

CBER CMC BLA Review Memorandum

BLA STN 125740/0

Product Name [Tick-Borne Encephalitis Vaccine/TicoVac®/PF-06830414]

Jie He/CSO/CBER/OCBQ/DMPQ/MRBII

1. **BLA#:** STN 125740/0

2. **APPLICANT:** Pfizer Ireland Pharmaceuticals. U.S. License # 2060

3. **PRODUCT NAME:** Tick-Borne Encephalitis (TBE) Vaccine, PF-06830414, TicoVac®

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

- a. Pharmacological category
Prophylactic vaccine
- b. Dosage form
Suspension for intramuscular injection in a pre-filled syringe.
- c. Strength/Potency [the concentration of drug product, type of potency assay(s)]
0.25 mL, with 1.2 mcg of the tick-borne encephalitis strain Neudörfl
0.5 mL, with 2.4 mcg of the tick-borne encephalitis strain Neudörfl
- d. Route of administration
For intramuscular injection only.
- e. Indication(s)
Indicated for active immunization to prevent tick-borne encephalitis (TBE) in individuals 1 year of age and older.

5. **MAJOR MILESTONES**

Application Received: 15-Dec-2020
First Committee Meeting: 05-Jan-2021
Filing Meeting: 29-Jan-2021
Filing Action: 13-Feb-2021 Filed
Mid-Cycle Communication with firm, 16-Apr-2021
First Action Due: 15-Aug-2021
Proprietary Name Review: 29-Apr-2021 PNR Acceptable

6. **CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Jie He, CSO, CBER/OCBQ/DMPQ/MRBII	CTD Module 1 (1.2, 1.2) CTD Module 2 (2.2, 2.3.1, 2.3.S, 2.3.P, 2.3.A, and 2.3.R), CTD Module 3 (3.2.S, 3.2.P, 3.3.A and 3.2.R)

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
Sreya Tarafdar, Visiting Associate, CDRH/OPEQ/OHTIII/DHTIIC	Device design control, risk control, Container closure system, functionality (Sections 3.2.P.7 and 3.2.R)	Yes

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
Dec. 15, 2020	STN125740.0	Original submission
Feb. 12, 2021	STN125740/0.3	Response to IR of Feb. 2, 2021
Apr. 9, 2021	STN125740/0.10	Response to IR of Mar. 26, 2021
Apr. 12, 2021	STN125740/0.11	Response to IR of Mar. 29, 2021
Jun. 1, 2021	STN125740/0.16	Response to IR of May. 17 & 24, 2021
Jun. 29, 2021	STN125740.0/24	Response to IR of Jun. 15, 2021

9. REVIEWER SUMMARY AND RECOMMENDATION**A. EXECUTIVE SUMMARY**

Pfizer Ireland Pharmaceuticals (Pfizer) submitted a Biologics License Application (BLA) under STN125740/0 for the licensure of the Tick Borne Encephalitis (TBE) Vaccine (Whole Virus, Inactivated) (TicoVac®) on December 15, 2020. This TBE vaccine is referred to by the compound number PF-06830414 and is known by the tradenames TicoVac® and FSMEIMMUN.

This DMPQ memo covered eCTD Modules 1, 2 and 3 that included: the upstream and downstream manufacturing processes, testing, packaging, shipping, container closure system and stability of the drug substance (DS); the formulation, filling, testing, labelling, packaging, shipping, container closure system and stability of the drug product (DP). The review also covered the manufacturing facilities and equipment for DS and DP. A record review for DS manufacturing facility under §704(a)(4) of the FD&C Act was conducted in lieu of an onsite Pre-License Inspection (PLI), and the facility is found adequate. The PLI for DP manufacturing facility and two other final release testing facilities are waived based on their inspection history and their criticalities.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Jie He, CSO, CMC Reviewer, OCBQ/DMPQ/MRBII		
Anthony Lorenzo., Branch Chief, OCBQ/DMPQ/MRBII		
John Eltermann, RPh, Director OCBQ/DMPQ		

Module 3

3.2.S DRUG SUBSTANCE¹

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

(b) (4)

[REDACTED]

[REDACTED]

(b) (4)

24 pages have been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

3.2.P DRUG PRODUCT

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

The TicoVac DP is a sterile, non-pyrogenic suspension of formaldehyde-inactivated and sucrose gradient purified TBE virus harvest, diluted in phosphate buffered saline solution containing 0.1% human albumin and bound to aluminum hydroxide. TicoVac is presented as a single use pre-filled syringe (PFS) available in two dosage forms, 0.5 mL PFS for adults and 0.25 mL PFS for children. The composition of both dosage forms is identical except the nominal volume of the pediatric dosage form is half of the nominal volume of the 0.5 mL dosage form. The composition of TicoVac in both presentations are shown in the table below:

