercial distribution. The qualified shipping containers are packed within established minimum and maximum product loads, according to defined summer and winter shipping requirements, using ----------
-----(b)(4)---------- for temperature control. Temperature monitoring devices are inserted and activated. The containers are transported by established transportation routes to distribution centers. Temperatures during shipment are verified and the product is stored in designated 2 – 8°C storage areas until final distribution to healthcare providers.

3.2.P.3.3.3. Labeling, Packaging and Shipping Process Controls

Labeling, Packaging and Shipping are operated under the following process controls:

Process Parameters for Labeling, Packaging and Shipping from Pfizer, (b)(4)

Parameter	**Acceptable Range**
Shipping Temperature (°C)	--(b)(4)--
----------(b)(4)----------	--(b)(4)--
----------(b)(4)----------	--(b)(4)--

----------(b)(4)----------

In Process Test for Packaging at Pfizer, (b)(4)

In-Process Test	**Acceptance Criteria**	**Rationale/Purpose**
----------(b)(4)----------	Positive for each subfamily	To confirm the contents of the final package.

Abbreviation: NMT=Not More Than

3 pages determined to be not releasable: (b)(4)

.

----------**(b)(4)**----------

----------(b)(4)----------

----------(b)(4)----------

----------(b)(4)----------.

----------**(b)(4)**----------

----------**(b)(4)**----------

----------**(b)(4)**----------

3.2.P.3.4. Inspection
The information provided within this section of the BLA is identical to the information provided in the table in Section 3.2.P.3.3.1 “Inspection Process Controls” of this review memorandum.

3.2.P.3.4. PACKAGING AND SHIPPING FROM PFIZER, --(b)(4)--
The information provided within this section of the BLA is identical to the information provided in the table in Section 3.2.P.3.3.3 “Packaging and Shipping Process Controls” of this review memorandum.

3.2.P.3.4. LABELING, PACKAGING AND SHIPPING FROM PFIZER, (b)(4)
The information provided within this section of the BLA is identical to the information provided in the two tables in Section 3.2.P.3.3.3 “Labeling, Packaging and Shipping Process Controls” of this review memorandum.

2.3.P.3.4.6 Process Step Hold Times and 2.3.P.3.5.4 Hold Times and 3.2.P.3.4 Process Step Hold Times and 3.2.P.3.5 Hold Times

3.2.P.3.5.1. In-Process Hold/Processing Times

12 pages determined to be not releasable: (b)(4)

----------**(b)(4)**----------

----------(b)(4)----------

----------(b)(4)----------

----------**(b)(4)**----------

----------(b)(4)----------

----------.

----------(b)(4)----------

----------***(b)(4)***----------

----------(b)(4)----------

----------(b)(4)----------

Review Comment: This process validation was acceptable. I do not have any comments.

3.2.P.3.5.6. Final Product Testing

Filled syringes were sampled for testing across each of the (b)(4) process validation lots. Samples for testing were obtained according to the production batch records and the validation protocol. The testing of the (b)(4) process validation lots was expanded from the routine release testing for commercial manufacture to include validation testing. Validation testing included appearance, pH, purity, ----------(b)(4)---------- and excipient testing to be performed at ----------(b)(4)--------- of each lot in addition to standard release testing. Final product test results are summarized in Table 3.2.P.3.5-15 below.

Final drug product from the (b)(4) process validation lots met the pre-determined acceptance criteria demonstrating that the manufacturing and filling processes produced MnB bivalent rLP2086 syringes that met the pre-determined quality attributes. In addition the expanded testing that included samples from the ----------(b)(4)----------.

Table 3.2.P.3.5-15. Final Product Test Results for Process Validation Lots

Test	**Acceptance Criteria[e]**
----(b)(4)----	--(b)(4)----------
Aluminum	--(b)(4)-------
Appearance	Homogeneous, white suspension (HWS)
Endotoxin	--(b)(4)----------
General Safety	Passes test / Meets requirements
Identity	Positive for each subfamily
----(b)(4)----------	--(b)(4)----------
----(b)(4)----	--(b)(4)-
pH	--(b)(4)-
----(b)(4)----	--(b)(4)-
Purity	--(b)(4)-
Sterility	No growth observed
Volume of Injection	(b)(4) 0.5 mL
Histidine Concentration	Report Results (mM)
-- (b)(4)-- Concentration Report	Report Results (mM)
-- (b)(4)-- Concentration Report	Report Results (mM)
----(b)(4)----------	----(b)(4)----------
----(b)(4)----	----(b)(4)----------
----(b)(4)----	----(b)(4)----------

e. Acceptance criteria in effect at the time of study
HWS = Homogenous White Suspension

Review Comment: The testing from the process validations was acceptable. I do not have any comments.

3.2.P.3.5.7. Deviations

Deviations encountered during the execution of the process validation study were investigated. The investigations assessed the potential impact on the validation studies and on the purified drug substance quality. The deviation description resolution and validation impact are summarized in the submission in Table 3.2.P.3.5-16 “Deviation Summary”.

Review Comment: I reviewed the three deviation summaries listed in the table and agree they did not impact the validation study. The deviations were appropriately investigated and closed out.

Review Comment: (b)(4) consecutive successful process validation lots met the pre-determined

protocol acceptance criteria for the study demonstrating that the formulation and filling process, executed within established operating parameters, produces MnB bivalent rLP2086 vaccine that meets its pre-determined quality attributes. All deviations were successfully resolved, with no impact to the process validation or final product quality attributes. Therefore, the formulation, ----------(b)(4)----------, filling of MnB bivalent rLP2086 bulk vaccine into syringes and the ---(b)(4)-------- visual inspection of the filled syringes in the Syringe Fill/Finish facility at Pfizer, -(b)(4)-- were validated.

3.2.P.3.5. Hold Times

----------***(b)(4)***----------

----------(b)(4)----------

----------(b)(4)----------

Review Comment: The different hold times were tested throughout the process validation runs and were found to be acceptable. I do not have any comments.

2.3.P.3.5.5. Qualification of Packaging at Pfizer, -(b)(4)- and 3.2.P.3.5. Qualification of Packaging at Pfizer, -(b)(4)-

Bulk unlabeled MnB bivalent rLP2086 vaccine syringes are packaged at Pfizer, -(b)(4)-, and shipped to Pfizer ---(b)(4)--- for labeling and final packaging.

----------(b)(4)----------

9 pages determined to be not releasable: (b)(4)

----------(b)(4)----------

----------(b)(4)----------

----------(b)(4)----------

----------(b)(4)---------

----------(b)(4)----------

Review Comment: The justification for the specifications for sterility and pH are acceptable.

3.2.P.4.5. Excipients of Human or Animal Origin

There are no excipients of human or animal origin.

3.2.P.4.6. Novel Excipients

There are no novel excipients used in MnB bivalent rLP2086 drug product production. However, since ----------(b)(4)---------- --- is a non-compendial excipient, additional information is provided in Section 3.2.A.3 Excipients.

3.2.P.4. Control of Excipients - Compendial

3.2.P.4.1. Specifications - Compendial

All of the excipients used for MnB bivalent rLP2086 drug product are compendial except for ----------(b)(4)-------, as detailed in 3.2.P.4.1 Specifications – Non-Compendial. The compendial excipients comply with the monographs of the ----------(b)(4)---------- as indicated in Table 3.2.P.4.1-1.

The excipients are accepted by Pfizer based on a Certificate of Analysis from a qualified supplier and may be tested by Pfizer with reduced testing requirements.

Table 3.2.P.4.1-1. Specifications of Compendial Excipients

Excipient	Quality Specifications
Sodium Chloride	----------(b)(4)---------
Histidine	----------(b)(4)---------

Water for Injection	----------(b)(4)---------

3.2.P.5. Control of Drug Product

3.2.P.5.1. Drug Product Specifications

The release and stability tests and specifications for MnB bivalent rLP2086 drug product are detailed in Table 3.2.P.5.1-1 below.

Table 3.2.P.5.1-1. MnB Bivalent rLP2086 Drug Product Specifications for Release and Stability Testing

Test	Method	Specification
Aluminum, mg/mL	---(b)(4)---	---(b)(4)---
Appearance[a]	Visual	Homogeneous white suspension
Container Closure Integrity[a, b]	---(b)(4)---	Pass
Endotoxin[a], EU/mL	---(b)(4)---	---(b)(4)---
Identity	---(b)(4)---	Positive for each subfamily
-(b)(4)- Potency[a], ------(b)(4)-----	---(b)(4)---	---(b)(4)---------- ---(b)(4)----------
----------(b)(4)---------- ------(b)(4)-----	---(b)(4)---	---(b)(4)---
------(b)(4)-----	---(b)(4)---	---(b)(4)---
pH[a]	---(b)(4)----------	6.0 -(b)(4)-
----------(b)(4)---------- ------(b)(4)-----	---(b)(4)---	---(b)(4)---
Purity[a], %	---(b)(4)---	---(b)(4)---
Sterility[a]	---(b)(4)---	Meets the requirements of the test. No growth observed
----------(b)(4)----------	---(b)(4)---	---(b)(4)---
----------(b)(4)---------- ------(b)(4)-----	---(b)(4)---	---(b)(4)---
Volume of Injection	---(b)(4)---	(b)(4)0.5 mL

a. These tests are performed for the stability assessment
b. CCI testing is not a release test, only performed annually on stability
Abbreviations: -----(b)(4)----, SBA=serum bactericidal assay, ----------(b)(4)----------

3.2.P.5.2 Analytical Procedures

3.2.P.5.2. Introduction

Non-compendial and compendial analytical procedures used to control the quality and consistency of MnB bivalent rLP2086 drug product are presented in this section.

Test methods, when appropriate, include control samples to ensure the system and method are in a state of control prior to and throughout analysis. The strategy for assessing method performance is developed specifically for a given method. Analytical assay controls are

instituted and associated data is monitored to ensure consistent performance of the method for its intended use.

----------(b)(4)----------. are considered as part of method development; however the selected system/assay suitability criteria implemented for routine testing have demonstrated ability to support delivery of consistent method performance and results as confirmed through validation of the method.

Review Note: I have included only the testing that DMPQ is responsible for reviewing for final product. The testing not discussed falls under the review responsibility of the Product Office of DBSQC.

3.2.P.5.2. Appearance

The drug product is tested for appearance by visually examining it for a qualitative physical appearance and descriptive product definitions.

The drug rug product syringes are ----------(b)(4)---------- and inspected in their original containers. The samples are mixed well by vigorous shaking until homogeneous to ensure uniformity. The color of the samples is recorded. The sample is assessed for clumps/aggregation. The sample is allowed to settle for several minutes to dissipate any air bubbles and let solids settle prior to examination for any extraneous substances.

The reportable value is homogenous, white suspension.

3.2.P.5.2. Container Closure Integrity

The purpose of the method is to confirm the container closure integrity of the MnB bivalent rLP2086 drug product.

The test for container closure integrity is used to assess the effectiveness of the seal in individual container closure components to prevent any leakages and serves as a surrogate for sterility assessment----------
----
----------(b)(4)----------
---------- constitutes a breach of sterility and a failure for container closure integrity.

----------(b)(4)----------

----------(b)(4)----------

----------(b)(4)----------

----------(b)(4)----------

----------(b)(4)----------

----------**(b)(4)**----------
----------(b)(4)----------

---(b)(4)----
----------(b)(4)----------

----------(b)(4)----------

----------**(b)(4)**----------

---(b)(4)---

3.2.P.5.2. Endotoxin
Endotoxin testing is performed using the (b)(4) method as described in ---(b)(4)----------

3.2.P.5.2. pH
pH testing is performed consistent with the compendia as described in ---(b)(4)----------

3.2.P.5.2. Sterility

Sterility testing is performed as described in -----(b)(4)---------- and meets 21 CFR 610.12 requirements.

3.2.P.5.2. Volume of Injection
Volume of injection testing is performed as described in -----(b)(4)-------.

