DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA, Center for Biologics Evaluation and Research

MEMORANDUM

Date: 27 October 2014

From: Tina S. Roecklein, M.S., Consumer Safety Officer, DBPAP, OVRR

Through: Jay E. Slater, M.D., Director, DBPAP, OVRR

Subject: Product Review Memo for BLA 125549/0 (Trumenba)

Sponsor: Wyeth Pharmaceuticals Inc.

To: File for 125549/0

Submissions Reviewed:

Amendment 2, received 29 May 2014 (CMC/Quality)
Amendment 4, received 16 June 2014 (Labeling)
Amendment 5, received 23 June 2014 (Extractable Leachable Data)
Amendment 17, received 21 August 2014 (Applicant referred to as Wyeth and not Pfizer)
Amendment 21, received 24 September (Response 8/22/14 LRP IR and 8/29/14 CMC IR)
Amendment 22, received 25 September (18 month *(b)(4)* potency stability data)
Amendment 24, received 9 October 2014 (Response to 9/30/14 CMC IR)
Amendment 30, received 21 October 2014 (Update to Electronic Sections to include responses to CMC IRs)

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1. Summary/Background:

Wyeth submitted their initial IND (ND 13812) for an investigational vaccine, recombinant lipoprotein 2086 (rLP2086), indicated for the prevention of *Neisseria meningitidis* (*N. meningitidis*) serogroup B invasive disease on 19 September 2008. Wyeth was granted Fast Track Designation on 23 October 2009.

Due to recent outbreaks of *N. meningitidis* infections in college campuses, CBER requested that Wyeth provide an update on the status of their Chemistry, Manufacturing, and Control (CMC)/Quality, manufacturing facility, and clinical data that could support a BLA submission for U.S. licensure under an accelerated approval pathway. A Type C meeting was held on 7 February 2014 (CRMTS #9280, IND #13812) in which CBER responded to Wyeth's CMC/Facility questions to ensure that the information meets the Agency's expectations for licensure under an "Accelerated Approval" pathway. During this meeting, it was highly suggested that a pre-BLA meeting be scheduled prior to submission of the original BLA. Breakthrough Therapy Designation for their Meningococcal B vaccine was granted on 19 March 2014 and approval to submit this BLA as a rolling submission was received on 23 April 2014. A Type B pre-BLA meeting was held on 1 May 2014 (CRMTS #9380, IND #13812) to discuss CMC/Quality contents of their planned BLA. Wyeth submitted four installments of the rolling Biologics License Application (BLA) for Trumenba (8 May 2014, 12 May 2014, 29 May 2014, and 16 June 2014). Wyeth completed their BLA submission on 16 June 2014 which initiated the clock for the PDUFA timelines. The CMC/Quality information was included in the 29 May 2014 submission.

Wyeth Pharmaceutical Inc. is seeking approval of Trumenba (*Neisseria meningitidis* Serogroup B Bivalent Recombinant Lipoprotein rLP2086 [subfamily A and B; *E. coli*] Vaccine). The proposed indication of Trumenba is for active immunization to prevent invasive meningococcal disease caused by *N. meningitidis* serogroup B in individuals aged 10 through 25 years. This vaccine is administered as a 3-dose series at months 0, 2, and 6.

This vaccine consists of recombinant lipidated meningococcal factor H binding proteins (fHBP), also called lipoprotein 2086 (LP2086), which are surface-exposed outer membrane proteins from *N. meningitidis*. The vaccine contains two variants, A05 and B01, one from each of the two major clusters of fHBP sequence types called family A and family B. The vaccine proteins are expressed individually in *Escherichia coli* and each protein is purified by several chromatography procedures. The vaccine formulation includes 60 µg of each LP2086 protein variant, 10 mM histidine (pH 6.0), --b(4)----

sodium chloride, and 0.25 mg aluminum phosphate. The vaccine is packaged as a single 0.5 mL dose in a 1 mL pre-filled syringe for administration via intramuscular injection.

Trumenba consists of two separate drug substances:

- *Neisseria meningitidis* Serogroup B Recombinant LP2086 (MnB rLP2086) Subfamily A Protein
- *Neisseria meningitidis* Serogroup B Recombinant LP2086 (MnB rLP2086) Subfamily B Protein

Both drug substance proteins are manufactured at ---b(4)----------

Drug Product (*Neisseria meningitidis* Serogroup B Recombinant Lipoprotein (rLP2086; subfamily A and B; *E. coli*) vaccine), also known as MnB bivalent rLP2086 Drug Product, is manufactured (formulated, filled, and visually inspected) at Pfizer –b(4)---------- (Pfizer –b(4)-----). Aluminum phosphate ($AlPO_4$) is a non-novel, ------b(4)---------- excipient which functions as a –b(4)------- for this vaccine. The final vaccine consists of a sterile liquid suspension.

A control strategy has been designed for Trumenba to ensure that a product of required quality will be consistently produced. Critical Quality Attributes (CQA) are selected for both drug substance and drug product based upon the potential of the quality attribute to impact safety or efficacy. Process risk assessment was performed to determine the process parameters. In addition, in process test for control (IPT-C) and in process test for monitor (IPT-M) are used throughout the process to ensure a consistent manufacturing process.

Trumenba is manufactured at several locations.

- --b(4)---------- – manufacture and storage of drug substance, quality control testing of drug substance including release and stability testing, cell bank storage
- Pfizer—b(4)---------- – drug substance --(b)(4)--, formulation/fill/visual inspection of drug product vaccine, manufacture of -b(4)---, final product testing (with exception of *–b(4)*--- potency testing), cell bank storage
- Pfizer,----------*–b(4)*--- potency testing of drug product vaccine
- Pfizer,---b(4)---------- – final labeling and packaging of drug product vaccine
- Wyeth, -b(4)-------- – manufacture of working cell banks, quality control testing of cell banks including release and stability, cell bank storage
- Pfizer, --b(4)---------– cell bank storage
- ---b(4)---------- – cell bank testing

It was noted that Wyeth/Pfizer is used interchangeably throughout the BLA submission. CBER noted that FDA Forms 356h were submitted to the BLA listing either Pfizer or Wyeth as the applicant even though Wyeth Pharmaceuticals Inc. is the official U.S. license holder. The applicant responded in their 21 August 2014 amendment stating that

Wyeth would be the applicant for this BLA under US License #3. Wyeth is a wholly owned subsidiary of Pfizer, Inc.

2. BLA Review of Drug Substance MnB rLP2086 Subfamily A:

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

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54 Pages determined to be not releasable: b(4)

4. BLA Review of Drug Product (DP):

MnB bivalent rLP2086 drug product is a sterile liquid suspension composed of rLP2086 subfamily A and B proteins formulated at 120 µg/mL/subfamily in 10 mM histidine buffer pH 6.0, -b(4)- sodium chloride (NaCl), and 0.5 mg/mL aluminum as aluminum phosphate ($AlPO_4$). Polysorbate 80 (PS80) is added to drug substance to –b(4)--- ---------- ---------- Therefore, PS80 is not added during the drug product formulation but is present in the final drug product ---------- The drug product is filled into 1 mL syringes. A single dose of vaccine is 0.5 mL with no preservative. The composition of the MnB bivalent rLP20865 drug product is summarized in Table 3.2.P.1-1 in Section 3.2.P.1 (Description and Composition of the Drug Product). No excipients of human or animal origin and no novel excipients are used.