Table 21. Composition of TicoVac 0.5 mL and 0.25 mL

Name of ingredient	Reference to Standard	Function	Unit Formula (per 0.25 mL)	Unit Formula (per 0.5 mL)
Formaldehyde-inactivated, sucrose gradient purified TBE-virus harvest	Company specification	Active ingredient	(b) (4)	(b) (4)
Aluminum hydroxide, (b) (4)	(b) (4)	(b) (4)	(b) (4)	0.35 mg (Al ³⁺)
Human Serum Albumin	(b) (4)	Stabilizer	(b) (4)	0.5 mg
Sodium Chloride	(b) (4)	(b) (4)	(b) (4)	3.45 mg
Disodium Phosphate Dihydrate	(b) (4)	(b) (4)	(b) (4)	0.22 mg
Potassium Dihydrogen Phosphate	(b) (4)	(b) (4)	(b) (4)	0.045 mg

Sucrose	(b) (4)			max. 15 mg
Formaldehyde	(b) (4)			Max 5 µg
Protamine sulfate	(b) (4)			Max 0.50 µg (traces)
Neomycin	(b) (4)	Process impurity	Trace	Trace
Gentamicin	(b) (4)	Process impurity	Trace	Trace
Water for injection	(b) (4)	Solvent	q.s. ad 0.25 mL	q.s. ad 0.5 mL

The 1 mL syringes are constructed of hydrolytic (b) (4) borosilicate glass. The syringes are (b) (4) at Pfizer, (b) (4) prior to filling. The syringes are closed, at the barrel shoulder side, by a tip cap, which is made of bromobutyl and synthetic polyisoprene, latex-free rubber. The syringes are closed by a plunger stopper composed of styrene-butadiene-bromobutyl latex-free rubber. The stoppers are received (b) (4) sterilized. The plunger rod is composed of polystyrene which does not have direct product contact.

The (b) (4) is shipped from Pfizer (b) (4) site to Pfizer (b) (4) site for formulation and fill.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

The active substance of Tick-borne Encephalitis (TBE) Vaccine (FSME-IMMUN) is a liquid preparation of TBE virus, strain Neudoerfl, grown in cultures of chick-embryo cells, (b) (4) inactivated and purified. FSME-IMMUN Vaccine is in compliance with the Ph. Eur monograph for Tick-borne encephalitis vaccine (inactivated) (1375). The DS is a (b) (4)

3.2.P.2.1.2 Excipients

All the excipients used for FSME-IMMUN drug product comply with the pharmacopoeias as indicated in Table 3.2.P.4-1. 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. Specification of (b) (4) Excipients

Excipient	Acceptance criteria (b) (4)	Acceptance criteria (b) (4)	Quality Specification
Disodium Phosphate Dihydrate*	(b) (4)		
(b) (4)			(b) (4)

(b) (4)			(b) (4)
Sodium Chloride*		(b) (4)	(b) (4)
Human Serum			(b) (4)
Aluminium			(b) (4)
Potassium Dihydrogen Phosphate*	(b) (4)	(b) (4)	(b) (4)
Aluminium Hydroxide*		(b) (4)	(b) (4)

* In addition to the specification requirements provided in Table 3.2.P.4-1, additional tests are performed for these excipients.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

Review of this section is deferred to product office.

3.2.P.2.2.2 Overages

There are no overages incorporated into the formulation of FSME-IMMUN. The vaccine is formulated to the target concentration of (b) (4) antigen per mL. There are no significant losses during the formulation process or on stability.

Review of this section is deferred to product office.

3.2.P.2.2.3 Physicochemical and Biological Properties

Review of this section is deferred to product office.

3.2.P.2.3 Manufacturing Process Development

Process development study was conducted for the technology transfer of the DP manufacturing of FSME-IMMUN 0.5 mL and 0.25 mL pre-filled syringes from Baxter, (b) (4) to Pfizer, (b) (4). Four process development lots were performed to support the replacement of Baxter, (b) (4) with Pfizer, (b) (4) as a drug product manufacturing site for FSME-IMMUN.

The development study included: (b) (4)

The quality testing results for the (b) (4) batches are shown in the table below:

(b) (4)

(b) (4)

Reviewer's comment

I have reviewed the DP manufacturing development studies conducted at (b) (4) site. The results from the DP development lots at Pfizer (b) (4) demonstrated that:

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

- (b) (4)

Deviations included (b) (4) high antigen content, (b) (4) lack of (b) (4) failed (b) (4) test were investigated. Root causes were identified, and corrective actions were implemented. The deviations were resolved.