3.2.P.5.3 Validation of Analytical Procedures
3.2.P.5.3. Validation of Analytical Procedures Overview
Validation of analytical methods were performed to ensure the quality, identity, antigenicity, purity and safety of MnB bivalent rLP2086 drug product met the requirements described in the International Conference on Harmonization (ICH) Guidelines on Validation of Analytical Procedure: Text and Methodology Q2(R1). Compendial methods were verified according --------
----------(b)(4)----------.

The quantitative methods were validated for precision, accuracy, specificity, linearity, and range. Those quantitative methods that are used to determine the content of minor constituents were further validated for quantitation limit (QL). The method performed for identity was validated for specificity and robustness.

The validation studies performed for each of the MnB bivalent rLP2086 drug product procedures used for batch release and stability studies are provided in this section.

Review Note: I only included the validation of the container closure integrity test since that is DMPQ Review responsibility. The remaining test validations are the responsibility of the Product Office or DSBQC.

Container Closure Integrity Test

SUMMARY REPORT FOR VERIFICATION OF THE CONTAINER CLOSURE INTEGRITY METHOD FOR MNB BIVALENT RLP2086 DRUG PRODUCT

Review Comment: I reviewed the 5 page report and found it did not contain sufficient information to determine the acceptability of the CCI validation / verification. An IR was sent to Pfizer on 11 Jun 2014. The IR questions are listed previously in this review memorandum. The review of the response is included in my Addendum Review memo.

This document summarizes the verification of the container closure integrity (CCI) method for MnB bivalent rLP2086 drug product.

Summary of the Method

----------(b)(4)----------

----

1 page determined to be not releasable: (b)(4)

3.2.P.5.6. Justification of Drug Product Specifications

3.2.P.5.6.1. Introduction and Summary

The specifications for MnB bivalent rLP2086 drug product are defined and established to ensure the quality, purity, potency and safety of the commercial drug product at the recommended storage temperature of 2-8 °C.

Analytical test methods and specifications were chosen to ensure the quality, identity, purity, potency and safety of the drug product. The analytical test methods and the proposed specifications were derived through (1) evaluation of the development experience with MnB bivalent rLP2086 drug product, (2) characterization and process validation data, (3) the manufacturing history at scale, (4) the release and ongoing stability data, and (5) the toxicological and clinical evaluation of drug product. In addition, compendia requirements for protein based products were considered in the evaluation.

The commercial specification setting strategy focused on batch analytical data obtained for drug product manufactured using commercial process and scale, so as to define the expected routine variability in drug product quality attributes. These drug product lots included Phase 2 and Phase 3 clinical lots, as well as process validation lots. Statistical analysis of available lot data and evaluation of commercial process variability (as described below) were used as a primary factor to guide setting of the proposed commercial specifications. Additionally, to reflect the full range of clinical experience with the product, analytical data from clinical lots used in Phase 2 studies and manufactured at pilot scale were taken into consideration. Phase 1 clinical lot results had limited utility in commercial specifications setting as these were at different doses and subject to testing using initial versions of the analytical methods, representing only a subset of quality attributes considered for commercial application.

3.2.P.5.6.4. Appearance

The appearance of the MnB bivalent rLP2086 drug product solution has been routinely monitored at release and during long term storage. The test method for appearance is based on compendial requirements and has been shown to be suitable for use through verification.

The results for the Phase 2 clinical lots were all reported as homogenous, white suspension at release (Section 3.2.P.5.4 Batch Analyses, located in the submission). As shown in the submission in Table 3.2.P.5.6-4 “MnB Bivalent rLP2086 Drug Product Release Testing Appearance Results”, the appearance data for all commercial scale representative drug product lots at release were reported as homogeneous, white suspension. The stability data demonstrate there was no change in the appearance at the recommended 2-8 degrees C condition.

The proposed commercial specification for appearance at release and during stability studies is “Homogeneous, white suspension “.

3.2.P.5.6.5. Container Closure Integrity

The container closure integrity (CCI) of the MnB bivalent rLP2086 drug product has been routinely monitored ---(b)(4)--- during long term storage in lieu of sterility testing. CCI is confirmed by assessing ----------(b)(4)----------. CCI

testing was not implemented for Phase 2 pilot scale lots. As shown in the submission in Section 3.2.P.8.3. Stability Data – Long Term, the container closure data for all commercial scale representative drug product lots on long term stability were reported as pass.

The proposed commercial specification for CCI during stability studies is "Pass"

3.2.P.5.6.6. Endotoxin

The ----------*(b)(4)*---------- is used to evaluate the endotoxin levels in MnB bivalent rLP2086 drug product lots at -----(b)(4)----------. The assay is used to ensure product safety and to demonstrate control for manufacture of drug product.

The results demonstrate the consistent and effective process capability in minimizing the introduction of endotoxin into the drug product. The results for the Phase 2 clinical lots were all reported as ---(b)(4)-- at release (Section 3.2.P.5.4 Batch Analyses).

As shown in the submission in Table 3.2.P.5.6-7 "MnB Bivalent rLP2086 Drug Product Release Testing Endotoxin Results", the endotoxin data for all commercial scale representative drug product lots at release were below the assay quantitation limit ---(b)(4)---

The stability data demonstrate there was no change in the endotoxin at the recommended 2-8°C condition.

The proposed commercial specification for endotoxin at release and during stability studies is "Endotoxin, ---(b)(4)---------". The proposed commercial specification of ---(b)(4)---- is equivalent ----------(b)(4)---------- guidance so provides a significant margin of safety.

3.2.P.5.6.11. pH

The pH of the MnB bivalent rLP2086 drug product has been routinely determined using ------(b)(4)------. pH is measured for every drug product lot for batch release and on stability.

The pH test results for Phase 2 clinical drug product ranged from (b)(4)-6.0 (Section 3.2.P.5.4 Batch Analyses, located in the submission). The release data for MnB bivalent rLP2086 commercial scale representative drug product lots presented in the submission in Table 3.2.P.5.6-19 were subjected to statistical analyses to derive the mean, standard deviation, and tolerance interval of the data set. The results of the two-sided statistical analyses are presented in the submission in Table 3.2.P.5.6-20 and Figure 3.2.P.5.6-6. The stability data demonstrate no significant trend at the recommended 2-8 degrees C condition.

The proposed commercial specifications for pH at release and during stability studies are "pH 6.0 (b)(4)".

3.2.P.5.6.14. Sterility

The sterility is of MnB bivalent rLP2086 drug product is assessed at release and end of shelf life. The assay is performed as described in compendia and is used to ensure product safety and to demonstrate control for manufacture of drug product.

The results demonstrate the consistent and effective process capability in minimizing the introduction of contaminants into the drug product.

As shown in the submission in Table 3.2.P.5.6-28 "MnB Bivalent rLP2086 Drug Product Release Testing Sterility Results", the sterility data for all commercial scale representative drug product lots at release were "No growth observed/meets requirements of test.

The proposed commercial specification for sterility at release and at the end of shelf life is "Sterility No growth/Meets requirements of test".

3.2.P.5.6.17. Volume of Injection

The volume of injection (VOI) of MnB bivalent rLP2086 drug product is assessed at release. The assay is performed as described in compendia and is used to demonstrate control for manufacture of drug product.

As shown in the submission in Table 3.2.P.5.6-36 "MnB Bivalent rLP2086 Drug Product Release Testing Volume of Injection Results", the VOI data for all commercial scale representative drug product lots at release were 0.5 mL.

The proposed commercial specification for VOI at release is "Volume of Injection, mL (b)(4) 0.5".

Review Comment: The justifications for the drug product specifications are acceptable.

2.3.P.7. Container Closure System and 3.2.P.2.4 Container Closure System and 3.2.P.7. Container Closure System

Container Closure

The container closure system for commercial MnB bivalent rLP2086 vaccine drug product is a 1 mL pre-filled syringe manufactured by (b)(4). The disposable syringes are constructed of ----------(b)(4)------ glass. The syringes are pre-assembled with a plastic Luer-Lok adapter with a rubber stopper and a synthetic ----------(b)(4)--------- rubber tip cap that is secured to the syringe barrel with a plastic rigid tip cap (PRTC) overseal. ----------(b)(4)----------

The tip cap is composed of --(b)(4)---- latex-free grey -----(b)(4)---------- rubber. The Luer-Lok adapter is composed of clear -----(b)(4)-------, and the PRTC is composed of -----(b)(4)-----. The Luer-Lok adapter and the PRTC overseal do not have product contact.

Table 3.2.P.7-1. List of Components in Container Closure System

Component	Description

Syringe	Standard 1 mL --(b)(4)-- Syringes -----(b)(4)------ glass with plastic Luer-Lok adapter.
	----------(b)(4)----------
Syringe Tip Cap	Synthetic -----(b)(4)------- blend gray --(b)(4)-- (PRTC[a]) latex free
Stoppers	Stopper 1-3 mL ---(b0(4)--gray ---------(b)(4)------, latex free

[a]Plastic rigid tip cap. Non-product contact.

2.3.P.7.1. Syringes and 3.2.P.7.1. Syringes

The syringes, manufactured by (b)(4), are 1 mL disposable syringes constructed of ---------- (b)(4)------- glass. ----------(b)(4)----------. A Certificate of Analysis in presented in the submission in Section 3.2.P.2.4 ----------(b)(4)----------

Review Comment: I reviewed the syringe CofA and found it to be acceptable. The CofA certifies that:

• The glass has been tested and is in compliance with specifications as set forth in the current revision of the ----------(b)(4)----------
• The glass has been tested and is in compliance with specifications as set forth in the current revision of ----------(b)(4)----------
• The glass has been tested and is in compliance with hydrolytic resistance of powder glass specifications as set forth in the current revision of the ----------(b)(4)----------
• This glass will meet the ----(b0(4)--- Test requirements for (containers to be fused) and for (containers not to be fused), as set forth in -------(b)(4)----------
• This glass will meet the ----(b)(4)------- requirements as specified in the current revisions of ----------(b)(4)----------

The syringes are pre-assembled with a Luer-Lok adapter and a tip cap that is secured to the syringe barrel with a plastic rigid tip cap (PRTC) overseal. ---------(b)(4)----------. The tip cap is composed of ----(b)(4)---------- latex-free grey -----(b)(4)---------- rubber. A Certificate of Analysis in presented in the submission in Section 3.2.P.2.4 Formulation Characteristics -(b)(4)--Gray.

Review Comment: I reviewed the syringe CofA for the tip cap and found it to be acceptable. The CofA certifies that:
• This formulation meets the requirements specified in -----(b)(4)----------.
• This formulation meets the chemical requirements for --(b)(4)--- Closures specified in ----------(b)(4)----------
• This formulation meets the requirements specified in ----------(b)(4)----------.

• This formulation meets the requirements of the ----------(b)(4)----------.

The Luer-Lok adapter is composed of clear ----(b)(4)----, and the PRTC is composed of -----(b)(4)-----. The Luer-Lok adapter and the PRTC overseal do not have product contact.

The syringes are illustrated in the submission in Figure 3.2.P.7-1 Drawing of Container Closure System, ---(b)(4)---- 1.0 mL Round Flange Barrel with Plastic Rigid Tip Cap (PRTC) for (b)(4) syringes and the tip cap is illustrated in the submission in Figure 3.2.P.7-2 Drawing of Tip Cap for ---(b)(4)------- 1.0 mL Round Flange Barrel. The supplier and ---(b)(4)--------- sterilization sites are listed in the submission in Table 3.2.P.7-2 Syringe Supplier and --------(b)(4)---------- Sterilization Sites.

Review Comment: I reviewed the drawings listed above and found them to be acceptable. I do not have any questions or comments.

3.2.P.7.1.1. Syringe Dimensions
The main dimensions of the glass barrel, tip cap and Luer-Lok adaptor are provided in the tables below.