Table 3.2.P.1-1. 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)			
Histidine	(b) (4)	10 mM	pH control	0.78 mg
Polysorbate 80[a] (PS80)		0.035 mg/mL	(b) (4)	0.018 mg
Aluminum phosphate	Company Specification	0.50 mg aluminum/mL		0.25 mg
Water for injection	(b) (4)		Diluent	(b) (4)

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

The syringes are 1 mL disposable syringes constructed of –b(4)---------- glass. The syringes are pre-assembled with a Luer-Lok® adapter, a tip cap, and a plastic rigid tip cap (PRTC) overseal. The syringes are received—b(4)-- ---------- . The tip cap is composed of –b(4)---------- latex-free –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 do not have product contact.

The closure for the syringes is a plunger stopper composed of –b(4)---------- latex-free

-b(4)---- rubber. The stoppers are received –b(4)---------- ---- The backstop and plunger rod are composed of -----(b)(4)-----. These components do not have product contact.

2.1. Pharmaceutical Development

A Target Product Profile (TPP) which lists the proposed product concept and essential elements was composed for drug product prior to the 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 DP. As a guide to development, the QTPP lists the intended product quality and performance characteristics to be achieved at the end of the DP manufacturing process. The list of QTPP for DP is listed in Table 3.2.P.2-1 of Section 3.2.P.2 (Pharmaceutical Development). The Pharmaceutical Development sections describe how DP was developed to meet the elements of the QTPP. Each of the DP critical quality attributes (CQAs), whether contributed from the drug substance process or the drug product process, is related to the QTPP.

The assignment of criticality to a quality attribute is based upon the potential for the quality attribute to impact safety or efficacy. CQAs for DP were distinguished from quality attributes (QAs) by an iterative process of quality risk and criticality assessment, and experimentation that determined the extent to which the CQAs variation had an impact on the quality of DP. The CQAs may contribute to the ability of the vaccine to elicit the desired immune response or to impact safety were further identified through nonclinical studies and *in vitro* functional assessments. For MnB bivalent rLP2086 drug product, the critical quality attributes are *–b(4)*----------and purity Table 3.2.P.2-2 of Section 3.2.P.2 (Pharmaceutical Development) summarizes the quality attributes as well as the rationale for the criticality assignment of MnB bivalent rLP2086 drug product.

Both MnB rLP2086 subfamily A and B drug substances are formulated at a target concentration of—b(4)-- ----------. Developmental data support the compatibility of the two proteins with each other and with all of the DP formulation components. Table 3.2.P.2.1-2 in Section 3.2.P.2.1 (Components of Drug Product) summarizes the DP excipients, concentrations, and rationale for use.

Table 3.2.P.2.1-2. MnB rLP2086 Drug Product Excipients

Excipient	Concentration	Function
Histidine	10 mM Histidine - [redacted] NaCl	Histidine, sodium chloride and WFI are used to prepare the final formulation buffer which provides two important functions: 1. Buffer capacity to maintain a stable final drug product pH of 6.0 [redacted] This pH ensures [redacted] 2. [redacted]
Sodium chloride		
Water for Injection		
Aluminum phosphate ($AlPO_4$)	0.5 mg aluminum/mL	0.5 mg/mL aluminum as aluminum phosphate ($AlPO_4$) is added as a [redacted]
Polysorbate 80	0.035 mg/mL	[redacted]

1.1. Pharmaceutical Development – Drug Product:

A summary of the formulation changes made during vaccine development is provided in Table 3.2.P.2.2-1 in Section 3.2.P.2.2 (Drug Product). The influence of –b(4)----------------

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-- ------------- was evaluated to define the final commercial formulation composition of the vaccine.

[b(4)]

--b(4)-- --

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

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

The conclusions of these studies are that the DP is stable and appropriate for the intended use.

2.2. Pharmaceutical Development – Developmental History:

The clinical drug product (DP) has been manufactured at –b(4)- different sites. The 120 µg dose presentation is the commercial dose presentation and Pfizer, -b(4)-- is the commercial manufacturing site.

Changes to the manufacturing process through clinical trial development to commercial manufacture consisted predominantly of the following.

19 Pages determined to be not releasable: b(4)

[b(4)]

2.3. Pharmaceutical Development – Container Closure:

Table 3.2.P.2.4-1 of Section 3.2.P.2.4 (Pharmaceutical Development – Container Closure System) provides a summary of the container closure systems used during clinical development.

[b(4)]

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.

The syringe barrel is composed of –b(4)---------- glass, which meets ---b(4)---------- requirements.

The Luer-Lok adapter is composed of clear -----(b)(4)----- and the plastic rigid tip cap (PRTC) is composed of -----(b)(4)-----. These components do not have product contact.

The plunger stopper is composed of –b(4)---------- Gray latex-free –b(4)----- rubber. The tip caps are composed of –b(4)------ Gray latex-free –b(4)---------- rubber.

The selection of primary packaging materials for use with the MnB bivalent vaccine DP 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 (as listed below) demonstrate the appropriateness of the primary packaging components based on the following review:

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4.8 Manufacture:

The responsible manufacturers and testing laboratories for –b(4)---------- Drug Product are listed below.

- Pfizer,--b(4)---------- MnB bivalent rLP2086 vaccine formulation and syringe filling, quality control testing of-b(4)------- drug product syringes (including release and stability), and release testing of drug product syringes

- Wyeth,-b(4)-- final labeling and packaging of drug product syringes
- Wyeth, ----------*b(4)*--potency assay (release and stability)
- ---b(4)---------- (contract testing site): sterility testing of $AlPO_4$

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

[b(4)]

The MnB bivalent rLP2086 drug product (DP) formulation contains subfamily A and B drug substance proteins in 10mM histidine/-b(4)--- sodium chloride (NaCl) buffer, pH 6.0, and 0.50 mg/mL aluminum as aluminum phosphate ($AlPO_4$) with polysorbate 80 a---b(4)-- ----------
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--b(4)-- ----------

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

All parameters are defined and controlled at the specified set point, or within the applicable ranges, detailed within the production records and standard operating procedures.

In-process controls (process parameters and in process tests) are used to ensure control of the individual process steps, process consistency and product quality. If the results of these controls are outside of the acceptable ranges/acceptance criteria, an evaluation of the deviation is performed and the material could subsequently be dispositioned for further manufacture, based on investigation conclusion.

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

[b(4)]

The –b(4)---------- excipients used for MnB bivalent rLP2086 drug product are sodium chloride, histidine, and water for injection. These excipients comply with the --b(4)----------. The excipients are accepted by Pfizer based on a --b(4)----------

There are no excipients of human or animal origin. There are no novel excipients.

4.11 Control of Drug Product:

The release and stability specifications for MnB bivalent rLP2086 drug product are detailed in Table 3.2.P.5.1-1 of Section 3.2.P.5 (Specifications).

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

a. These tests are performed for the stability assessment
b. CCI testing is not a release test, only performed (b) (4) on stability

(b) (4)

The analytical test methods and the proposed specification were derived through evaluation of the following.
- development experience with MnB bivalent rLP2086 drug product
- characterization and process validation data
- manufacturing history at scale
- release, and ongoing stability data
- toxicological and clinical evaluation of drug product

In addition, compendial requirements for protein based products were considered.
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 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 specification setting as these were at different doses and subjected to testing using initial versions of the analytical methods. Drug product lots used in the evaluation and justification of specifications are listed in Table 3.2.P.5.6-1 of Section 3.2.P.5.6 (Justification of Specifications).