3.2.P.2.4 Container Closure System

The TBE vaccine in a prefilled syringe (PFS) is defined as a single-entity (biologic/device) combination product under 21 CFR Part 3.2(e). The primary container closure system of FSME-IMMUN vaccine consists of the following components:

- (b) (4) syringe barrels are composed of (b) (4) borosilicate glass.
- The plunger stopper is composed of (b) (4) Gray latex-free chlorobutyl rubber. The stopper (b) (4).
- The tip caps are composed of (b) (4) Gray latex-free isoprene bromobutyl rubber.
- As a part of the finished product, a polystyrene plunger rod is included.

Table 22. Syringe Container Closure Components

Component Type	Description	DMF Reference
Barrel	(b) (4) 1ml (b) (4) borosilicate glass barrel with Luer cone.	(b) (4)
	(b) (4) 1ml (b) (4) borosilicate glass barrel with Luer cone	
Tip Cap	(b) (4) latex-free bromobutyl and synthetic polyisoprene rubber Tip Cap	
	Siliconized (b) (4)	
Plunger stopper	(b) (4) latex-free styrene-butadiene-bromobutyl rubber plunger stopper	
	Siliconized (b) (4)	
Plunger rod	(b) (4) Polystyrene plunger rod	

Design Verification

Attributes included in the design input requirements have been verified. FSME-IMMUN vaccine prefilled syringes have undergone design verification in accordance with 21 CFR Part 820.30(f). Additional document review and bench-top lab tests demonstrated that the FSME-IMMUN prefilled syringe meets all design input requirements necessary for safe and effective drug administration at the point of use by the intended users. The tests included:

- Leachables from drug product contact materials
- Drug product quality attributes
- (b) (4)
- Deliverable volume (extractable volume)

Analysis of the design and functional attributes tested during design verification was performed to determine which functional performance tests are considered essential and would therefore be routinely tested as part of release or stability.

Reviewer's comment

The suitability and biocompatibility review of the container system is deferred to product office. Container Closure System Delivery Performance is deferred to consult reviewer from CDRH. Container Closure Integrity and shipping validation is reviewed in Section 3.2.P.7 in this memo.

3.2.P.2.5 Microbiological Attributes

The FSME-IMMUN DP is a single use sterile suspension which contains no antimicrobial preservative. Sterility is achieved by using a completely closed production system that assures aseptic working conditions as reviewed in the DP CCIT section.

The (b) (4) studies provide evidence of container closure integrity for the FSME-IMMUN DP container closure system with (b) (4) and (b) (4) barrels filled at Pfizer, (b) (4)

3.2.P.2.6 Compatibility

The DP lots showed comparability for bioburden test results. Review of other quality attributes in this section is deferred to product office.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The sites that have responsibilities in the production of TicoVac DP and their specified functions are shown in the table below:

Table 23. Sites and Responsibilities for Manufacture and Test for TicoVac DP

Name and Address	FEI and/or DUNS Number	Responsibilities and Quality System Provisions
Pfizer (b) (4) (b) (4) (b) (4)	(b) (4)	Quality Control Testing <ul style="list-style-type: none"> • (b) (4) Formaldehyde Content • Antigen Content • Extraneous Agents • Sucrose Content • Potency • (b) (4) • Sterility
Pfizer (b) (4) (b) (4) (b) (4)	(b) (4)	Formulation and Filling (Primary Packaging) Quality Control Testing <ul style="list-style-type: none"> • Sterility • Protein Content • (b) (4) • Endotoxin • Sodium Content • (b) (4) • Aluminum Content • Identity • Extractable Volume • Visual Inspection Labelling and Secondary Packaging
(b) (4)	(b) (4)	Quality Control Testing: Aluminum Content
(b) (4)	(b) (4)	Quality Control Testing: Sodium Content

3.2.P.3.2 Batch Formula

The FSME-IMMUN (b) (4) lot size may vary between (b) (4) for both FSME-IMMUN 0.25 mL and 0.5 mL presentations. The batch formula for a representative maximum lot size is shown in Table 3.2.P.3.2-1 and Table 3.2.P.3.2-2 for FSME-IMMUN 0.5 mL and FSME-IMMUN 0.25 mL respectively. The target amount for each component present in the DP is listed.