Barrel Dimensions

Measurements	**Limits (mm)**
Overall Length of Glass Barrel	---(b)(4)----
Outer Diameter of Barrel	---(b)(4)----
Flange outer Diameter	---(b)(4)----
Flange Thickness	---(b)(4)----
Inner Diameter of Barrel Bore	---(b)(4)----
Depth of Barrel Bore	---(b)(4)----

Tip Cap Dimensions

Measurements	**Limits (mm)**
Overall Length (Tip Cap + Luer-Lok)	---(b)(4)----
Tip Cap Depth of Seal Tip	---(b)(4)----

Luer-Lok Adaptor Dimensions

Measurements	**Limits (mm)**
Overall Length	---(b)(4)----
External Diameter	---(b)(4)----

3.2.P.7.1.2. Syringe Barrel Quality Control Testing
The testing performed on the syringe barrels is detailed in the table below.

Quality Control Testing of the Syringe Barrels

Test	**Requirements**
Visual Inspection of the Syringe Package	Performed per lot
Visual Inspection of the Barrel	Performed per lot

Physical Inspection of the Barrel	Performed per lot
Functionality Testing of Syringe	Performed per lot
----(b)(4)---- Test	Performed per lot
----(b)(4)--------- Glass tests	Manufacturer's certification is accepted per lot. Annual verification is performed on one lot per year to ensure testing requirements are met.
----------(b)(4)----------	Manufacturer's certification is accepted per lot. Annual verification is performed on one lot per year to ensure testing requirements are met.
Sterility	Manufacturer's certification is accepted per lot. Annual verification is performed on one lot per year to ensure testing requirements are met.
----------(b)(4)----------	Manufacturer's certification is accepted per lot. Annual verification is performed on one lot per year to ensure testing requirements are met.

Review Comment: The testing performed on the incoming syringe barrels is acceptable. I do not have any comments. Functionality testing (syringability) is discussed in this review memorandum in Section 3.2.P.2.4.6. Performance.

2.3.P.7.2. Plunger Stoppers and 3.2.P.7.2. Plunger Stoppers

The closure for the syringes is a plunger stopper composed of ----(b)(4)----- latex-free gray ---(b)(4)---- rubber, formulated and molded by ----------(b)(4)----------. A Certificate of Analysis in presented in the submission in Section 3.2.P.2.4 *Formulation Characteristics -- (b)(4)--- Gray*. -----(b)(4)-- stoppers are formulated and molded at (b)(4) and then ----------(b)(4)----------. The stoppers are illustrated in the submission in Figure 3.2.P.7-3 *Drawing of Container Closure System, Stopper 1-3 mL (Regular Threaded) for ---(b)(4)-------- 1.0 mL Syringes*. The stoppers are sterilized by ----(b)(4)---------- at the sites listed in Table 3.2.P.7-7 Stopper -----(b)(4)----- Sites.

Review Comment: I reviewed the CofA for the rubber stoppers and found it to be acceptable. The CofA certifies that:

- This formulation meets the requirements specified in ----------(b)(4)----------.
- This formulation meets the chemical requirements for (b)(4) Closures specified in ----------(b)(4)----------
- This formulation meets the requirements specified in ----------(b)(4)----------.
- This formulation meets the requirements of ----------(b)(4)----------.

I reviewed the drawings listed above and found them to be acceptable. I do not have any comments.

3.2.P.7.2.1. Stopper Dimensions

The dimensions of the stoppers are provided in the table below.

Stopper Dimensions

Measurements	Limits (mm) - ----(b)(4)----
Overall Height	--(b)(4)--
Overall Diameter	--(b)(4)--
Internal Diameter	--(b)(4)--

3.2.P.7.2.2. Stopper Quality Control

The testing performed on the stoppers is detailed in the table below.

Quality Control Testing of the Stoppers

Test	Requirements
Identification of ----------(b)(4)----------	Performed per lot.
Visual Inspection of package (bags) and stoppers.	Performed per lot.
Sterility	Manufacturer's certification is accepted per lot. Annual verification is performed on one lot per year to ensure testing requirements are met.

Review Comment: The testing listed appears to be acceptable. I do not have any comments. During the ---(b)(4)--- inspection performed by TeamBio and the Product Office, I requested TeamBio check if ---(b)(4)--- testing was performed on incoming stoppers. Per the documents sent to me from the inspection ---(b)(4)-------- is performed on incoming stoppers and the specification is ----------(b)(4)-------- per stopper.

3.2.P.7.3. Plunger Rod

The plunger rod is made of ------(b)(4)------- and does not contact product.

3.2.P.7.4. Backstop

The backstop (finger guard) is made of -------(b)(4)------ and does not contact product.

3.2.P.2.2.3.6. Container Closure Selection

A study that examined and compared stability of the drug product in three different container/closure systems supported the choice of container closure. All samples were stored at (b)(4) for up to --(b)(4)-- and at 2-8°C for up to 24 months. All stability samples were evaluated for appearance, pH, ----------(b)(4)----------. Prior to testing, all samples were placed on a ----------(b)(4)----------. Different container/closure systems did not appear to affect the appearance or pH of the formulation----------(b)(4)---------- at 2-8ºC for 6 months and (b)(4) for --(b)(4)-- . Although all container closure systems showed comparable drug product stability, the choice of container closure was based on previous experience with these syringes (same container closure as ---(b)(4)------). Additional details on the compatibility of the formulation with the container closure system of choice can be found in the submission in Section 3.2.P.8.3 Stability Data.

3.2.P.2.4.2. Suitability

The selection of the primary packaging materials for use with MnB bivalent rLP2086 vaccine drug product was made on the basis of results of various physical, chemical, biological and functional tests of the components that meet ----------(b)(4)---------- requirements. The data provided in the submission in this section and the stability data presented in the submission in Section 3.2.P.8.1 Stability Summary and Conclusions, demonstrate the appropriateness of the primary packaging components based on the following considerations:

- Chemical compatibility of materials of construction with drug product
- Safety of materials of construction with drug product
- Protection
- Performance

The primary packaging was tested for the attributes listed in the table below.

Attribute	**Test Type**
Chemical Compatibility	----------(b)(4)----------
	----------(b)(4)----------
	----------(b)(4)----------
Safety of Materials of Construction	-----(b)(4)----------
Protection	---(b)(4)---
	Container Closure Integrity (CCIT)
	Stability
Performance	CCIT
	Dose Delivery
	Syringeability

Review Comment: I only reviewed container closure integrity and performance testing. All other tests fall under the review purview of the Product Office.

3.2.P.2.4.5.1. Container Closure Integrity

--(b)(4)- testing is performed during stability studies to demonstrate the integrity of the container closure over time (Section 3.2.P.2.5 Microbiological Attributes in this review memorandum).

3.2.P.2.2.3.6.1. Syringeability and 3.2.P.2.4.6. Performance

Syringeability refers to the force required for the injection of a given solution at a given injection rate via a needle of predetermined gauge and length. The force is attributed to the break loose force (initial force required to set the plunger in motion) and extrusion force (or glide force) needed to sustain the plunger movement. The break loose (BL) and extrusion force (EF) was measured for syringes placed in (b)(4) different orientations on stability. Data presented in the submission in Table 3.2.P.2.2-5 “Break Loose and Extrusion Forces for Syringes from --(b)(4)---------- ICH Lots” and Table 3.2.P.2.2-6 “Break Loose and Extrusion Forces for Syringes from Pfizer, -(b)(4)- ICH / Process Validation Lots” indicate that the average break loose and extrusion force is ----(b)(4)----------, respectively, and range between ----------(b)(4)---------- respectively and no differences between -----(b)(4)-------- and Pfizer, -(b)(4)- manufactured DP syringes were observed. The break loose (BL) and extrusion forces (EF) do not increase with age or syringe orientation.

The integrity of the container closure system was demonstrated by ----(b)(4)----------methods (Section 3.2.P.2.5 Microbiological Attributes in this review memorandum). The ability to deliver the required dose was demonstrated by the consistent delivery of (b)(4) 0.5 ml (Section 3.2.P.5.4 Batch Analyses in the submission) for all clinical lots manufactured. The effects of ----(b)(4)---------- on the drug product were also studied. The results from these two studies are included in the submission in Table 3.2.P.2.2-7 "The Effect of ----(b)(4)----------(b)(4) into Drug Product Formulation" and Table 3.2.P.2.2-8 "The Effect of ----(b)(4)------- into Drug Product Formulation".

Review Comment: The testing performed to demonstrate suitability of the container closure selection is acceptable. I do not have any comments.

3.2.P.7.5. Secondary Packaging Components

MnB bivalent rLP2086 vaccine drug product syringes are placed into sealed thermoformed trays. The carton is constructed of paperboard. Each carton consists of the drug product syringes in a thermoformed tray(s) and the package insert or instructions for use that fit inside the outer carton. Tamper evident seal is placed on both carton flaps.

3.2.P.8. Stability

3.2.P.8.1. Stability Summary and Conclusions

3.2.P.8.1.1. Summary of Stability Studies

Stability information for MnB bivalent rLP2086 drug product stored under the long term condition of 5 ± 3˚C, the accelerated condition of ----------(b)(4)---------- are provided in the submission. The stability program is designed to follow ICH guidelines for stability of drug product (ICH Guideline Q1A (R2): Stability Testing of New Drug Substances and Products; ICH Guideline Q5C: Quality of Biotechnological Products, Stability Testing of Biotechnological / Biological Products).

Primary and supportive stability studies are performed on drug product produced using the commercial scale process. (b)(4) process validation lots manufactured at Pfizer, -(b)(4)- were used for the primary stability studies and have been carried through 18 months at the long term storage condition. A summary of the drug product lots used for primary and supportive stability are shown in the submission in Table 3.2.P.8.1-1 "Pfizer, -(b)(4)- Drug Product Stability Studies" and Table 3.2.P.8.1-2 "----(b)(4)-- Stability Studies". Studies are ongoing for both the primary stability lots and the supportive stability lots.

MnB bivalent rLP2086 120mcg drug product lots were packaged into 1 mL syringes, which are the same as the proposed commercial packaging. Syringes were stored inverted (tip-up), unless otherwise noted.

Stability Tests, Test Intervals, and Specifications

Stability Tests, Test Intervals, and Specifications are listed in the submission in the following tables. I only included the testing related to DMPQ review.

Table 3.2.P.8.1-1 "Pfizer, -(b)(4)- Drug Product Stability Studies"
Table 3.2.P.8.1-2 "----(b)(4)--- Stability Studies"

Table 3.2.P.8.1-3 "Stability Protocol for MnB Bivalent rLP2086 Drug Product PV/Primary Stability Lots at the Long Term Condition: 5 ± 3˚C"

Tests	**Test Interval[a] (months)**	**Specification**
Appearance	0, 3, 6, 9, 12, 18, 24, -(b)(4)-	Homogeneous white suspension
pH	0, 3, 6, 9, 12, 18, 24, -(b)(4)-	6.0-(b)(4)-
Container Closure Integrity	12, 24, -(b)(4)-	Pass
Sterility	0, 24, -(b)(4)-	Meets the requirements of the test. No growth observed.
Endotoxin	-(b)(4)-	-(b)(4)-

a. Initial data (t0) are from release testing, unless otherwise noted.

Table 3.2.P.8.1-4 "Stability Protocol for MnB Bivalent rLP2086 Drug Product Supportive Lots at the Long Term Condition: 5 ± 3˚C"

Tests	**Test Interval[a] (months)**	**Specification**
Appearance	0, 3, 6, 9, 12, 18, 24, -(b)(4)-	Homogeneous white suspension
pH	0, 3, 6, 9, 12, 18, 24, -(b)(4)-	6.0 -(b)(4)-
Container Closure Integrity	12, 24, -(b)(4)-	Pass
Sterility	0, -(b)(4)-	Meets the requirements of the test. No growth observed.
Endotoxin	0, -(b)(4)-	-(b)(4)-

a. Initial data (t0) are from release testing, unless otherwise noted.