[b(4)]

Statistical evaluation included b(4) commercial scale MnB bivalent rLP2086 drug product lots including those used for process validation. DP lots at pilot scale were not included in the statistical evaluation. The mean, standard deviation, and tolerance interval range for the data set are included. Tolerance intervals were applied to set one- or two-sided

specification limits where α is set at 1% and the γ is set to 5%. This directly implies that the tolerance intervals will contain 99% of the process output with 95% confidence. The 99% coverage was chosen since that represents a targeted ±3σ limit commonly used in SPC charts.

Once the tolerance interval was calculated for each attribute, the specifications were further evaluated and adjusted, as appropriate and justified based on various factors, including experience during stability studies, relevant development data, experience with the analytical procedure, and alignment of drug substance and drug product specification. Details for the justification of the specifications are provided in Section 3.2.P.5.6 (Justification of Specifications). Stability specifications for drug product are set at the same values as the release specification for those attributes tested for stability. Justifications are summarized below.

- Aluminum: The aluminum concentration for all commercial scale representative drug product lots at release was reported as –b(4)----------Drug product formulation robustness studies have demonstrated that MnB bivalent rLP2086 vaccine drug product formulation was acceptable in the range of –b(4)---------- with no apparent changes observed in product quality attributes. However, a tighter release specification range of-b(4)---mg/mL is proposed. Aluminum is not tested on stability.
- Appearance: The appearance data for all commercial scale representative drug product lots at release were reported as homogenous, white suspension. The stability data demonstrate no change. The proposed specification for release and stability is homogenous, white suspension (HWS).
- Container Closure Integrity Test (CCIT): CCIT is tested –b(4)-------- during stability in lieu of sterility testing. The commercial scale representative drug product lots on long term stability were reported as pass. The proposed stability specification is passing. CCIT is not tested at release.
- Endotoxin: The *–b(4)*---------- is used to evaluate the endotoxin levels in drug product lots at –b(4)----------. The endotoxin data for all commercial scale representative drug product lots at release were below the assay quantitation limit of –b(4)----. The stability data demonstrate no change. The proposed commercial specification of ----b(4)----------.
- Identity: The identity of drug product is determined by –b(4)---------- (not stability). Test results were reported as positive for each subfamily. The proposed commercial specification is positive for each subfamily.
- ----*b(4)*----- ----------

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

- -*b(4)*- potency –b(4)---------- is determined using a –b(4)---------- test. –b(4)- is measured for ----b(4)---------- for commercial lots. The test results are reported as % relative potency (%RP). The tolerance interval (----------b(4)--------
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----------. The clinical range b(4) batches) is ----b(4)----------. The proposed specification is ----------b(4)----------
The firm acknowledges that the tolerance intervals derived specifications are wide due to the know variability of the –b(4)- assay and the relatively limited experience testing commercial scale drug product lots with the -b(4)- assay. The firm commits to re-evaluate the specifications for the (b)(4) assay and appropriately adjust following the testing of an additional –b(4)- lots at release.

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

- pH: The pH of the drug product is determined using ----b(4)----------. The tolerance interval (b(4) commercial batches) is –b(4)-. The clinical range is –b(4)-. The proposed specification is –b(4)----------. Drug product formulation robustness studies have demonstrated that the drug product formulation was robust in the pH range of –b(4)---------- with no apparent changes observed in product quality attributes.

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

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

- Purity: As a measure of degradation, purity is a CQA of drug product measured at both release and stability. Purity is determined by –b(4)----------
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----------A purity result of –b(4)- was obtained for all b(4) commercial scale lots and for all b(4) clinical lots. Although current data suggests a purity specification of –b(4)-, the operational feasibility of such a strict specification is uncertain given the limited experience to date. Purity was designated as a CQA because a potential impact of –b(4)------- material on product potency. Development studies demonstrated that product potency is maintained, even with a considerable loss of purity. –b(4)----------
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----------. Accordingly, the proposed purity specification of –b(4)- for release and stability is considered appropriate for drug product as it is well above the level at which product potency may be affected.
- Sterility: The sterility of drug product is assessed at release and end of shelf life on stability. The assay is performed as described in the compendial. The sterility for all commercial scale representative drug product lots at release was “No growth observed/meets requirements of test”.
- ----b(4)---------- ----------

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

- Volume of Injection: The volume of injection (VOI) is assessed at release as described in the compendial. The VOI data for all commercial scale lots at release were 0.5 mL. The proposed specification is b(4) 0.5 mL.

A summary of the analytical procedures is provided in Section 3.2.P.5.2. A summary of the analytical method validation is provided in Section 3.2.P.5.3. The review of these methods and corresponding validation were divided between several different reviewers.

I reviewed the Purity by –b(4)--- method and the corresponding validation for MnB bivalent rLP2086 drug product. ----b(4)---- --
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------------------------------------ The validation evaluated Precision/Repeatability, Intermediate Precision, Accuracy, Specificity, Linearity, and Range.

MnB bivalent rLP2086 drug product lots (120 µg) used for demonstration, clinical trials, non-clinical stability, and primary stability / process validation are summarized in Table 3.2.P.5.4-1 in Section 3.2.P.5.4 (Batch Analysis). MnB bivalent rLP2086 drug product lots formulated at 20 µg, 60 µg, and 200 µg used in nonclinical toxicology and clinical trials are summarized in Tables 3.2.P.5.4-2, 3.2.P.5.4-3, and 3.2.P.5.4-4 in Section 3.2.P.5.4 (Batch Analysis). The batch analysis data for MnB bivalent drug product lots are provided in Tables 3.2.P.5.4-5 through 3.2.P.5.4-14 in Section 3.2.P.5.4 (Batch Analysis). All data met the specifications at the time of release.

[b(4)]

[b(4)]

No additional impurities are introduced by the drug product manufacturing process.

4.13. Reference Standards and Materials:

The reference materials used for analysis of drug product are the ----b(4)----------
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4.14Container Closure System:

The syringes, manufactured by b(4), are 1 mL disposable syringes constructed of –b(4)---------- glass. 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. 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 closure of the syringes is a plunger stopper composed of –b(4)---------- latex-free grey –b(4)---------- rubber, manufactured by –b(4)----------

The plunger rod and backstop are made of -----(b)(4)----- and do not contact product.

MnB bivalent rLP2086 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 instruction for use that fit inside the outer carton. Tamper evident seal is placed on both carton flaps.

4.15 Stability:

Stability information for MnB bivalent rLP2086 drug product stored under the long term condition of 5 ± 3 ^{o}C, -----b(4)---------- are provided in Section 3.2.P.8. 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 provided in Tables 3.2.P.8.1-1 and 3.2.P.8.1-2 of Section 3.2.P.8 (Stability Summary and Conclusion).