Table 3.2.P.3.2-1. Batch Formula for FSME-IMMUN 0.5 mL Lot

Component
Formaldehyde-inactivated, sucrose gradient purified TBE-Aluminium ^c
Human Serum Albumin
Sodium Chloride
Disodium Phosphate Dihydrate

(b) (4)

Potassium Dihydrogen Phosphate
Sucrose
Formaldehyde
Protamine sulfate
Neomycin
Gentamicin
Water for injection

(b) (4)

- Maximum lot size that was filled for FSME-IMMUN 0.5 mL
 - Maximum amount present in the bulk drug product
 - Present as aluminum hydroxide, (b) (4)
- Abbreviation: q.s.=quantum satis

Table 3.2.P.3.2-2. Batch Formula for FSME-IMMUN 0.25 mL Lot

Component
Formaldehyde-inactivated, sucrose gradient purified TBE-Aluminum ^c
Human Serum Albumin
Sodium Chloride
Disodium Phosphate Dihydrate
Potassium Dihydrogen Phosphate
Sucrose
Formaldehyde
Protamine sulfate
Neomycin
Gentamicin
Water for injection

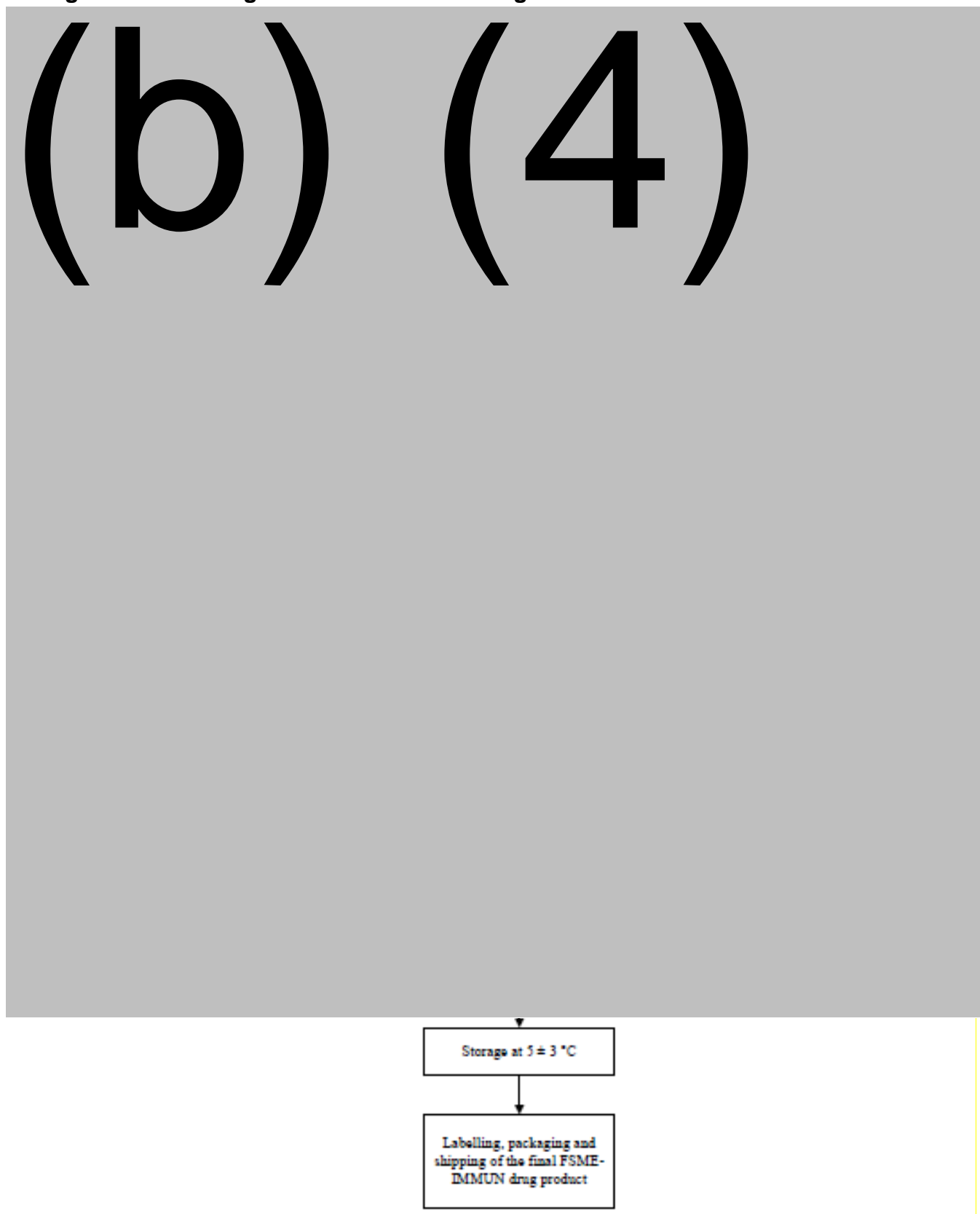
(b) (4)