----------(b)(4)----------

[(b)(4)]

----------(b)(4)----------

[(b)(4)]

----------(b)(4)----------

[(b)(4)]

[**(b)(4)**]

----------**(b)(4)**----------

[**(b)(4)**]

----------**(b)(4)**----------

[**(b)(4)**]

[**(b)(4)**]

3.2.P.8.1.6. Summary of Stability Data

The analytical data for the testing listed above is detailed in the submission in the following sections:
3.2.P.8.3 Stability Data - Long Term Stability Data
3.2.P.8.3 Stability Data – Accelerated Stability Data.
3.2.P.8.3 Stability Data– ---(b)(4)-------

3.2.P.8.3 Stability Data - ----(b)(4)------

3.2.P.8.1.7. Shelf Life and Conclusions

The data currently available provide rationale and justification for the drug product shelf life claim of 18 months when stored at the recommended temperature of 5 ± 3 degrees C. The shelf life for drug product will be based on 24 months of stability data from Pfizer, -(b)(4)- process validation / primary stability lots generated at the long term condition of 5 ± 3 degrees C. As agreed with CBER at the February 7, 2014 Type C CMC meeting, the 24 month stability data (and 18 months stability data for -(b)(4)- potency) will be submitted in Q4 2014 during the BLA review period. The proposed shelf life of MnB bivalent rLP2086 drug product is 24 months.

The accumulated data for the Pfizer, -(b)(4)- process validation / primary stability lots demonstrate that the quality attributes remain in conformance with the proposed commercial stability specifications for the corresponding analytical procedure throughout the time points tested. Data accumulated from supportive stability lots further demonstrate that quality attributes remain in conformance with the proposed commercial stability specifications throughout the time points tested.

In addition, the data demonstrate that MnB bivalent rLP2086 drug product is stable through:

- ----------(b)(4)----------
- ----------(b)(4)----------
- ----------(b)(4)----------
- ----------(b)(4)----------
- ----------(b)(4)----------
- ----------(b)(4)----------

Review Comment: The stability testing performed and the data presented appear to be acceptable. The Product Office will make the final determination of the acceptability of a 24 month expiration date.

3.2.P.8.2. Post-Approval Stability Protocol and Stability Commitment

Post-approval, a minimum of one lot of drug product will be enrolled in the commercial stability program at the long term storage condition of 5 ± 3˚C each year that drug product is manufactured. The protocol is provided in Table 3.2.P.8.2-1 below.

Table 3.2.P.8.2-1. Stability Protocol for MnB Bivalent rLP2086 120 mcg Drug Product at the Long Term Condition: 5 ± 3˚C

Tests	Test Interval (months)	Acceptance Criteria
Appearance	0, 12, 24, (b)(4)	Homogeneous white suspension
pH	0, 12, 24, (b)(4)	6.0 (b)(4)
--(b)(4)--	----(b)(4)-----	----------(b)(4)------

---(b)(4)---	------(b)(4)------	----------(b)(4)----------
Purity	0, 12, 24, (b)(4)	----------(b)(4)----------
----(b)(4)-----	------(b)(4)------	----------(b)(4)----------
-(b)(4)- Potency	0, 12, 24, (b)(4)	----------(b)(4)----------(b)(4)----------
Container Closure Integrity	12, 24, (b)(4)	Pass
Sterility	0, (b)(4)	Meets the requirements of the test. No Growth
Endotoxin	0, (b)(4)	----------(b)(4)----------

a. Testing will be performed at the currently approved end of shelf life

Review Comment: The post-approval stability study appears to be acceptable; however, the final decision will be determined by the Product Office.

3.2.P.2.4.7. Summary Plan for Demonstrating Compliance with Quality System Regulation for the Injection System

The container closure system for commercial MnB bivalent rLP2086 vaccine drug product is a 1 mL pre-filled syringe with plastic Luer Lok adapter with a rubber stopper and a synthetic ---(b)(4)---------- rubber tip cap with a plastic rigid tip cap cover as detailed in Section 3.2.P.1 Description and Composition of the Drug Product. MnB bivalent rLP2086 vaccine drug product is single entity combination product. An overview of plan to demonstrate compliance with the following Quality System Regulation (QSR) is provided in this section.

- 21 CFR § 820.20 Management Responsibility
- 21 CFR § 820.30 Design controls
- 21 CFR § 820.50 Purchasing controls
- 21 CFR § 820.100 Corrective and preventive action

3.2.P.2.4.7.1. Management Responsibility (21 CFR § 820.20)

Regulation (21 CFR Part 820) and ISO13485 (Medical Devices – Quality Management System) aligned with ICH Q10 (Pharmaceutical Quality System).

The Quality system establishes requirements for all stages of the product lifecycle from product design to product discontinuation. All sections of the FDA Quality System Regulation, ISO13485 Medical Devices – Quality Management System and ICH Q10 are addressed in three broad categories:

- Management Processes -for establishment, documentation, implementation, management and maintenance of an effective and suitable quality management system;
- Product Realization Processes for establishment, documentation, implementation, management and maintenance of effective and suitable product;
- Process Control Tools -for addressing specific regulatory requirements. May apply to multiple processes.

Periodic management reviews are conducted (according to procedures) for product development, manufacturing process performance, product quality and performance of the quality systems. The results are documented and necessary actions communicated, implemented and tracked. Inputs into these reviews include audit results, customer feedback, process performance and

product conformity, preventive and corrective action status, recommendations for improvements, action from previous management reviews, changes that could affect the Quality Management System and new or revised regulatory requirements.

Tables 3.2.P.2.4-6 through Table 3.2.P.2.4-8 outline the quality system structure.

Table 3.2.P.2.4-6. Management Process

Management Process	ISO 13485	QSR	Quality Procedures
	5.5.3 Internal Communication 7.2.3 Customer Communication 8.2.1 Feedback		PQS Q1215 Product Complaints SOP-QAC-00388 Complaint Handling DVC01 Medical Device Complaint Handling
Communication		820.20 Management Responsibility 820.198 Complaint Files	PQS Q1213 Notification to Management SOP-QAC-00360 Notification to Management SOP-QAC-00271 R&D Quality Review Teams
Internal Auditing	8.2.2 Internal Auditing	820.22 Quality Audit	GPS-QAC-030 Pharmaceutical Sciences Audit Program
Corrective Action	8.5.1 Improvement: General 8.5.2 Corrective Action	820.100 Corrective & Preventive Action 820.198 Complaint Files 803.17 Procedures for MDRs	PQS Q1215 Product Complaints GPS-QAC-022 Handling of Corrective Actions/Preventive Actions (CAPA) in the Quality Tracking System (QTS) SOP-QAC-00388 Complaint Handling DVC01 Medical Device Complaint Handling
Preventive Action	8.5.1 Improvement: General 8.5.3 Preventive Action	820.100 Corrective & Preventive Action	PQS Q1234 Medical Device Corrective Action, Preventive Action (CAPA) GPS-QAC-022 Handling of Corrective Actions/Preventive Actions (CAPA) in the Quality Tracking System (QTS)

Table 3.2.P.2.4-7. Product Realization Process

Realization Process	ISO 13485	QSR	Quality Procedures
Customer relations (external - enquiries / contacts / orders)	5.2 Customer focus 7.2.1 Determination of requirements 7.2.2 Review of requirements 7.2.3 Customer communication	Not Applicable	PQS Q1215 Product Complaints GPS-MDD-00373 Design Control System Life Cycle DVC01 Medical Device Complaint Handling SOP-QAC-00388 Complaint Handling
Distribution & Materials Management	7.4.3 Verification of purchased product 7.5.5 Preservation of product 8.2.4 Monitoring and measurement of product	820.80 Receiving, in-process and finished device acceptance 820.130 Device packaging 820.150 Storage 820.160 Distribution	SOP-MDD-00373 Design Control System Life Cycle GPS-MAT-022 Initial Receipt of Inventory Materials
Purchasing	7.4 Purchasing	820.50 Purchasing Controls	GPS-MAT-010 Approval and Maintenance of New and Novel Materials by the Global Material Review Panel BP-MDD-00852 Creation of a Purchase Specification

Production	6.3 Infrastructure 6.4 Work Environment 7.5.1 Control of production and service provisions 8.2.4 Monitoring and Measurement of product 8.3 Control of nonconforming product	820.70 Production and Process controls 820.90 Nonconforming product 820.181 Device master records 820.184 Devise history records	PQS Q1231 Batch Records and Device History Record SOP-QAC-00928 Drug Product Material Quality Disposition GPS-QAC-033 Packaged and/or Labelled Supplies Quality Disposition SOP-MDD-00373 Design Control System Life Cycle SOP-QAC-00378 Event and Deviation Reporting in the Manufacturing Investigation Report (MIR) Module in Quality Tracking System (QTS GPS-QAC-022 Handling of Corrective Actions/Preventive Actions (CAPA) in the Quality Tracking System (QTS) SOP-PKG-00283 Global CMC Approval of Packaged Lots in Clinical Supplies Distribution System
Inventory	7.4.3 Verification of purchased product 7.5.3 Identification and Traceability 7.5.5 Preservation of product	820.80 Receiving, in-process and finished device acceptance 820.130 Device packaging 820.140 Handling 820.150 Storage	GPS-MAT-022 Handling of Corrective Actions/Preventive Actions (CAPA) in the Quality Tracking System (QTS) GPS-MAT-036 Sampling of Materials Received by Supply Chain GPS-LAB-517 BTxPS Process for Establishing Manual and LIMS Product Specifications GPS-MAT-017 Management and Maintenance of Retention Samples within Pharmaceutical Sciences

Design & Development	7.1 Planning of product realization 7.3 Design & Development 7.5.2 Validation of Processes	820.5 Quality System 820.30 Design Control 820.130 Device packaging 820.181 Device Master Records 820.184 Device History records 820.30 (h) Design Transfer 820.75 Process validation	PQS Q1233 Medical Device Design Controls PQS Q1235 Device Master / Device History Record SOP-MDD-00373 Design Control System Life Cycle GPS-POL-006 Validation and System Life Cycle (SLC) Policy

Table 3.2.P.2.4-8. Process Control Tools

ISO 13485	QSR	Quality Procedures
4.2.3 Control of Documents	820.40 Document Controls	GPS-VAL-004 Requirements for GMP Change Control in The Current Approved Compliance Tracking System GPS-POL-008 GMP Documentation and Document Life Cycle Policy GPS-GEN-002 Documentation Requirements for Original Written Documents GPS-GEN-015 Management of Controlled Copies of Procedures SOP-QAC-00001 Procedure for Pharmaceutical Sciences Standard Operating Procedures SOP-QAC-00005 Pharmaceutical Sciences Business Procedures
4.2.4 Control of Records	820.180 Records - General	SOP-QAC-00433 Pharmaceutical Sciences Active Library Management
	Requirements	PQS Q1203 Documentation Practices GPS-POL-008 GMP Documentation and Document Life Cycle Policy
7.5.2 Validation of process	820.75 Process Validation	SOP-MDD-00373 Design Control System Life Cycle GPS-POL-006 Validation and System Life Cycle (SLC) Policy
7.5.3 Identification & traceability 7.5.3.3 Status Identification 7.5.5 Preservation of Product	820.60 Identification 820.65 Traceability 820.80 Acceptance records & status 820.120 Device Labelling	PQS Q1221 Product Change Management GPS-MAT-022 Goods Receiving Process GPS-MAT-003 Non-conforming Product SOP-QAC-00928 Drug Product Material Quality Disposition
7.6 Control of Monitoring & Measurement Equipment	820.72 Inspection, measuring & test equipment	GPS-VAL-002 Equipment & Computerized Systems Life Cycle (SLC) Requirements GPS-POL-003 Metrology System Policy BP-EQP-01126 Equipment, Acquisition, Control and Disposal within DCoE

8.2.3 Monitoring & Measurement of Process 8.4 Analysis of Data	820.250 Statistical Techniques	SOP-MDD-00373 Design Control System Life Cycle GPS-QAC-030 Pharmaceutical Sciences Audit Program GPS-LAB-501 Laboratory Investigations for BTx Pharmaceutical Sciences SOP-RTN-00272 Investigational Medicinal (Drug) Product and Medical Device Recall GPS-RTN-002 Alerting Process for Non-Pfizer Commercial Drug Product Recall

3.2.P.2.4.7.2. Design Control (21 CFR § 820.30)

The design and development process for the prefilled syringe is consistent with the FDA Quality Systems Regulation (21 CFR Part 820) as well as the concepts included in ISO 13485:2003 (Medical Devices Quality Management Systems – Requirements for Regulatory Purposes). Design control elements include the formalization of design requirements into a product specification containing design inputs, performance of design verification testing to confirm design outputs and use of Risk Analysis according to ISO 14971 (Medical Devices: application of risk management to medical devices) and periodic design review meetings to assess progress of design and development.