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

Lot Number	DP Lot Use	Study Type	Storage Condition	Data Available	Study Status
(b) (4)	GMP Demonstration	Long Term	5 ± 3˚C	24 months	Ongoing
		(b) (4)			
	GMP Demonstration	Long Term	5 ± 3˚C	18 months	Ongoing
		(b) (4)			
	Process Validation/ Primary Stability	Long Term	5 ± 3˚C	18 months	Ongoing
		(b) (4)			
G35808	Phase 3 Clinical, Process Validation/ Primary Stability	Long Term	5 ± 3˚C	18 months	Ongoing
		(b) (4)			

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

Lot Number	DP Lot Use	Study Type	Storage Condition	Data Available	Study Status
G53398	Phase 2 and 3 Clinical, Process Validation/ Primary Stability	Long Term	5 ± 3˚C	18 months	Ongoing
		(b) (4)			

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

Lot Number	DP Lot Use	Study Type	Storage Condition	Data Available	Study Status
(b) (4)	GMP Demonstration	Long Term	5 ± 3˚C	24 months	Ongoing
		(b) (4)			
	GMP Demonstration	Long Term	5 ± 3˚C	18 months	Ongoing
		(b) (4)			
	Process Validation/ Primary Stability	Long Term	5 ± 3˚C	18 months	Ongoing
		(b) (4)			
G35808	Phase 3 Clinical, Process Validation/ Primary Stability	Long Term	5 ± 3˚C	18 months	Ongoing
		(b) (4)			

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

Lot Number	DP Lot Use	Study Type	Storage Condition	Data Available	Study Status
G53398	Phase 2 and 3 Clinical, Process Validation/ Primary Stability	Long Term	5 ± 3˚C	18 months	Ongoing
		(b) (4)			

Table 3.2.P.8.1-2. (b) (4) Drug Product Supportive Stability Studies

Lot Number	DP Lot Use	Study Type	Storage Condition	Data Available	Study Status
(b) (4)	GMP Stability	Long Term	5 ± 3°C	(b) (4)	Ongoing
		(b) (4)			
(b) (4)	GMP Stability	Long Term	5 ± 3°C	(b) (4)	Ongoing
		(b) (4)			

Table 3.2.P.8.1-2. (b) (4) Drug Product Supportive Stability Studies

Lot Number	DP Lot Use	Study Type	Storage Condition	Data Available	Study Status
(b) (4)	GMP Stability	Long Term	5 ± 3°C	(b) (4)	Ongoing
		(b) (4)			
7-5104-013A	Phase 2 and 3 Clinical	Long Term	5 ± 3°C	24 months	Ongoing
7-5104-014B	Phase 3 Clinical Lot	Long Term	5 ± 3°C	24 months	Ongoing
(b) (4)	GMP Stability	Long Term	5 ± 3°C	24 months	Ongoing
7-5104-016A	Phase 2 Clinical Lot	Long Term	5 ± 3°C	24 months	Ongoing

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

The stability protocol for the Pfizer,-b(4)---- process validation/primary stability lots at the long term storage conditions of 5 ± 3 °C is presented in Table 3.2.P.8.1-3 of Section 3.2.P.8.1. The stability protocol for the supportive lots from Pfizer, -----b(4)---------- at the long term storage of 5 ± 3 °C is presented in Table 3.2.P.8.1-4 of Section 3.2.P.8.1.

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,	6.0 (b) (4)
(b) (4)		
Purity	0, 3, 6, 9, 12, 18, 24, (b) (4)	
(b) (4)		
(b) (4) Potency	0, 18, 24, (b) (4)	(b) (4)
Container Closure Integrity	12, 24 (b) (4)	Pass
Sterility	0, 24,	Meets the requirements of the test. No growth observed.
Endotoxin	(b) (4)	

a. Initial data (t0) are from release testing, unless otherwise noted.
b. Specification at time zero (t(0)) was "Report Result (% relative potency)"

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,	6.0 (b) (4)
(b) (4)		
Purity	0, 3, 6, 9, 12, 18, 24, (b) (4)	
(b) (4)		
(b) (4) Potency[b]	0, (b) (4)	(b) (4)
Container Closure Integrity	12, 24, (b) (4)	Pass
Sterility[d]	0, (b) (4)	Meets the requirements of the test. No Growth
Endotoxin	(b) (4)	

a. Initial data (t0) are from release testing, unless otherwise noted.
b. (b) (4) potency is not required for supportive lots (b) (4)
c. Specification at time zero (t(0)) was "Report Result (% relative potency)"
d. Sterility testing is not required for lot (b) (4) as these are demonstration lots

Analytical data for all drug product lots stored at 5 ± 3 °C (long term storage condition) are provided in Section 3.2.P.8.3. To date 18 months of data are available from the

Pfizer,-b(4)-------process validation/primary stability lots. The 18 month data was submitted for all tests except –*b(4)*- potency in the 29 May 2014 submission. The 18 month-*b(4)*--- potency data was submitted in the 25 September 2014 submission. Up to -b(4)------- of data are available from the supportive stability lots. All data remain within the clinical stability specifications and the proposed commercial stability specification.

Results from stability studies on drug product stored at the accelerated condition of –b(4)---------- are presented for b(4) stability lots in Section 3.2.P.8.3. The studies are complete with 6 months of data. Data for all studies remained within clinical stability specifications and the proposed commercial stability specifications. The data indicate that there have been no significant changes in terms of antigenicity or quality when stored at accelerated storage condition. A small decrease in purity for the drug product was observed in each study. Changes in purity at an elevated temperature are not unexpected and demonstrate the method is stability indicating. The purity results remained within clinical stability specification and proposed commercial stability specification in all studies. The accelerated condition provides additional supportive data for long-term storage under recommended conditions, and supports temporary temperature excursions from the recommended storage conditions.

Results from stability studies on drug product stored at the ---b(4)---------- described in Section 3.2.P.8.1.4.4 are presented in 3.2.P.8.3. The-----b(4)---------- conditions support temporary temperature from the recommended storage conditions.

----b(4)----------
data available. All data remained within the clinical stability specifications and proposed commercial stability specifications with the exception of b(4) appearance result. The appearance result for the –b(4)----------was “non-homogenous white suspension due to particles observed in the samples. ----b(4)----------

----b(4)----------
available. All data remained within the clinical stability specifications and proposed commercial stability specifications.

--b(4)----------. Eighteen months of data are available for the process validation/primary stability lot and 24 months of data are available for each of the supportive lots. All data remained within the clinical stability specifications and proposed commercial stability specifications.

Results for one supportive stability lot of drug product stored at the –b(4)---------- ---------- are presented in Section 3.2.P.8.3. The---b(4)---------- study is complete with 28 days of data. All results, with the exception of appearance, were within the clinical stability specifications and proposed commercial stability specifications. –b(4)---------- ---------- ---------- ----------

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

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 °C. The proposed shelf life of MnB bivalent rLP2086 drug product is 24 months. The 24 month data for all testing except *–b(4)--* potency will be provided as a written commitment in November 2014.

Post-approval, a minimum of –b(4)- of drug product will be enrolled in the commercial stability program at the long term storage condition of 5 ± 3 °C –b(4)----- that drug product is manufactured. The protocol is provided in Table 3.2.P.8.2-1 in Section 3.2.P.8.2.

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,	6.0 (b) (4)
(b) (4)		
Purity	0, 12, 24, (b) (4)	
(b) (4)		
(b) (4) Potency	0, 12, 24, (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	(b) (4)	

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

5. BLA Review of Adventitious Agents:

MnB bivalent rLP2086 vaccine is composed of components derived from bacterial fermentation, and is not a viral product.

Although ingredients of animal origin are used in the preparation of the vaccine component, the main theoretical risk of associated with these ingredients is a contamination of the product by Transmissible Spongiform Encephalopathy (TSE) agents. Raw material vendors are qualified to sourcing materials from then for use in the manufacturing process. Human or animal-derived materials are provided in Table 3.2.A.2-1 of Section 3.2.A.2. All other materials are of synthetic and/or biological origin.

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

Materials of construction of equipment (stoppers, filters, manifold, and/or containers) that come into contact with drug substance and drug product during their manufacture as well as packaging components (syringe tip cap and plunger stopper) used in the final packaging process may contain trace levels of animal –b(4)-- derivatives. As-b(4)-- is process under rigorous conditions, it is considered compliant with the TSE guideline.