- Maximum lot size that was filled for FSME-IMMUN 0.25 mL
 - Maximum amount present in the bulk drug product
 - Present as aluminum hydroxide, (b) (4)
- Abbreviation: q.s.=quantum satis

3.2.P.3.3 Description of Manufacturing Process

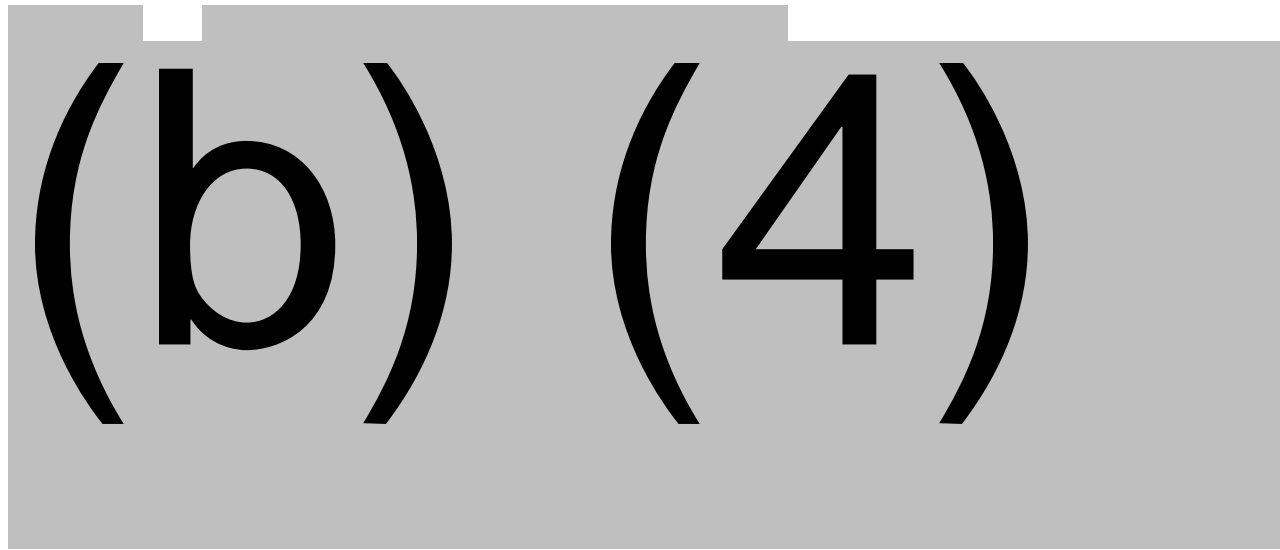


FSME-IMMUN DP formulation contains formaldehyde-inactivated, sucrose gradient purified TBE-virus antigen adjuvanted with aluminum hydroxide in a solution of phosphate buffered saline and human serum albumin (HSA). In this process the (b) (4) FSME-IMMUN drug product. A flow diagram detailing the steps of the FBP manufacturing process TicoVac vaccine is shown below in Figure 4:

Figure 4. Flow Diagram of the TicoVac Drug Product



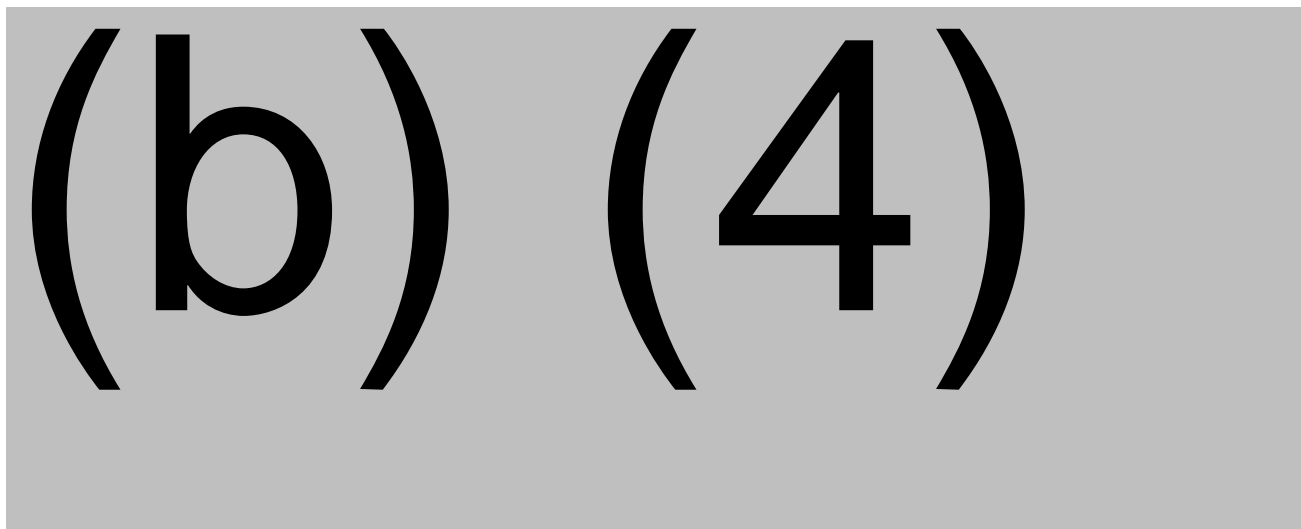
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(b) (4)