The design control requirements will be governed by Pfizer's internal procedure (SOP-MDD-00373 – Design Control System Life Cycle Procedure for Medical Devices and Combination Products). Design and development planning will include activities required to ensure the design process is appropriately controlled, and device quality objectives are met.

These will be collated in a design and development plan which defines the activities, roles and responsibilities for implementation of the deliverables for all the project lifecycle stages from Planning/Feasibility through to Post Launch, including, if appropriate, interfacing with external vendors. The plan also will identify major reviews and decision points for the MnB bivalent rLP2086 drug product. The design and development plan will also outline risk management deliverables associated with MnB bivalent rLP2086 drug product and will be captured in the Risk Management Plan. The risk management is performed based on Pfizer internal procedure (SOP-MDD-00374 – Risk Management for Pfizer Design Control System Life Cycle). This may include assessment of the design, users, the use environments and the user interfaces.

Design inputs will include user requirement specifications and product specifications.
Design outputs will include component drawings and specification, instructions for use, component qualification information, packaging design information, extractables and leachables. These documents will be reviewed and approved as part of design control.

Design Reviews will be conducted as required based on Pfizer's internal procedure (SOP-MDD-00373 – Design Control System Life Cycle Procedure for Medical Devices and Combination Products). Based on the stage of development of the MnB bivalent rLP2086 drug product, design reviews may be combined and will be detailed in the design and development plan.

Design verification strategy for the MnB bivalent rLP2086 drug product will follow the requirements of Pfizer procedure SOP-MDD-00373 – Design Control System Life Cycle Procedure for Medical Devices and Combination Products. The design verification testing will incorporate, as appropriate, recommendations in FDA Guidance, Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products, FDA Guidance, Container Closure Systems for Packaging Human Drugs and Biologics, Chemistry, Manufacturing and Controls Documentation, and Standard ISO 11040-4 Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO). The design verification strategy will be defined within a Design Verification Plan. This plan will describe how all requirements in the Product Specification and those testable outputs from risk management activities. The output will be captured in the design verification report.

The MnB bivalent rLP2086 drug product will undergo design validation and human factors evaluation according to Pfizer internal procedure (SOP-MDD-00375 - Device Design and Human Factor Evaluation). A design validation plan will be written to document the strategy for validating the combination product user requirements from the User Requirement Specification and will include the human factors strategy for validating the safety and effectiveness of the combination product presentation taking into consideration the users, the use environments and the user interfaces. Based on the risk assessment outlined in the risk management plan, the need for Human Factor studies will be evaluated. The output of the design validation will be captured in the design validation summary report.

MnB bivalent rLP2086 drug product is intended to be administered in a physician's office by trained healthcare professionals. Prefilled syringes are common to healthcare professionals and the selected prefilled syringe are widely available and commonly used by healthcare professionals such that no further training would be required for this user group. The container closure for MnB bivalent rLP2086 drug product is commonly used in commercial products. In addition, Pfizer has experience with this container closure which is identical to the one used for --(b)(4)-------- which is also dosed by healthcare professionals. Pfizer intends to perform risk analysis which will take into account user information from ---(b)(4)--- and information obtained during the clinical trials of MnB bivalent rLP2086 drug product. Based on the results of the risk analysis, Pfizer intends to mitigate all identified risks. If all risk can be mitigated, Pfizer does not intend to perform human factor validation studies in the user group (healthcare professionals).

Design transfer will be performed based on Pfizer internal procedure (SOP-MDD-00373 - Design Control System Life Cycle Procedure for Medical Devices and Combination Products). The transfer will be based on the compilation of information required to ensure the design is correctly translated into production specifications and the manufacturing process is successfully transferred to the production facility. Any design changes will be conducted in accordance with Pfizer internal procedure (SOP-MDD-00373 – Design Control System Life Cycle Procedure for Medical Devices and Combination Products).

The design history file will be will be prepared in accordance with Pfizer internal procedure (SOP-MDD-00373 – Design Control System Life Cycle Procedure for Medical Devices and Combination Products). The document will include the following sections:

- Design and Development Planning
- Design Inputs
- Design Outputs
- Risk Management File
- Design Review
- Design Verification
- Design Validation
- Design Transfer
- Design Changes

Pfizer intends to complete design control package by 1Q 2015.

Following information will be provided during the BLA review period:

- Risk Management plan along with Pfizer commercial product (---(b)(4)-----) user complaint data analysis which uses the identical container closure as MnB bivalent rLP2086 drug product will be submitted within 30 days of the last rolling submission.
- Risk Management summary report (summary of all the risks that Pfizer identified) in compliance with ISO14971 will be submitted in Oct 2014.

Following documents will be available for review during Pre-approval Inspection (PAI):

- Concept review report
- User Requirement Specification
- Product Specification
- Design and Development plan

Note: In the telecon held with Pfizer on 12 Jun 2014, the FDA informed Pfizer that it would not be necessary to provide this information to the BLA. This is documented in my Addendum Review memorandum.

3.2.P.2.4.7.3. Purchasing Control (21 CFR § 820.50)

The purchasing controls for the prefilled syringe is consistent with the FDA Quality System Regulation (21 CFR Part 820), ISO 13485 (Medical Devices – Quality management system) and aligned with ICH Q9 (Quality Risk Management) & Q10 (Pharmaceutical Quality System.)

A proactive quality oversight approach is used when working with suppliers to ensure alignment between Pfizer expectations and the supplier systems for Quality and Compliance. All materials used in the manufacture, packaging and comparison of drug products must be obtained from a Pfizer approved supplier/manufacturer and must satisfy the requested specifications to ensure suitability for its intended use. An initial evaluation of supplier's capability to provide fit for purpose materials is conducted by the appropriate sourcing group. If the initial evaluation reveals an appropriate supplier has been selected, qualification activities are determined by the applicable supplier oversight procedures.

Supplier quality oversight activities utilize a risk-based approach to assess, control, communicate and review the required level of quality oversight of suppliers. Elements of this oversight may include but are not limited to: ensuring manufacturing meets specifications, accomplishing

verification testing, ensuring continued knowledge of regulatory status, if applicable, and review of Pfizer product related investigations, if applicable. A list of Suppliers is maintained and includes the Supplier Name, Address, Supplier type (i.e. Manufacturer, Distributor, Broker) and Qualification Status.

Pfizer systems are in place that ensures prefillable syringe components used in the manufacture of MnB bivalent rLP2086 drug product are purchased from suitable, qualified vendors. The systems include requirements for supplier initial selection, evaluation, and qualification, as well as continued monitoring of the approved supplier via testing, auditing, and change control notification. Components used for MnB bivalent rLP2086 drug product are described in Section 3.2.P.7 Container Closure System.

3.2.P.2.4.7.4. Corrective and Preventive Action (21 CFR § 820.100)

The Corrective and Preventive action process focus on improving product and process quality at all stages of the lifecycle ensuring that Pfizer's CAPA systems are effective in driving continuous improvement and knowledge gained from CAPAs is captured and disseminated to key stakeholders. The key elements of this system start with Investigation and root cause analysis. There are two elements to the investigation process: a) determination of the root cause of the non-conformance and b) assessment of the impact of the non-conformance on product quality.

A key element of the CAPA system is ensuring that the true root cause of a problem /deviation is correctly identified and supported with evidence so that the most effective CAPA can be put in place. The process is initiated with a Cross Functional Team that reviews the risk assessment whenever a change in device risks and/or complaints may have occurred. A change in device risk can occur at any time during the life cycle of the device (from the clinical trial phases through product launch and commercial marketing).

Information indicating a potential risk change is reviewed at appropriate Design Reviews as described in Pfizer's procedures.

Sources of information that may indicate a change in risk include:

- Product design changes
- Manufacturing process or material changes
- Post Market Surveillance (PMS)

Data gathered from any of the causes identified above for the device is used to determine if the risk assessment file for the device requires updating. The assessment determines at minimum:

- Potential impact on product quality, including potential to impact downstream
- Processing and/or patient
- Regulatory commitment/filing impact
- Validation impact
- Other lots potentially impacted
- Need for market action
- Final disposition of the batch

PMS data information is gathered from sources such as vigilance reporting, clinical data and on-market planned reviews. Post market information that indicates the device may be performing differently than at the time the risk assessment is performed.

If a new risk assessment is required, the Cross Functional Team performs the assessment and adds all documentation to the Risk Management File.

Review Comment: Pfizer's plan for demonstrating compliance with Quality System Regulations for combination products is acceptable. I do not have any comments.

Drug Substance

2.3.A.1. FACILITIES AND EQUIPMENT and 3.2.A.1. FACILITIES AND EQUIPMENT ----(b)(4)---

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Drug Product

3 2 A 1 Facilities and Equipment ----(b)(4)--- Drug Product
Facility Overview
----------(b)(4)---------- and MnB bivalent rLP2086 formulation and filling take place in the Syringe Fill/Finish Suite located at Pfizer,-(b)(4)-. The Syringe Fill/Finish suite is designed as a multi-product manufacturing facility.

The --(b)(4)-- facility is located at ----------(b)(4)----------
The facility is located on an approximately (b)(4) site approximately 7 miles from (b)(4)----,

-(b)(4)-. The building arrangement on the portion of the site currently developed is illustrated in Drawing 3.2.A.1, Pfizer, -(b)(4)- DRW 00/RD/0001: Overall Site Plan.

Review Comment: I reviewed DRW 00/RD/0001: Overall Site Plan and found it to be acceptable. I do not have any comments.

Manufacturing areas at --(b)(4)-------- are located in (b)(4) buildings; the Manufacturing Suites Building and the Drug Substance Building. The ---(b)(4)---- facility also includes support laboratories, development laboratories, warehouse space, and utilities areas. All production areas and systems are built in conformance with current Good Manufacturing Practices.

3.2.A.1.1.1. Manufacturing Suites Building Overview

The Manufacturing Suites Building is a --(b)(4)-------- structure, divided into a number of independent production suites, with a footprint of approximately -(b)(4)- for a total floor area of approximately ----------(b)(4)---------- is currently used for MnB bivalent rLP2086 drug product ----------(b)(4)----------.

----------**(b)(4)**----------

----------**(b)(4)**----------

----------**(b)(4)**----------

Syringe Fill/Finish, Building Description

The Syringe Fill/Finish Building is a multi-product manufacturing facility. The facility is used for ----------(b)(4)----------, MnB bivalent rLP2086 drug product and ---(b)(4)----------. Drug product manufacturing steps include formulation, filling and inspection. All product contact parts for formulation and filling will be dedicated for --(b)(4)---------- products. The suite is ----------(b)(4)----------

3.2.A.1.1.2.1. Area Classifications

Syringe Fill/Finish area classifications are illustrated in drawing 3.2.A.1, Pfizer, -(b)(4)-, DRW 03/RD/0031: Pressurisation & Classification. Environmental monitoring procedures and specifications supporting these area classifications are detailed this review memorandum in Section 3.2.A.1.3.