6.BLA Review of Excipients (Aluminum Phosphate):

Raw materials are tested by Pfizer or a qualified contract laboratory, or are accepted based on the Certificate of Analysis from qualified suppliers. Raw materials used in the manufacturing of Aluminum Phosphate ($AlPO_4$) Suspension are listed in Table 3.2.A.3-1 of Section 3.2.A.3

6.1 Development of Aluminum Phosphate Manufacturing:

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

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

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

---

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

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

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

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

[b(4)]

7. BLA Review of Lot Release Protocol:

I reviewed the Lot Release Protocol (LRP) submitted for MnB bivalent rLP2086 vaccine.

7 BLA Review of Batch Production Records:

Representative, executed batch records from the manufacture of drug substance batches (one batch of subfamily A and one batch of subfamily B) manufactured at---b(4)—in --b(4)----------that were used to produce a drug product process validation lot, were provided and reviewed

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

Representative, executed batch records from the manufacture of a process validation drug product lot manufactured a Pfizer's ---b(4)----------were provided and reviewed

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

Executed batch records from the manufacture of the additional two process validation drug product lots manufactured at Pfizer's –b(4)----------were brought back from the June 2014 inspection and reviewed

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

8 BLA Review of Labeling:

I reviewed and provided comments on the proposed labeling for MnB bivalent rLP2086 vaccine (container, carton, and package insert).

9 UNII Code Designation:

I reviewed the UNII code designations and found them to be acceptable.

9.1 Component Information Table:

For this BLA, I reviewed the components that are used to manufacture of MnB bivalent rLP2086 vaccine. I reviewed the raw materials, ingredients, and components control strategy to make sure that it is appropriate to determine the potential risk. I determined that the components are free of adventitious agents. In addition, all components have been investigated for the origin of animal material and have been determined to comply with the relevant guidance. Therefore, the components are acceptable for use. This is documented throughout my review.

10 Information Requested from Original Submission dated 29 August 2014:

After a complete and thorough review of the submission, the following information was needed to complete my review. These comments were sent to the firm in the form of an Information Request dated 29 August 2014. The firm responded to our comments on 30 September 2014. The IR comment sent to the firm is in bold. Their response to the comment directly follows our comment.

Drug Substance:

1. ----------

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

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

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

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

2. ----**b(4)**--- ----------

----

15 Pages determined to be not releasable: b(4)

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

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

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

Drug Product:

20. Filter Extractable Studies (Section 3.2.P.3.5) were performed only on -b(4)----------. Please provide a comparison of all filters used during the manufacture of drug product. Please provide filter extractable studies for all filters used during drug product manufacture. Alternatively, provide your justification that the chosen filter is representative of all the filters used during drug product manufacture.

The drug product manufacturing process uses b(4) product contact filters. Table 1 of the firm's response to Question 20 provided detailed information on these filters. All the filters use ---b(4)---------- for filtration. The –b(4)--------- represents worst case due to the larger filtration surface area.

The response is adequate.

a. You have provided a summary of the extractable results in Section 3.2.P.3.5.3. However, you have not included the identity of the residues. Please provide the extractable study report. This report should include details on how the study was performed, the identity of the residues extracted, and the acceptance criteria for these residues.

Wyeth provided the requested extractable report. This report includes the details on the study set up, the identity of the residues extracted, and the acceptance criteria used for these residues.

The response is adequate.

b. You have not provided data for leachables on the filters. Please provide leachable data for your filters used during manufacture of drug product.

Wyeth proposes to provide the leachable data post approval since the data are currently not available. Wyeth will submit the information by 30 June 2015.

The response is adequate.

21. You have proposed a ----------b(4)---------- ----------. You state in Section 3.2.P.2.3.1.1.1 that the "…proven acceptable range (PAR) for b(4) storage temperature was determined to be between –b(4)---------- You also state that you have a robustness study that "suggests that b(4) quality attributes –b(4)---------- remained unchanged for—b(4)---------- at these temperatures." Please provide data to support a –b(4)---------- at the temperature limits that you propose as your proven acceptable range (between ---b(4)----------. Please clarify at what temperature –b(4)---------- will be stored at in the Pfizer, -b(4)---- facility.

The intended storage conditions for ----b(4)----------. At the Pfizer, -b(4)-- facility, ----------b(4)---------- Wyeth does not intend to store b(4) at the long term storage condition of either –b(4)---------- The PAR was determined based on a technical study. The PAR is established to support short term temperature excursions.

The response is adequate.

22. You state in Section 3.2.P.2.3.1.1.2 that the ----b(4)---------- ---------- at Pfizer, ---b(4)----------. You state in Table 3.2.P.2.3-6 that the proven acceptable range (PAR) for ----b(4)----------. Please clarify and provide data to support the validated –b(4)---------- -- In addition, please provide the –b(4)---------- used to manufacture your commercial scale lots at your Pfizer,-b(4)--- facility.

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

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

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

23. You state in Section 3.2.P.2.3.1.1.2 that the hold time for ----b(4)---------- ---------- Please clarify if

b(4) can be –b(4)---------- or if it can be ----b(4)---------- ------temperatures. You have provided data to support the ---b(4)---------- individually. If this is a –b(4)----------, please provide data to support the –b(4)----------

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

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

The response is adequate.

24. We note in Table 3.2.P.3.5-1 "Drug Product Manufacturing Process Validation Lots" that you used ---b(4)---------- $AlPO_4$ lots in the manufacture of the three drug product validation lots. We prefer process validation lots be manufactured with three different lots of starting material. In lieu of using three different lots of $AlPO_4$, please provide the batch genealogy for all drug product lots manufactured post process-validation.

Table 1 of the firm's response to Question 24 summarizes the batch genealogy of all DP lots manufactured post PV to date. The table includes details of the $AlPO_4$ used. These lots differ in the 2 lots used in the DP PV batches. The DP listed in this table met all release testing criteria, with the exception of the *–b(4)-* potency testing which is pending.

The response is adequate.

25. The following comments relate to the control of $AlPO_4$ (Section 3.2.P.4).

a. You propose an aluminum concentration release specification for $AlPO_4$ of –b(4)---------. This specification is based on b(4) batches of $AlPO_4$ –b(4)---------- and the limits were based on b(4) sigma limits. Please revise your specifications to reflect batches –b(4)---------- and base the limits on b(4) sigma limits.

The tolerance intervals have been calculated using historical analysis on batches of $AlPO_4$ ---b(4)----------
Tolerance intervals were calculated based on at least 99.73% coverage of the population with 95% confidence. Unrounded QC results were used for statistical analysis. The tolerance interval was calculated –b(4)--------
which is in line with the proposed specification of –b(4)----------

The response is not adequate. The basis for the tolerance interval calculation is not what we requested in the 7 February 2014 meeting. In addition, specifications should be evaluated where the manufacture is occurring. Please see comment 4a of the IR dated 30 September 2014.

b. You propose a release specification for ---b(4)---------- based on batches produced in –b(4)---------- based on b(4) sigma limits. Please revise your specifications to reflect batches manufactured at -b(4)---------- and base the limits on b(4) sigma limits. In addition, please include ----b(4)----------

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

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

----

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

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

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

26. The following comments relate to the Purity Determination of Drug Product by –b(4)------(Sections 3.2.P.5.2 and 3.2.P.5.3).

a. Please provide your detailed procedure for the determination of purity in drug product.

Wyeth submitted the detailed procedure in the form of the current SOP.

The response is adequate.

b. The procedure includes----b(4)---------- ---------- Please provide detailed information on the control material to include manufacture, qualification, storage, and expiry.