3.2.P.3.4 Controls of Critical Steps and Intermediates

In-process control tests are listed in Table 3.2.P.3.4-1. If the results of these controls are outside of the acceptable ranges or control limits, an evaluation is performed, and the disposition decision will be determined based on the investigation conclusion. In addition, in-process monitoring tests during filling are listed in Table 3.2.P.3.4-2.



Process Step	In-Process Control Test	Method	Control limits
Aseptic filling of FSME-IMMUN 0.5 mL	(b) (4)	(4)	
Aseptic filling of FSME-IMMUN 0.25 mL			
Aseptic filling of FSME-IMMUN final bulk vaccine into syringes			

3.2.P.3.5 Process Validation and/or Evaluation

The BLA contains the process development study report for the manufacturing process validation by Baxter as supportive information for historical purposes for technology transfer from Baxter to (b) (4) Pfizer. (b) (4), Pfizer then transferred the DP manufacturing process to (b) (4), Pfizer.

The TicoVac DP manufacturing process at Pfizer, (b) (4) is validated through process validation, filter validation, media fill qualification, comparability assessment, and shipping qualification. A total of (b) (4) TicoVac final (b) (4) vaccine validation lots comprising of (b) (4) TicoVac 0.5 mL and (b) (4) TicoVac 0.25 mL final DP lots. Process validation lots were manufactured at (b) (4) to validate the manufacturing process of TicoVac DP.

(b) (4)

An investigation was initiated for the PV stability study of lot (b) (4) following an atypical result for (b) (4) which determined that (b) (4) can affect TicoVac (b) (4). As a result, (b) (4) confirmatory lot was manufactured under previously validated normal operating conditions to confirm and support the Pfizer, (b) (4) process validation stability study.

5 pages have been 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)	(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)	(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)

Media Fill Study for Syringe Filler

Aseptic simulations (media fills) were performed to demonstrate that the formulation and filling operations are performed aseptically at Pfizer, (b) (4). The filling line is in the (b) (4). The aseptic process was simulated using (b) (4). (b) (4) was selected based on its support for aerobic growth of a broad spectrum of microorganisms. Product-specific aseptic process simulations (media fills) were performed to demonstrate that the manufacturing of FSME-IMMUN is performed aseptically at Pfizer, (b) (4) utilizing the FSME-IMMUN drug product container-closure system.

The media fill runs were required to meet the protocol acceptance criteria presented in Table 40.

(b) (4)

(b) (4)

The media fill studies simulated the aseptic filling for the container closure for FSME-IMMUN as well as the impact of routine and non-routine interventions that can occur during normal production operations such as aseptic handling of syringes, filling interruptions and personnel shift changes. The (b) (4) which is considered worst case due the maximum exposure of the open units to the environment, is used during media fill.

Standard planned and non-standard interventions were involved as part of the study and are listed as follows:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

During the APS runs, empty or non-intact units are rejected; This includes units, manually removed during an intervention (empty units or filled units without plunger) and automatic rejects of the filling machine (empty units or non-intact units). All growth promotional tests passed with 100% meeting acceptance criteria.

Reviewer's comment

The Media fill study was conducted with (b) (4) runs using the 1 mL syringes from (b) (4) vendors under worst case conditions. All (b) (4) media fill runs met the protocol acceptance criteria resulting in no positive growth in the syringe barrels. The growth promotion tests conform to (b) (4). The APS was done using worst case conditions with (b) (4) and all possible interventions. This

confirms effective aseptic processing of the formulation and filling process of FSME-IMMUN DP.

Inspection

Inspection of the FSME-IMMUN 0.5 mL and FSME-IMMUN 0.25 mL syringes was performed via (b) (4)


(b) (4) runs for each presentation were conducted and the percent defects are tabulated in Table 43 and 44 for the FSME-IMMUN 0.5 mL validation lots, and in Table 45 and 46 for the FSME-IMMUN 0.25 mL validation lots.