In addition to Grade ----------(b)(4)----------

Review Comment: I reviewed DRW 03/RD/0031: Pressurisation & Classification and found it to be acceptable. The different room classifications, air flow directions, and room pressures where illustrated in this floor plan.

Differential Pressure, Temperature and Relative Humidity

The HVAC systems were designed and qualified to meet the following criteria:

- Differential Pressure: the integrity of areas with differing classifications is maintained by a cascade of airflow from areas of higher classification to areas of lower classification within the manufacturing facility. The differential pressure maintained between areas of different classification in the aseptic processing suite is ----(b)(4)------- being set as the critical alarm limit.
- Temperature: the normal operating temperature specification is --(b)(4)- in Grade (b)(4) and (b)(4) areas, with alarm conditions of ----------(b)(4)----------
- Relative Humidity: the normal operating relative humidity specification is ----(b)(4)--- in Grade (b)(4) and (b)(4) areas, with alarm conditions of ----------(b)(4)-------

Automated Control Systems and Information Systems Qualification/Validation

Automated Control Systems and Information Systems involved in GMP operations require installation and operational qualification, with validation activities following a basic qualification framework known as the ---(b)(4)-- for direct impact systems. This model describes the relationship between the user requirements, the design and specifications prepared to meet these requirements, and the level of inspection and testing performed as part of qualification. Software applications undergo complete qualification through installation, operational and performance qualification, including integration testing as necessary.

3.2.A.1.2. Flows

Personnel Flow

Personnel flows for the ground and first floors are outlined in 3.2.A.1, Pfizer, -(b)(4)-, DRW 03/RD/0017: Personnel Flow, Ground Floor and 3.2.A.1, Pfizer, -(b)(4)-, DRW 03/RD/0032: Personnel Flow, First Floor, respectively.

Review Comment: I reviewed DRW 03/RD/0017: Personnel Flow, Ground Floor and DRW 03/RD/0032: Personnel Flow, First Floor and found them to be acceptable. Personnel flows along with employee uniform grades (i.e. plant uniform, manufacturing suit, sterile manufacturing suit, Tyvek suit, street clothes, and street clothes and shoe covers) were illustrated

as appropriate.

Personnel enter the suite through the ----------(b)(4)----------. Visitors may enter the Grade (b)(4) areas only. Gowning for personnel and visitors is performed according to site procedures.

Grade (b)(4) areas are accessed through ----------(b)(4)----------. Grade (b)(4) areas are accessed through rooms ----------(b)(4)---------- Rooms). Additional gowning as applicable is performed at each indicated access points. Exit from the Grade --(b)(4)-- areas is through the same rooms as entry.

Product, Material, Equipment and Waste Flow
Product, material, equipment and waste flows for the ground and first floor are outlined in 3.2.A.1, Pfizer, -(b)(4)-, DRW 03/RD/0018: Product, Material and Waste Flow. Ground Floor and 3.2.A.1, Pfizer,-(b)(4)-, DRW 03/RD/0020: Product, Material and Waste Flow, First Floor.

Review Comment: I reviewed DRW 03/RD/0018: Product, Material and Waste Flow. Ground Floor and DRW 03/RD/0020: Product, Material and Waste Flow, First Floor and found them to be acceptable.

Product Flow

----------(b)(4)----------

----------(b)(4)----------

Material and Equipment Flow

----------(b)(4)----------

----------(b)(4)----------

----------(b)(4)----------

----------**(b)(4)**----------

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Note: At the time of submission, the ----------(b)(4)---------- operate to a Grade (b)(4) classification. A facility change ----------(b)(4)---------- classification is to be submitted to the ---(b)(4)---------- during the BLA review. As these areas are shared for MnB bivalent rLP2086 and ---(b)(4)--- drug product manufacturing, this section and its associated drawings reflect the proposed classification upon BLA approval.

----------(b)(4)----------

3.2.A.1.3. Environmental Qualifications and Monitoring

All areas within Syringe/Fill Finish used for ----------(b)(4)---------- manufacture and the formulation and filling of MnB bivalent rLP2086 drug product are classified in accordance with the activities that occur within the area and the level of containment and environmental control that is required. Areas are classified per EU "Rules Governing Medicinal Products in the European Community, Volume IV, GMP for Medicinal Products".

Environmental Qualifications

A summary of the environmental qualifications the classified rooms in Syringe/Fill Finish is provided in 3.2.A.1, Pfizer, -(b)(4)-, Summary Report for Environmental Monitoring Performance Qualification. The environmental qualifications involved sampling over extended periods of time at rest and in operation. The testing evaluated multiple sample sites in the various environments for ----------(b)(4)----------) for each classified environment defined in the protocol. The environmental qualification of the ---(b)(4)--- is detailed in 3.2.A.1, Pfizer -(b)(4)-, Summary Report for Environmental Monitoring Performance Qualification for the ---(b)(4)--. The results of the qualifications demonstrated that the classified areas in Syringe/Fill Finish met the environmental quality requirements defined in the protocol.

Review Comment: I reviewed the 25 page document, “Summary Report for Environmental Monitoring Performance Qualification” and found it to be acceptable. The facility heating, ventilation, and air conditioning (HVAC) units in Syringe Fill/Finish met established environmental specifications and quality attributes for controlled spaces. All deviations were resolved. The installation, operation, and performance qualifications for the HVAC system have

been completed. I also reviewed the 15 page document, "Summary Report for Environmental Monitoring Performance Qualification for the -----(b)(4)--------" and found it to be acceptable. The Environmental Monitoring Performance Qualification demonstrated that the ----------(b)(4)---------- consistently and effectively met established environmental specifications and quality attributes. All deviations have been successfully resolved. The operation and performance qualifications for the environmental control of the ---(b)(4)--- have been satisfactorily completed.

A summary of each document is provided below.

Summary Report for Environmental Monitoring Performance Qualification at ---(b)(4)----------

This document summarizes environmental performance qualifications for the Heating, Ventilation and Air Conditioning (HVAC) systems serving the Grade (b)(4) and Grade (b)(4) Areas of the Syringe Fill/Finish facility at ----(b)(4)-----

The rooms were tested during dynamic (in-operation) conditions to verify their performance in accordance with manufacturer's and company specifications. For the Grade (b)(4) areas, PQ environmental testing of the classified areas was conducted over a ---(b)(4)--- period. No additional testing was required. For the Grade (b)(4) areas, PQ environmental testing of the classified areas was conducted over a ---(b)(4)--- period, with additional PQ testing conducted over a -(b)(4)- period for closure of deviations. Rooms were monitored for ----------(b)(4)----------. Dynamic testing was conducted with all appropriate equipment operating and personnel present to simulate routine production activities.

The table below provides a list of validation efforts with the performed activities summarized in the reports.

Qualification Final Reports

Report Number	Report Title	Activities
------(b)(4)------	HVAC PQ Summary Report for Manufacturing Suite Syringe Fill/Finish Grade (b)(4) Areas	---------(b)(4)---------- ---------(b)(4)---------- ---------(b)(4)---------- ---------(b)(4)---------- ---------(b)(4)----------
------(b)(4)------	HVAC PQ Summary Report for Manufacturing Suite Syringe Fill/Finish Grade (b)(4) Areas	---------(b)(4)---------- ---------(b)(4)---------- ---------(b)(4)---------- ---------(b)(4)---------- ---------(b)(4)----------

PERFORMANCE QUALIFICATION (PQ)

Performance Qualification served as the system in operation performance test for the HVAC systems serving the Grade (b)(4) and Grade (b)(4) Areas.

Temperature and Relative Humidity Monitoring

Temperature and Relative Humidity were monitored during in operation environmental monitoring. The protocol requirements for Grade (b)(4) classified rooms were ----(b)(4)---------- relative humidity. The protocol requirements for Grade (b)(4) and Grade (b)(4)classified rooms were ---------- relative humidity. The temperature and relative humidity test results for all of the areas met the associated protocol requirements.

Environmental Monitoring Testing
Testing was performed in accordance with the acceptance criteria during in-operation conditions identified in the PQ protocol and presented in the submission in Table 2, Table 3, Table 4 and Table 5. If less than 10 test points are monitored, statistical evaluation of the particle monitoring data is performed and both the average and 95% Upper Confidence Limit (UCL) values are recorded. If 10 or more test points are monitored the average count is calculated.

Review Comment: I reviewed the following tables and found them to be acceptable. Acceptance criteria met applicable EU and ISO specifications.

Table 2 Acceptance ----------(b)(4)----------
Table 3 Acceptance ----------(b)(4)----------
Table 4 Acceptance ----------(b)(4)----------
Table 5 Acceptance ----------(b)(4)----------

Additional Changes / Qualification Testing
-------(b)(4)-------- Grade (b)(4) Area
An additional Environmental Performance Qualification for the HVAC serving the Grade (b)(4) Areas (Gown Room, Material Airlock, Filling Room, Tub Debagging and Inspection Room) for ----------(b)(4)---------- was executed following construction and fit out of the new line. The PQ was executed to verify that the system was capable of maintaining environmental conditions within the rooms served in accordance with design specifications.

There were four deviations, all of which were resolved and did not impact the qualified status of the HVAC system. PQ was completed and all acceptance criteria met.

Shutdown Upgrades
An additional Environmental Performance Qualification for the HVAC serving modified Grade ----(b)(4)---- rooms was executed after modifications were made during the introduction of the future filling line. The PQ was executed to verify that the system was capable of maintaining environmental conditions within the rooms served in accordance with Design specifications. There were six deviations, all of which were resolved and did not impact the qualified status of the HVAC system. PQ was completed and all acceptance criteria met.

Grade (b)(4) Area Reclassification
Although Room ----(b)(4)---- and its corresponding airlocks (----------(b)(4)----------) have been qualified to a Grade (b)(4) classification, these rooms will operate under Grade (b)(4) conditions. As these rooms have met all of the prescribed acceptance criteria for Grade (b)(4), they automatically meet the acceptance criteria for Grade (b)(4) and no further qualification is required.

RESULTS AND DISCUSSION

The results provided in the submission in Table 6, Table 7, Table 8 and Table 9 for the initial PQ demonstrate that total ----------(b)(4)---------- meet the acceptance criteria during in-operation conditions. A summary of deviations is presented in the submission in Table 10.

Review Comment: I reviewed the following tables and all specifications were met. Any deviations noted were investigated and closed out as applicable. If needed, additional monitoring was performed and all specifications were met. The deviations did not have an impact on the acceptability of the validation.

- Table 6 ----------(b)(4)----------
- Table 7 ----------(b)(4)----------
- Table 8 ----------(b)(4)----------
- Table 9 ----------(b)(4)----------
- Table 10 Summary of Deviations

Summary Report for Environmental Monitoring Performance Qualification for the ---(b)(4)----------

This document summarizes environmental monitoring performance qualifications for the ---(b)(4)------ at in the Syringe Fill/Finish facility at ----(b)(4)---------- as outlined in LMREP-000017178.

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----------(b)(4)----------

3.2.A.1.4. Contamination and Cross Contamination Controls

Overview

The Syringe Fill/Finish facility is designed as a multi-product facility and is used in the manufacture of ----(b)(4)---- drug products. All new products are evaluated for potential impact to existing products prior to introduction into the area. ----------(b)(4)----------

Contamination Controls

The Syringe Fill/Finish facility has been designed to minimize the potential of product contamination and personnel exposure using a combination of controls including separate air handling units, pressure differential zones, air-locks, gowning rooms and defined pathways for the flow of personnel, equipment, materials and waste. Manufacturing areas are classified as Grade (b)(4) and Grade (b)(4) controlled environments, and are appropriate to the operations that take place within each area. Air pressure cascades are maintained from areas of higher classification to areas of lower classification. A gowning room or airlock is located between all areas of lower and higher classification. An --(b)(4)--, providing a Grade (b)(4) environment, is used in the aseptic filling of syringes.