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

The response is adequate.

c. The method as described does not include measurement and acceptance criteria for ----b(4)---------- ---------- performance in terms of –b(4)---------- as well as –b(4)---------- should be part of acceptance criteria for the assay. –b(4)---------- should include the degradant compounds intended to be monitored by this procedure. Please incorporate these additional system suitability criteria into your procedure.

Wyeth will update the purity method for drug product to include measurement and acceptance criteria for –b(4)---------- as well as --b(4)----------. In order to gather the appropriate historical data to set relevant acceptance criteria, Wyeth proposes to add the –b(4)---------- system suitability parameters to the method post approval by 31 December 2015. In addition, Wyeth proposes to perform –b(4)---------- ---------- as this will provide a more robust and accurate calculation than calculating these on the ---b(4)---------- ----------

The response is adequate.

d. The percent purity is calculated as the ---b(4)-- ---------- ---------- ---------- of purity. We do not concur with this proposal. Please include all –b(4)---------- ---------- in your calculation of purity.

Wyeth will update the method for determination of purity of –b(4)---------- to include integration criteria that include ---b(4)----------, in the calculation of purity. In order to make this change, Wyeth must first assess the impact of the changes of the existing method validation. As this will require additional work, Wyeth proposes to provide the revised method and any relevant validation data by 30 September 2015. The updated method will be applied to assess the purity of batches produced after implementation of the revised method. Additionally, the purity specification will be re-assessed using data from the revised assay.

The response is adequate.

e. You have included data for % purity in your evaluation of repeatability, intermediate precision, and linearity. Please include data to evaluate integration of the following in these studies as well: --b(4)- ----------

Wyeth proposes to provide the repeatability, intermediate precision, and linearity of the----b(4)-- ---------- ------- post approval as this work has not yet been performed. Wyeth will provide the updated validation data by 31 December 2015.

The response is adequate.

f. Accuracy was established across the range of the method using –b(4)---------- concentration of the sample. As this method is described as an—b(4)----------, please provide an evaluation of accuracy by spiking the Drug Product with actual product-related impurities to levels that would bracket the b(4) specification.

Wyeth will perform accuracy validation experiments by spiking drug product with isolated or prepared product-related impurities to support the –b(4)- specification. Wyeth proposes to provide the accuracy data post approval by 31 December 2015.

The response is adequate.

g. You have determined that the linearity/range of the assay is –b(4)---------- which is equivalent to the 20-120 µg drug product doses prepared according to the method. Please clarify what the (b)(4)---------- is according to the SOP. Please provide data to show that –b(4)---------- is equivalent to 20-120 µg drug product.

The range for –b(4)----- determined in the linearity/range study is wider than the 20-120 µg drug product dose range. For example, the 120 µg drug product dose is ---b(4)--- ----------. This will be updated in the BLA. For other drug product concentrations used during development, ---b(4)---------- (see Table 4 of the firm's response to Question 26).

The response is adequate.

h. Please provide data to support the lower limit of quantitation of the method.

Wyeth proposes to provide the validation data supporting the lower limit of quantitation of the method post approval by 31 December 2015.

The response is adequate.

27. The following comments relate to the Aluminum Determination of Drug Product (Sections 3.2.P.5.2 and 3.2.P.5.3).

a. Please provide a fully descriptive procedure.

I defer review of this comment to DBSQC.

b. In Section 3.2.P.5.2.3.1 (Standard Curve Preparation), it states that "Typically b(4) concentrations ranging from approximately –b(4)-- are prepared." Please specify the actual concentration range to be used in practice of the assay. Please revise your procedure to use b(4) concentration points.

I defer review of this comment to DBSQC.

c. In Section 3.2.P.5.2.3.3 (Sample Preparation), it states that samples are –b(4)----------. Please specify the time to which samples of the MnB rLP2086 Drug Product are to be –b(4)---- or what other criteria is used to determine the time of –b(4)-----

I defer review of this comment to DBSQC.

d. The Validation report summary for Aluminum (Section 2.5.11, Experimental Design) describes the evaluation of linearity based on --b(4)---------. Please submit an evaluation of linearity using at least –b(4)--

concentrations levels to cover the intended range of the assay procedure.

I defer review of this comment to DBSQC.

28. The following comments relate to the Assay for ---b(4)---------- ---------- of Drug Product (Sections 3.2.P.5.2 and 3.2.P.5.3).

a. The method as described does not include measurement and acceptance criteria for –b(4)---------- system suitability. –b(4)----------performance in terms of ----b(4)---------- well as ---b(4)---------- should be part of acceptance criteria for the assay. Please incorporate these system suitability parameters into your method.

I defer review of this comment to DBSQC.

b. On page 23 of 25 of SOP-13655 we saw a –b(4)---------- ----------. Please provide the identity of this b(4). Please provide an approximate area percent of this –b(4)-

I defer review of this comment to DBSQC.

c. In the "Summary Report for the Validation of the Method for –b(4)---------- for MnB Bivalent rLP2086 Drug Product" (Section 2.3, Accuracy), it states that b(4) different concentrations were prepared and each concentration was analyzed b(4) times. The concentration was calculated and compared to the theoretical value." Please explain what the basis for the "theoretical value" is.

I defer review of this comment to DBSQC.

d. Batch Results for b(4) batches of 120 mcg Process Validation / Primary Stability Lots b(4) show –b(4)---------- ----------. Please explain the relationship between the observed higher recoveries relative to the Accuracy results ---b(4)---------- ----------

I defer review of this comment to DBSQC.

29. The following comments relate to the release and stability testing of drug product.

a. You propose to remove the –b(4)------- pyrogenicity as a release test. We acknowledge that while –b(4)------ was not included as a release test in your pre-BLA meeting material, we did not discuss concerns about the removal of this test in the 1 May 2014 meeting. During review of the BLA, we have determined that we do not concur with removal of the pyrogenicity test as the MnB rLP2086 vaccine can

induce some degree of pyrogenicity. Please add the modified pyrogenicity test as a release test.

Wyeth will continue to test commercial batches of drug product for -b(4)------- pyrogenicity at release. The section of the BLA will be updated and submitted prior to approval. The proposed commercial specification is passes test / meets requirements. The –b(4)---------- test is performed according to –b(4)---------- Wyeth developed a –b(4)---------- ---------- test for MnB rLP2086 vaccine in accordance with ---b(4)---- ---- ----------has been routine monitored at release. All Phase 2 clinical lots and commercial scale representative lots met specification. I conferred with DBSQC on the acceptability of the method.

The response is adequate.

b. You propose to remove the General Safety Test (GST) as a release test for drug product. You state that other tests are in place to guarantee the safety of the vaccine, such as the bacterial and fungal sterility. We do not concur with your proposal at this time. Please add the GST as a release test. You may submit a post approval supplement to request exemption from the GST once an adequate amount of lots have been manufactured and tested.

Wyeth will continue to test commercial batches of drug product for General Safety at release. The impacted section of the BLA will be updated accordingly and submitted prior to approval. The proposed commercial specification for the General Safety Test (GST) is passes test / meets requirements. The GST is ---b(4)-- ----------. GST has been routinely monitored at release. The results for Phase 2 clinical lots an all commercial scale representative lots were reported as “passes test”.

The response is adequate.

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

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

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

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

30. You have provided the list of various lots on stability. In addition, you are required by the regulations to keep retention samples. Please confirm that none of the retention or stability samples have "Agglomeration" which is defined as "Liquids with Inhomogenous Suspension".