(b) (4)

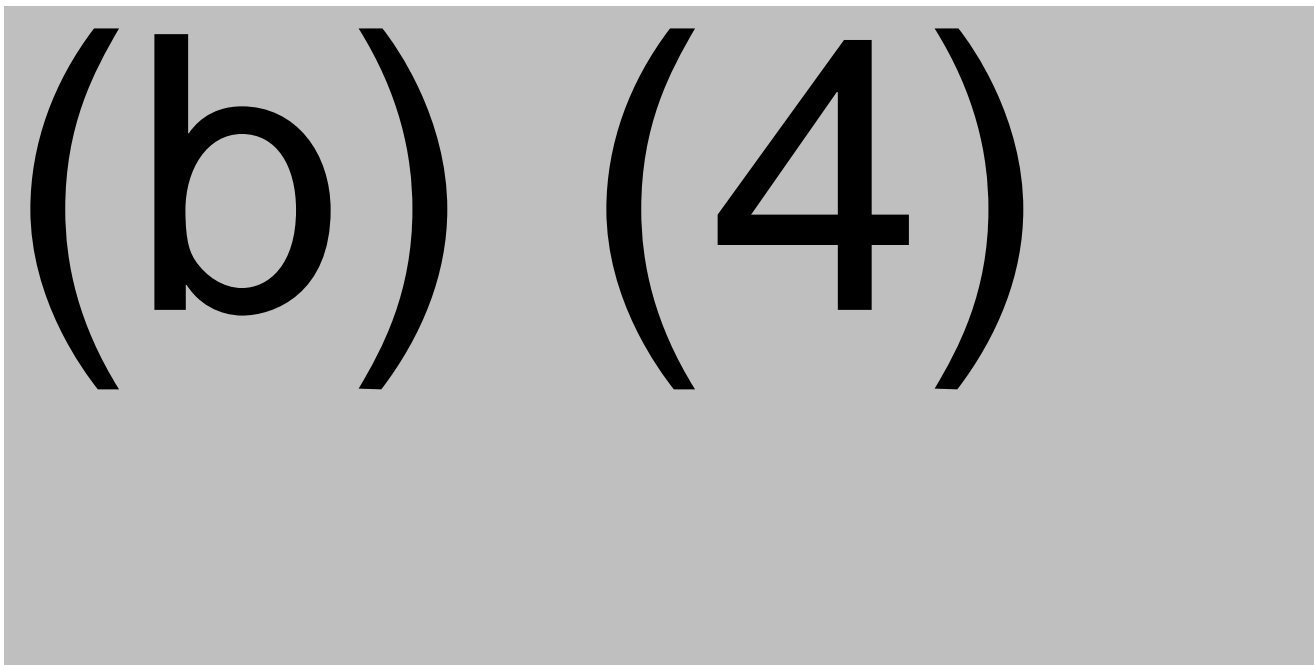
Reviewer's comment:

All tests were successfully completed, and the system effectiveness and reproducibility have been demonstrated. There was no relevant deviation that occurred with an impact on the system qualification outcome or on the product quality.


(b) (4)

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(b) (4)

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(b) (4)

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(b) (4)



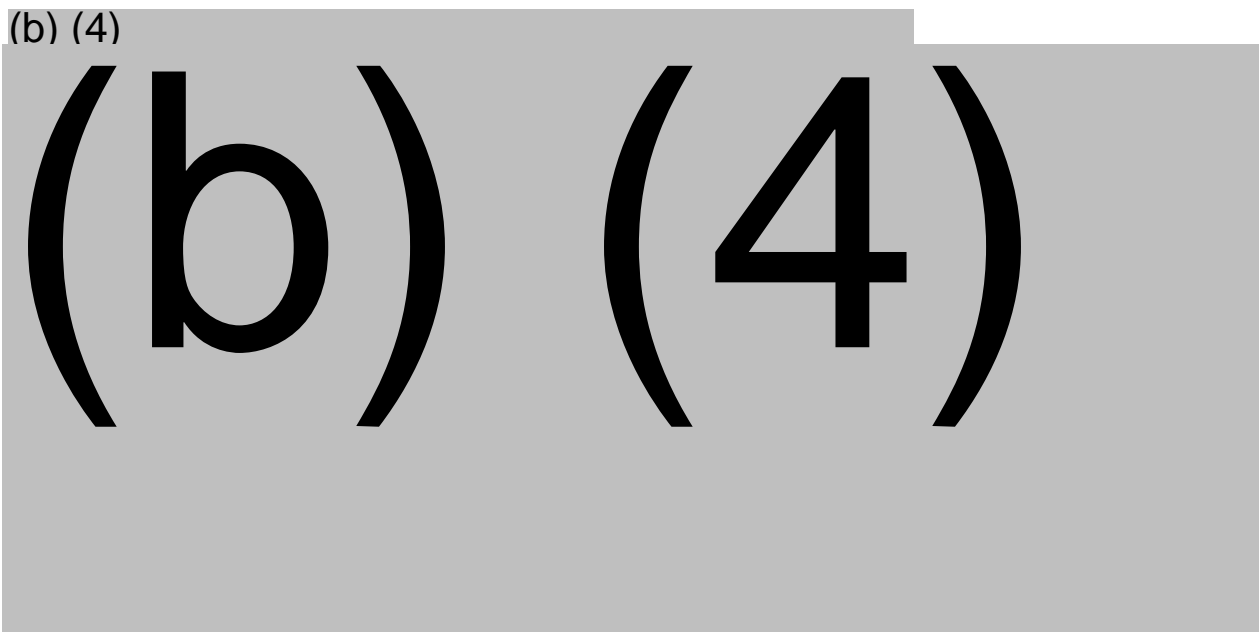
DP PPQ lots manufacturing and comparability evaluation