Site Standard Operating Procedures (SOPs) describe the flow of materials, equipment and personnel through the facility to prevent contamination and mix-up. Procedures also ensure that appropriate storage conditions are met throughout the manufacturing process.

Routine environmental monitoring is performed in Syringe Fill / Finish to ensure that microbial and particulate levels remain within specifications set.

Cross-contamination Controls

Product contact equipment is dedicated and labeled appropriately or controlled by a validated Manufacturing Control System (MCS). Segregated product manufacturing stations are procedurally controlled to allow concurrent manufacture of multiple lots of the same product in a designated area. Product station and room clearance procedures for components and equipment, together with area inspections, provide assurance that no specific materials or documents remain from a previous manufacture of a different product or different lot of the same product at a product manufacturing station. All portable equipment is cleaned in accordance with validated written procedures after each use. Stationary (fixed) equipment and process piping is cleaned in place using a CIP (Clean in Place) system.

Containment Features

The following sections summarize the contamination or cross contamination controls during manufacturing operations.

Contamination from other Products

- Only one batch of product per segregated manufacturing area is dispensed, formulated or filled at a time.
- Production and dispensing areas are regularly cleaned and sanitized as per site procedures.
- Line clearance occurs when applicable according to site procedures.
- Cleaning procedures are validated and designed to remove product soil and to clean to sanitary conditions.

Contamination from Equipment

- Equipment is cleaned using validated procedures. Cleaned and soiled equipment are identified and segregated.
- Product contact equipment and components are cleaned and sterilized via validated processes prior to use for each batch.
- The exterior surfaces of mobile equipment parts and materials are wiped down with an approved sanitizing agent as per site procedures.
- Product contact ----(b)(4)--------- is one time use and discarded after each process order. ----------(b)(4)----- are prepared for reuse using validated procedures.
- Equipment is properly maintained through a preventative maintenance program.

Contamination from People

- Personnel entering production areas require gowning qualification or a trained escort per site procedures.
- Personnel monitoring is conducted as per site procedures.
- Site procedures adhere with cGMPs and are used for production activities.

Contamination from System Failures

- Classified production areas and cold rooms are monitored for temperature through automated control systems, with appropriate warnings and alarms, and are maintained as per site procedures.
- Differential pressure between rooms of the same and different classifications are monitored and maintained as per site procedures.
- Power back up for monitoring system conditions is available during shutdown or failure.
- Recovery from a disruption to a controlled area is performed as per site procedures.

Contamination from Waste

- Production waste is disposed according to site procedures.
- Production waste receptacles are emptied and sanitized as applicable per site procedures.
- Production areas are cleaned and sanitized per site procedures.

3.2.A.1.5. Critical Process Equipment – Syringe Fill/Finish

Critical process equipment supporting ----------(b)(4)---------- formulation and filling of MnB bivalent rLP2086 drug product ----------(b)(4)---------- Groninger filling and stoppering machine and the -(b)(4)- syringe inspection machine.

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3.2.A.1.5.5. Autoclaves

The steam sterilization autoclaves are located in room (b)(4) in Syringe Fill/Finish and are used for sterilization of the process equipment used for the production of -(b)(4)- and MnB bivalent rLP2086 drug product. The major components of the autoclaves are:

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The autoclaves have been qualified by performing Installation, Operation and Performance Qualifications. The autoclaves are re-qualified --(b)(4)--. The validation of the autoclaves demonstrated that the equipment operates according to design specifications and is maintained within the design parameters. The validation of the autoclaves is detailed in 3.2.A.1, Pfizer, -(b)(4)-, Autoclave PQ Summary Report for -(b)(4)- Loads and Autoclave PQ Summary Report for Drug Product Loads.

Review Comment: I reviewed Autoclave PQ Summary Report for -(b)(4)- Loads and Autoclave PQ Summary Report for Drug Product Loads and found them to be acceptable.

The Installation (IQ), Operational (OQ) and Performance Qualification (PQ) runs were successfully performed to validate the defined loads in ----------(b)(4)----------, located in Syringe Fill Finish at ---(b)(4)----, to support -(b)(4)- manufacture. The PQ runs consisted of both ----------(b)(4)----------. The data obtained met the acceptance criteria for ----------(b)(4)----------, including inactivation of Biological Indicators.

The Installation (IQ), Operational (OQ) and Performance Qualification (PQ) runs were successfully performed to validate the defined loads in ----------(b)(4)---------- located in Syringe Fill Finish at ---(b)(4)-----, to support drug product manufacture. The PQ runs consisted of both ----------(b)(4)----------

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Autoclave PQ Summary Report for Drug Product Loads

----------(b)(4)---------- are used for the steam sterilization of porous components and equipment parts used in support of drug product manufacturing. The Autoclaves are located between ----------(b)(4)----------, in the Syringe Fill Finish Manufacturing Suite.

This report is a summary of the IQ, OQ and PQ studies performed for these autoclaves. The loads qualified on these autoclaves related to the components and equipment parts used in the formulation and filling of -------(b)(4)----------. However, a risk assessment (ASMT-3017) was subsequently performed to determine if any additional PQ studies were required for the MnB bivalent rLP2086 (MnB) drug product formulation load. This concluded that the MnB formulation load was equivalent to the existing qualified load for ---(b)(4)-------- formulation and therefore no further qualification work was required. An additional risk assessment (ASMT-2397) was performed for the MnB filling parts and concluded that the existing -----(b)(4)-- filling

load contained equivalent parts and therefore the load did not require modification or further qualification work. Since both risk assessments concluded that the existing drug product loads met the qualification requirements for MnB, the PQ studies summarized in the submission fulfilled the autoclave qualification requirements for MnB drug product.

Review Comment: Since equivalent loads have already been qualified and approved for ----(b)(4)------ I performed a high-level review of the qualification summary and it is acceptable. IQ, OQ and PQ runs were performed to qualify the defined loads in the ----(b)(4)----------, located in Syringe Fill Finish at ----(b)(4)----------, to support drug product manufacture. The PQ runs consisted of fixed load configurations along with worst case minimum and maximum load configurations. The data obtained met the acceptance criteria for ----------(b)(4)----------. I do not have any questions or comments.

Autoclave System Overview

The -----(b)(4)--------- autoclaves, located in Syringe Fill Finish, sterilize equipment and components used for drug product manufacturing. The autoclaves have ----------(b)(4)----------

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3.2.A.1.6. Utilities

3.2.A.1.6.1. Clean Steam System

The Clean Steam System serving Syringe Fill/Finish consists of (b)(4) Clean Steam Generators (----(b)(4)----------), which are located on the -(b)(4)- floor in the Manufacturing Suites mechanical plant rooms. The Clean Steam generators are designed to process feed water to produce clean steam. Clean steam produced by the CSGs is delivered to clean steam headers and distributed to the points of use located in the clean rooms and to other use points. The CSGs have been qualified as detailed in 3.2.A.1, Pfizer, -(b)(4)-, Summary Report for Clean Steam Qualification.

The Clean Steam System is illustrated in Drawing 3.2.A.1, Pfizer, -(b)(4)-, DRW 03/RD/0023: WFI System and Clean Steam System.

Review Comment: I reviewed DRW 03/RD/0023: WFI System and Clean Steam System and found it to be acceptable.

I also reviewed "Summary Report for Clean Steam System Qualification" and found it to be acceptable. The Clean Steam System serving the Syringe Fill Finish Suite was qualified based on meeting established Installation, Operational, Performance Qualification and Qualification Verification requirements and quality specifications. One minor deviation was noted and resolved. It did not impact the qualification studies. The Clean Steam meets ---(b)(4)---- requirements for ----------(b)(4)----------. A routine monitoring program for the Clean Steam System was established and implemented.

A summary of the report is included below.

Summary Report for Clean Steam System Qualification

SYSTEM DESCRIPTION

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3.2.A.1.6.3. Heating, Ventilation and Air Conditioning

The Heating, Ventilation and Air Conditioning (HVAC) system serving Syringe Fill/Finish consists of an arrangement of a primary Air Handling Unit (AHU) and a number of recirculating AHUs. The areas served by this HVAC System are illustrated in 3.2.A.1, Pfizer, -(b)(4)-, DRW 03/RD/0021: Pressurisation & Classification. A Qualified Building Management System (QBMS) controls air changes, temperature, relative humidity, and pressurization of each room.

Review Comment: I reviewed DRW 03/RD/0021: Pressurisation & Classification and found it to be acceptable.

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HVAC Qualification

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The HVAC systems are re-certified as specified per area classification (i.e. recertification intervals for tests executed in Grade (b)(4) areas vary between -(b)(4)-).

Review Comment: I reviewed the reports "Summary Report for HVAC Qualification" and "Summary Report for Environmental Monitoring Performance Qualification" and found them to be acceptable. The Installation and Operational Qualification and Qualification Verification of the Heating, Ventilation, and Air Conditioning (HVAC) systems serving Syringe Fill/Finish demonstrated that the system is installed as designed and specified, and operate within the established design parameters. Environmental monitoring was performed as a Performance Qualification of the HVAC system, as detailed in 3.2.A.1, Pfizer -(b)(4)-, Summary Report for Environmental Monitoring Performance Qualification. All deviations have been resolved and did not impact the qualifications.

I have included a summary for the "Summary Report for HVAC Qualification" below. A discussion for the "Summary Report for Environmental Monitoring Performance Qualification" is included in this review memorandum in Section 3.2.A.1.3 Environmental Qualifications and Monitoring.

Summary Report for HVAC Qualification
The Heating, Ventilation, and Air Conditioning (HVAC) system serving Syringe Fill/Finish consists of (b)(4) recirculation Air Handling Units (AHU) detailed in the submission in Table 1 HVAC Systems and Areas Served.

The AHUs are located in the ----------(b)(4)---------- and supply the (b)(4) floor production area rooms with conditioned air.

The AHUs are designed to process a mix of outside air and return air from the areas served. Each AHU is equipped with ----------(b)(4)----------.

The supply air processed by each AHU is delivered to terminal High Efficiency Particulate Air (HEPA) filters, which are located in the ceilings of the production areas. The duct work providing the processed air is equipped with ----------(b)(4)----------. The return air from the production areas is removed from low-level return air grills and ducted to the return air fans. These return air fans deliver return air to the mixing section of the AHU.

Computer Based Control System
A Qualified Building Management System (QBMS) monitors and controls the HVAC systems. HVAC controls include startup, shutdown, room temperature, pressure, relative humidity, and airflow.

System controllers connect these systems to a distributed control network and automatically control the associated motors, fans, valves, and dampers. The control system captures alarm conditions and communicates on the network for alarm reporting, data sharing and global control.

The control systems have printing capabilities for alarms, event logs and reports. Operator Interface Terminals (OITs) are available throughout the facility. The servers for the control systems are located in a building separate from the manufacturing area. There are redundant servers and redundant networking.

INSTALLATION QUALIFICATION

Installation Qualification (IQ) for the HVAC System was successfully executed to verify that all utilities, instrumentation and equipment were installed and documented according to engineering specifications. The following verifications were documented in the IQ:

- Pre-requisite checklist for IQ execution
- Documentation Verification
- Design Specification Verification
- Instrument Calibration Verification
- Drawing Verification
- Maintenance Verification
- Utility Verification
- Terminal Supply Unit Verification

The IQ reports are listed in the submission in Table 2 Installation Qualification for HVAC System. Per Pfizer, all deviations encountered during IQ executions were investigated and satisfactorily addressed. All IQs were successfully completed.

OPERATIONAL QUALIFICATION

Operational Qualification (OQ) for the HVAC System was successfully executed to demonstrate that the systems operate in accordance with design requirements and that all classified environments met air quality requirements. The following verifications were documented in the zonal OQs:

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All zonal OQ reports are listed in the submission in Table 3 Zonal Operational Qualification for HVAC System. Per Pfizer, any deviations encountered during zonal OQ executions were investigated and satisfactorily addressed. All zonal OQs were successfully completed.