Samples of MnB bivalent rLP2086 drug product are retained for all materials intended for commercial use. During the inspection, drug product syringes are re-suspended to ensure that a homogenous suspension is obtained. Annual inspection of commercial drug product lots has not yet occurred for MnB bivalent rLP2086 drug product retention samples.

Stability samples are assessed at each time point for appearance. The MnB bivalent rLP2086 syringes are re-suspended to ensure a homogenous suspension is obtained. To date all stability samples, stored at the intended storage condition of storage condition of $5 \pm 3\ ^{o}C$, have resuspended to homogenous suspensions and no agglomeration was detected.

The response is adequate.

31. You have provided the Post Approval Stability Protocol and Stability Commitment in Table 3.2.P.8.2-1. You propose to perform the ---(b)(4)--- and sterility at time zero and –b(4)----. Please add ---(b)(4)--- testing time-points on an –b(4)-basis. In addition, you also state that testing will be performed at the currently approved end of shelf life. Please confirm that you will perform ---(b)(4)--- and sterility testing at 24 months.

Wyeth agrees to ---(b)(4)--- testing at-b(4)- time points for MnB rLP2086 drug product lots enrolled in the post approval stability program. Additionally, Pfizer confirms that ---(b)(4)--- and sterility testing will be performed at 24 months for MnB rLP2086 drug product lots enrolled in the post approval commercial stability program.

The response is adequate.

32. You state in Section 3.2.P.2.3.3 that "Based on the release, characterization, and stability data generated to date on b(4) lots and b(4) Pfizer lots, the DP manufactured at the b(4) sites are considered comparable." You have provided the release and stability data. Please provide the characterization data that you are referencing in this Section.

-b(4)- Pfizer, -b(4)- lots and –b(4)---------- lots were evaluated for physical property characterization using the –b(4)---------- The characterization results are provided in Table 1 of the firm's response to Question 32. The results show no differences among the lots from the –b(4)-manufacturing sites.

The response is adequate.

33. Please provide your definition of date of manufacture from which the expiry date is calculated.

The date of manufacture is defined as the date when filling is initiated. Expiration dating is from the date of manufacture of the filled syringes to 1 month less than the established expiration date.

The response is adequate.

34. You are requesting the following potential drug product exposure times and temperatures from the end of filling to market receipt.

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

You have provided 6 months of accelerated stability data –b(4)---------- process validation lots. You have also provided 12 months of -b(4)--------- data on b(4) process validation lot (--b(4)---------- ---------- for the duration of the study). We note that the –b(4)---------- data does not mimic the storage conditions requested above. In addition, -*b(4)*- potency data was not included in the -----(b)(4)-------- study. Please provide data, including –*b(4)*- potency, to support the above exposure time and temperature request. Alternatively, please revise your shipping storage temperature to between –b(4)----------.

Wyeth proposes a revision of shipping storage temperature to –b(4)------ rather than the –b(4)---- This request is based on long term storage temperature data at 2-8 ^{o}C. In addition, this lower temperature limit is consistent with the shipper temperature qualification range of 2-8 ^{o}C. The stability chambers are qualified with acceptance criteria of 2-8 ^{o}C.

The response is adequate.

LRP: Please note that additional comments for the LRP may arise based on your response to this IR.

35. **You have added the –b(4)---------- for Drug Substance Subfamily A and B. Please also add the –b(4)---------- for Filled Vaccine.**

The –b(4)---------- for filled vaccine (drug product) has been added to the lot release protocol.

The response is adequate.

General:

36. **Please confirm that no Comparability Protocols were submitted with this BLA to request a future change to be downgraded to an Annual Report. We note that you submitted a section for qualification of future reference material (Section 3.2.S.5). The information provided in this section does not include a detailed Comparability Protocol. A post approval supplement can be submitted to request a Comparability Protocol for downgrading future changes to Annual Report. Please confirm.**

As discussed in the pre-BLA meeting on 1 May 2014, Wyeth is experiencing a -b(4)---------- Wyeth provided a Comparability Protocol (CP) for future reference materials so that data may be submitted in the BLA Annual Report.

The response is not adequate. The CP provided in your response does not provide enough details on the preparation, testing, and qualification of the new reference materials. In addition, CPs should be assay specific. Please see comment 5 of the IR dated 30 September 2014.

37. **You committed to submit the results of other characterization studies, including data from –b(4)---------- , to the BLA to address purity in our meeting on 1 May 2014. These characterization studies were not included in your submission. Please provide the results of the characterization studies, including data from –b(4)---------- to address purity of your-b(4)---------- drug product.**

The characterization data mentioned in the 1 May 2014 meeting referred to the holistic product knowledge generated through development. In-depth, orthogonal testing reveals that product-related impurities, substances, and degradants that are both prevalent and expected to impact antigenicity, are appropriately monitored by –b(4)----. Table 1 of the firm's response to Question 37 summarizes the characterization tests performed as part of structural elucidation and are included in the BLA. In addition, as requested in the telecon of 15 September 2014, the -b(4)---------- from the IND are provided in this response. The –b(4)-------- method has been solely used to measure –b(4)---------- The relative levels of the –b(4)---------- have been determined to range from –b(4)---------- at release. Wyeth will identify this species, and will provide the relative area percent for the species, together with the subfamily A and subfamily B protein species, present in –b(4)---------- bivalent rLP2086 drug product lots. Wyeth proposes to submit this data post approval by 30 September 2015.

The response is adequate.

38. In Section 3.2.S.2.2 entitled, Description of Manufacturing Process and Process Controls – Filling, Storage and Transportation, subsection 3.2.S.2.2.2 entitled,-b(4)-------- you state that, ----b(4)---------- ---------- ---------- ---------- Please submit information on the -b(4)------; specifically, equipment description, equipment qualification and –b(4)-----validation.

I defer review of this comment to DMPQ.

11 Information Requested from Original Submission dated 30 September 2014:

The responses provided to CBER's IR letter of 29 August 2014 are acceptable with the exception of the following. These comments were sent to the firm in the form of an Information Request dated 30 September 2014. The firm responded to our comments on 9 October 2014. The IR comment sent to the firm is in bold. Their response to the comment directly follows our comment.

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

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

5 Pages determined to be not releasable: b(4)

a. **----b(4)-------** ----------

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

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

2. **We do not concur with the Comparability Protocol (CP) that you submitted in your response to Question 36 of the 29 August 2014 IR. The CP provided in your response does not provide enough details on the preparation, testing, and qualification of the new reference materials. In addition, CPs should be assay specific. Please withdraw your CP for future reference materials. We note that you had stated in the 1 May 2014 meeting that you are –b(4)--- ------**

---------- **Please submit the qualification data for the new reference materials in lieu of a CP. If the qualification data are not available at this time, please submit this request as a supplement post approval. We will commit to do an expedited review of the supplement post approval.**

Wyeth agreed to withdraw the comparability protocol for qualification of future reference materials submitted to Question 36 of the 29 August 2014 IR from Section 3.2.R of the BLA. ----b(4)--- ----------
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The response is adequate.

3. **The following commitments were noted during review of the file. Please provide a complete list of all commitments made for the BLA. This list should include the commitments listed below as well as any made in response to an IR comment.**

a. **---b(4)--** ----------

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

b. **The proposed purity specification for –b(4)----------. This specification will be redefined as additional commercial process experience is obtained. (Section 3.2.S.4.5.12).**

c. **The proposed –*b(4)*-- potency test for drug product has not been validated in the final testing laboratory. The validation report will be submitted when validation is complete.**

d. **The proposed –*b(4)*- potency for drug product is –b(4)----------. The specification for –*b(4)*potency will be re-evaluated and appropriately adjusted following the testing of an additional b(4) commercial lots at release. (Section 3.2.P.5.6.9).**

e. **-----b(4)--- ----------**

Wyeth provided a complete list of commitments made for BLA STN# 125549 including those referenced above.