QUALIFICATION VERIFICATION

Qualification Verification (QV) is an integrated commissioning and qualification approach used as an alternative approach to IQ and OQ protocol execution. QV modules were executed following:

1. Modifications to the existing qualified HVAC systems ----------(b)(4)---------- ---------- serving Grade --(b)(4)-- classified rooms in the Syringe Fill Finish Manufacturing Suite.
2. Addition of qualified HVAC system -(b)(4), serving the Grade (b)(4) manufacturing area for a future filling line.

The modifications to the existing qualified HVAC systems at --(b)(4)-- were made under change control. The modifications included ----------(b)(4)---------- The following verifications were documented in the QV modules:

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All Qualification Verification (QV) summary reports are listed in the submission in Table 4 Qualification Verification for HVAC Systems. Per Pfizer, any deviations encountered during QV executions were investigated and satisfactorily addressed. All QV modules were successfully completed.

PERFORMANCE QUALIFICATION
The performance qualifications of the HVAC systems were performed by environmental monitoring, as detailed in 3.2.A.1, Pfizer -(b)(4)-, Summary Report for Environmental Monitoring Performance Qualification.

HVAC Monitoring
The airflow, room pressure, temperature, and relative humidity are continuously monitored and control elements in the HVAC system are modulated to maintain the desired parameters using the QBMS. The facility pressurization is managed by dynamic pressure control system.

The room pressures are controlled with respect to common reference pressure such that desired pressurization across each closed door is achieved. Refer to Section 3.2.A.1.3 for additional HVAC routine monitoring information.

3.2.A.1.6.4. Water for Injection System
The WFI system is illustrated in the submission in Drawing 3.2.A.1, Pfizer, -(b)(4)-, DRW 03/RD/0023: WFI and Clean Steam System.

Review Comment: I reviewed DRW 03/RD/0023: WFI and Clean Steam System and found it to be acceptable.

WFI is generated in the ----------
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Validation of the WFI System
The following test functions have been met for the Water Systems:

1. All critical controls, alarms, and indicators operate according to design specification.
2. Chemical tests meet ----(b)(4)---. requirements.
3. ----------(b)(4)----------.
4. ----------(b)(4)----------

The validation of the Syringe Fill Finish WFI system is detailed in 3.2.A.1, Pfizer, -(b)(4)-, Summary Report for WFI System Qualification.

Review Comment: I reviewed the document, "Summary Report for WFI System Qualification" and found it to be acceptable. The WFI Generation and Distribution System serving Syringe Fill/Finish met established installation, operational and quality specifications. The installation, operation and performance of the Syringe Fill/Finish WFI Distribution System were qualified. Any deviations noted were appropriately investigated and closed out. They did not have an impact on the qualification studies.

A summary of the report is included below.

Summary Report for WFI System Qualification
WFI Storage and Distribution System Overview
WFI is generated in ----------
----------(b)(4)----------

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Installation Qualification (IQ)
IQ for the Syringe Fill/Finish WFI Storage and Distribution System (---(b)(4)---------) was executed to verify that the system was installed in accordance with design specifications. The IQ tests included verification that the WFI Generation System and instruments/components were adequately tagged, accompanied by adequate documentation, and installed correctly according to drawings and specifications. System utilities were verified to be within the required specifications. In addition, all critical instruments were confirmed as calibrated and preventive maintenance checklists were confirmed to be in place and maintained. There were no deviations during the IQ. The IQ was completed and all acceptance criteria met.

Operation Qualification (OQ)
OQ for the Syringe Fill/Finish WFI Storage and Distribution System (-----(b)(4)-----) was executed to demonstrate that the system, including the control system and its components, operates in accordance with design and manufacturers' specifications. The OQ tests included verification of operating procedures, sequence of operations, alarms and interlocks, security, human machine interface (HMI), manufacturing control system (MCS) interface, power loss and recovery, and verification of WFI flow, pressure and quality. The OQ tests for new user points included verification of operating procedures, sequence of operations, alarms and interlocks, sanitization flush and quality. Per Pfizer, all deviations encountered during OQ executions were investigated and resolved. OQ was completed and all acceptance criteria met.

Performance Qualification (PQ)

PQ for the Syringe Fill/Finish WFI Storage and Distribution System (-----(b)(4)------) was executed to verify that the system performs in accordance with design specifications. The parameters qualified are detailed in the submission in Table 1 Parameters Qualified. These are the same parameters as listed in this review memorandum in Section 3.2.A.1.6.1 Clean Steam System and meet USP specifications.

----------(b)(4)----------

Additional Installation and Operational Qualification (IOQ)
Additional IOQ for the WFI system (-----(b)(4)-----) was executed following modifications to the existing qualified system. The changes were to ----------(b)(4)----------. The IOQ was executed to verify that system modifications were installed and operate and perform in accordance with design specifications. All deviations encountered during the IOQ execution were investigated and resolved. The IOQ was successfully completed and all acceptance criteria met.

Additional Installation and Operational Qualification (IOQ) Phase 1 Shutdown Upgrades
Additional IOQ for the WFI system (LMREP-000015665) was executed following modifications to the existing qualified system to facilitate the installation of a -----(b)(4)------. These modifications included the ----------(b)(4)---------- IOQ was executed to verify that system modifications were appropriately installed and the system continues to operate and perform in accordance with design specifications. There were no deviations during IOQ execution. IOQ was successfully completed and all acceptance criteria met.

Qualification Verification (QV) and PQ for Phase 2 Upgrades
Phase 2 modifications to the WFI system consisted of the ----------(b)(4)----------. Qualification Verification (QV) (LMREP-000015703) was performed to support these upgrades. QV is an alternative equipment qualification strategy to IQ/OQ qualification approach, where testing is performed and documented only once in the equipment qualification lifecycle. QV verified that the system modifications were appropriately installed and that the system continues to operate and perform in accordance with design specifications. All deviations encountered during QV were investigated and resolved. QV was successfully completed and all acceptance criteria were met.

A PQ study (LMREP-000015745) was performed on the new use points. ----------(b)(4)----------

Performance Qualification (PQ) Test Results

1 page determined to be not releasable: (b)(4)

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----------(b)(4)----------

Description Test
The WFI samples from the Distribution System serving Syringe Fill/Finish consistently met the acceptance criteria of 'clear and colorless'.

Qualification Verification (QV)
QV for the modifications to the Syringe Fill/Finish WFI Storage and Distribution System was successfully executed, QV tests included verification that the WFI Generation System and instruments/components were accompanied by adequate documentation, and installed correctly according to drawings and specifications. In additional, all critical instruments were confirmed as calibrated and preventive maintenance checklists were confirmed to be in place and maintained. Operating procedures, sequence of operations, alarms and interlocks, sanitization flush and quality were also verified. All deviations encountered during QV were investigated and resolved.

DEVIATIONS
There were two deviations generated during execution of the WFI Storage and Distribution System PQ. All deviations encountered during the PQ execution were investigated and resolved. Deviations are summarized in the submission in Table 5 Deviation Summary.

Review Comment: I reviewed Table 5 Deviation Summary and found it was acceptable. The two deviations noted did not have an impact of the qualification study and they were appropriately investigated and closed out.

Routine Monitoring of the WFI System
The WFI supply and return sample points of each WFI distribution loop are sampled and tested for biologic content as per the monitoring program. All WFI points of use in Syringe Fill/Finish are routinely sampled and tested for biological content as per the monitoring program. The return sample points are tested for -----(b)(4)---------- and the supply to each loop is tested for --(b)(4)--- as per the monitoring program. The testing is performed to current ----------(b)(4)---------- analysis of WFI.

2.3.A.1.2.5 and 3.2.A.1.7 Equipment and Cleaning
Cleaning validation has been performed for the equipment and parts used in the manufacture of ----------(b)(4)---------- MnB bivalent rLP2086 drug product. The product contact equipment and parts used for -(b)(4)- are dedicated. The product contact equipment and parts used for ---(b)(4)--- MnB bivalent rLP2086 drug product are dedicated except the ----------(b)(4)----------. All the equipment and parts are cleaned using validated procedures.

Cleaning Procedures
The production equipment and systems are cleaned to prepare the equipment and systems for each subsequent batch. Large fixed equipment, such as vessels, are either Cleaned in Place (CIP) or moved to designated locations and Cleaned out of Place (COP). The CIP (b)(4) forms a closed system with no solution exposure to the outside environment. Small, easily removed, equipment such as valves, may be Cleaned out of Place (COP).

COP and CIP procedures generally consist of an ----------(b)(4)----------

Routine monitoring of the cleaning process is performed by testing for ---(b)(4)--- and visual inspection to verify cleanliness.

3.2.A.1.7.2. Cleaning Validation
The results of cleaning validation are summarized in the submission in 3.2.A.1, Pfizer, -(b)(4)-, Cleaning Validation Summary Report for ----------(b)(4)---------- and 3.2.A.1, Pfizer, -(b)(4)-, Cleaning Validation Summary Report for MnB Drug Product. Prior to cleaning validation, commissioning, qualification and cleanability / development studies were performed to demonstrate, through testing, that the equipment / systems perform as designed and are able to reduce challenge material to within the predefined acceptance criteria.

For the cleaning validation of --(b0(4)-- MnB bivalent rLP2086 drug product equipment, (b)(4) consecutive studies were performed with the equipment held for defined Dirty Hold Times (DHT) and Clean Hold Times (CHT). Grouping of equipment was utilized during cleaning validation studies, where appropriate.

Sample plans and sample locations were clearly defined in the cleaning validation protocols and were dependent on the equipment being cleaned. Sample locations were selected based on most difficult to clean and representative product contact locations.

Sampling and testing was performed to demonstrate that the intended cleaning was effective, robust and consistently met the requirements for ----------(b)(4)----------

The cleaning validation studies included the following evaluations:

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All of the results met the acceptance criteria detailed in the applicable cleaning validation protocols, establishing validation of the cleaning procedures.

Review Comment: I reviewed "Cleaning Validation Summary Report for ----------(b)(4)----------and "Cleaning Validation Summary Report for MnB Drug Product" and found them to be acceptable.

The Cleaning validation runs for ----------(b)(4)---------- were successfully performed to validate the cleaning procedures used to clean the ----------(b)(4)---------- manufacturing equipment in Syringe Fill Finish at ---(b)(4)-----. All results met the pre-determined acceptance criteria for ----------(b)(4)----------. All deviations observed were resolved.

(b)(4) cleaning validation runs for MnB Drug Product were performed for each equipment group to validate the cleaning procedures used to clean the MnB formulation and filling equipment used in Syringe Fill Finish at ---(b)(4)----------. All results obtained met the pre-determined acceptance criteria for ----------(b)(4)----------. All deviations observed were resolved and did not impact the cleaning validation performed.

A summary of each report is included below.

Cleaning Validation Summary Report for ----------(b)(4)----------
Cleaning Process
----------(b)(4)----------

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Cleaning Validation Summary Report for MnB Drug Product
Cleaning validation was performed using dedicated product contact, formulation equipment, filling equipment and associated parts designated for use in MnB drug product manufacture. ----
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Review Comment: I reviewed the results listed in the tables above and found them to be acceptable.

Visual Inspection
All equipment passed visual inspection for removal of product and detergent residues for all successful cleaning validation runs.

There was one deviation associated with visual inspection of ----------
----------(b)(4)----------

DEVIATIONS

Four events occurred during the execution of cleaning validation on filling load line ---(b)(4)--- One event was a documentation print error and was amended in the protocol. The other three events were deviations and are detailed in the submission in Table 13 Deviation/ Event Summary.

Review Comment: I reviewed Table 13 Deviation/ Event Summary and all deviations recorded were minor deviations that did not impact the qualification runs.

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8 pages determined to be not releasable: (b)(4)