The response is adequate.

12 Final Agreed Upon Specifications/Stability:

During review of this BLA, CBER and Wyeth had discussions concerning the testing that would be performed on drug substance and drug product at both release and on stability. These discussions also included the acceptability of the specifications proposed. I have included tables in this section of the updated specifications and post approval stability protocols for drug substance and drug product that were agreed upon for BLA approval.

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

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)	
Appearance[a]	Visual	Homogeneous white suspension
Container Closure Integrity[a, b]	(b) (4)	Pass
Endotoxin[a], EU/mL	(b) (4)	
General Safety	(b) (4)	Passes Test/Meets Requirements
Identity		Positive for each subfamily
(b) (4) Potency[a], % for each subfamily	(b) (4)	
(b) (4)		
(b) (4)		
pH[a]	(b) (4)	6.0 (b) (4)
(b) (4)		
Purity[a], %	(b) (4)	
Sterility[a]	(b) (4)	Meets the requirements of the test. No growth observed
(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

(b) (4)

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)	
Appearance[a]	Visual	Homogeneous white suspension
Container Closure Integrity[a, b]	(b) (4)	Pass
Endotoxin[a], EU/mL	(b) (4)	
General Safety	(b) (4)	Passes Test/Meets Requirements
Identity		Positive for each subfamily
(b) (4) Potency[a], % for each subfamily	(b) (4)	
(b) (4)		
(b) (4)		
pH[a]	(b) (4)	6.0 (b) (4)
(b) (4)		
Purity[a], %	(b) (4)	
Sterility[a]	(b) (4)	Meets the requirements of the test. No growth observed
(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

(b) (4)

[b(4)]

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,	6.0 (b) (4)
(b) (4)		
Purity	0, 12, 24, (b) (4)	
(b) (4)		
(b) (4) Potency	0, 12, 24, (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	(b) (4)	

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

13 Written Agreements Made by Pfizer:

Wyeth agreed to perform the following post approval and submit to CBER as Product Correspondence. While these agreements are important to ensure future consistency of manufacture, they are not critical for evaluation of safety, potency, or effectiveness for licensure.

Table 1. Written Agreements Made by Pfizer for MnB Bivalent rLP2086

Commitment #	Commitment	PMC Submission Date	Date CBER Question Received	CBER Question Number
b(4)-------	---b(4)---------- ----------	-b(4)-------	b(4)-------	b(4)-------
b(4)-------	--b(4)-- ----------	b(4)-------	b(4)-------	b(4)-------
b(4)-------	--b(4)-- ----------	b(4)-------	b(4)-------	b(4)-------
b(4)-------	----b(4)-- ----------	b(4)-------	b(4)-------	b(4)-------
b(4)-------	----b(4)-- ----------	b(4)-------	b(4)-------	b(4)-------
b(4)-------	---b(4)-- ----------	b(4)-------	b(4)-------	b(4)-------
b(4)-------	-b(4)- ----------	b(4)-------	b(4)-------	b(4)-------
b(4)-------	--b(4)-- ----------	b(4)-------	b(4)-------	b(4)-------
9	Update the purity method for drug product to include measurement and acceptance criteria for—b(4)-- ----------	12/31/15	08/29/14	26c

Commitment #	Commitment	PMC Submission Date	Date CBER Question Received	CBER Question Number
10	Update the method for determination of purity of drug product to include integration criteria that include –b(4)---------- in the calculation of purity. The updated method will be applied to assess the purity of drug product lots produced after implementation of the post-marketing commitment. Additionally, the purity specifications will be re-evaluated based on the data obtained using the revised method.	12/31/15	08/29/14	26d
11	Provide the repeatability, intermediate precision and linearity of the intact rLP2086 MnB, --b(4)---------- for the drug product impurity method.	12/31/15	08/29/14	26e
12	Perform accuracy validation experiments by –b(4)---------- drug product purity specification.	12/31/15	08/29/14	26f
13	Provide validation data supporting the lower limit of quantitation of the drug product purity method.	12/31/15	08/29/14	26h
14	Update the method for aluminum determination of drug product to include -b(4)- concentration points within the validated range of the assay and provide an assessment of linearity of the-b(4)-standard curve.	09/30/15	08/29/14	27b and 27d
15	Update the—b(4)---------- method for drug product to include measurement and acceptance criteria for –b(4)----------	06/30/15	08/29/14	28a
16	Isolate and identify the---b(4)---------- using the drug product method for—b(4)----------	09/30/15	08/29/14	28b
17	Identify the-----b(4)----------and bivalent rLP2086 drug product lots for characterization purposes.	09/30/15	08/29/14	37

Commitment #	Commitment	PMC Submission Date	Date CBER Question Received	CBER Question Number
18	----b(4)--- ------------------ --------------------------------- --- --- --- ------------------------------------	after b(4) additional commercial batches –b(4)--- ------------------- ------ years (whichever comes first)	9/30/14	6a
19	--b(4)- -- --- --- --- -----------------------------	09/30/2015	9/30/14	3d
20	--b(4)-- --- --- --- -----------------------------	09/30/2015	9/30/14	3d
21	The purity specification of—b(4)-- -------- -- will be re-evaluated following will be re-evaluated after b(4) additional commercial batches –b(4)------------------- ----------------- (whichever comes first).	after b(4) additional commercial batches (-b(4)-- ------------------- -------------- (whichever comes first)	9/30/14	6b
22	Provide the in b(4) potency assay validation data from the final testing laboratory.	03/31/16	9/30/14	6c
23	The –b(4)- potency specification for drug product of –b(4)------------------------------- -------------------------------- will be re-evaluated following the testing of b(4) additional commercial lots.	b(4) additional commercial lots	9/30/14	6d
24	----b(4)--- -------------------------------------- --- --- --- ---------------------------------	b(4) additional commercial lots	9/30/14	6e

Commitment #	Commitment	PMC Submission Date	Date CBER Question Received	CBER Question Number
25	The release specifications for –b(4)---------- will be revised for $AlPO_4$ used for the manufacture of commercial MnB rLP2086 drug product batches. The new specifications will be calculated using tolerance intervals with 95% confidence and 99% coverage as requested and based solely on –b(4)----------	06/30/15	9/30/14	4a
26	---b(4)----------	06/30/15	9/30/14	4b
27	Submit 24 month drug product stability data from the 3 drug product PV lots by November 14, 2014. Please note, as discussed at the pre-BLA meeting on May 1, 2014, the 24 month –b(4)- data will not be available for this submission; therefore the 18 months –b(4)-- stability data were submitted on September 25, 2014.	11/14/2014	Email from CBER dated 10/02/14	N/A

14 Approval Recommendation:

After a complete and thorough review of the original BLA submission and all amendments listed on the first page of this memo, I recommend approval of Trumenba. BLA approval was supported by the above listed written agreements submitted in Amendment 24 on 9 October 2104. The drug substances for Trumenba will be manufactured at ---b(4)----------. Trumenba will be formulated and filled at Pfizer, --b(4)---------- and will be labeled and packaged at Pfizer,-b(4)----------. The expiry of the drug substances (MnB rLP2086 subfamily A and B) will be –b(4)---------- at the recommended temperature of --b(4)---- The expiry of drug product will be 24 months from the date of initiation of filling when stored at the recommended temperature of 2-8 ^{o}C.