Process Performance Qualification (PPQ) was completed by manufacturing (b) (4) TicoVac final (b) (4) vaccine validation lots at (b) (4) comprising (b) (4) TicoVac 0.5 mL and (b) (4) TicoVac 0.25 mL final drug product lots.

(b) (4)



(b) (4)



(b) (4)

A comparability assessment was performed to demonstrate that the TicoVac DP manufactured at Pfizer, (b) (4) is comparable to the TicoVac DP produced at (b) (4) (b) (4). Demonstration of comparability for TicoVac included a statistical analysis of historical DP release results obtained from (b) (4) commercial DP lots of TicoVac manufactured at (b) (4) to the (b) (4) PPQ lots manufactured at Pfizer, (b) (4). The assessment included the evaluation of the following criteria:

- (b) (4)

The compared product quality attributes and their respective acceptance criteria are listed below:

Table 50. Product Quality Attributes and their Acceptance Criteria for the Comparability Assessment

(b) (4)

Reviewer's comment:

The results for each of the (b) (4) PPQ lots of FSME-IMMUN produced at Pfizer, (b) (4) are all within the historical process ranges for each quantitative product quality release parameter and conform the release specifications with the exception of some results for (b) (4) formaldehyde which are outside of the historical control limits. Firm stated these results are close to the historical minima and maxima obtained. I defer review of these data to product office.

(b) (4) confirmatory lot was manufactured under previously validated normal operating conditions for stability study, because an atypical result for (b) (4)

during the stability study of (b) (4) determined that (b) (4) can affect FSME-IMMUN (b) (4). Review of this is deferred to product office.

Stability Study

The TicoVac DP shelf life is 30 months when stored at the recommended temperature of 5 ± 3 °C. Stability study for TicoVac DP stored under the recommended long-term condition and accelerated condition of (b) (4) as well as (b) (4) conditions are ongoing with up to (b) (4) month stability data available for DP produced at (b) (4) facility.

(b) (4) PPQ DP lots consisted of both 0.5 mL and 0.25 mL presentations manufactured at (b) (4) at Pfizer, (b) (4) were enrolled in the stability program. (b) (4), referred to as a confirmatory lot) of TicoVac was manufactured and placed on a long-term stability study, as well as a (b) (4) study in accordance with (b) (4).

Table 51. Pfizer (b) (4) DP Stability Program

(b) (4)

(b) (4)

The BLA submission contained stability data for all (b) (4) lots in the program as shown in the table below:

Table 52. Long Term Stability TicoVac DP batches used in the Stability Study

(b) (4)

The batch samples that were stored at $5 \pm 3^\circ\text{C}$ with samples tested at the 0, 3, 6, 9, 12 and 18 months were all sterile and met acceptance criteria. The batch samples that were stored at (b) (4) for the accelerated studies with samples tested at the (b) (4) all remained sterile and met acceptance criteria.

The stability study report reviewed also included (b) (4) studies for these PPQ lots. The (b) (4) stability study is to (b) (4) $5 \pm 3^\circ\text{C}$ storage for the duration of the study. The purpose of the (b) (4) study is to evaluate stability to support processing (inspection, packaging, transport) on site. There are up to 18 months data made available for the (b) (4) study, and all PPQ lots tested were sterile.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

All the excipients used for FSME-IMMUN drug product comply with the (b) (4) as indicated in Table 3.2.P.4-1. 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. Specification of (b) (4) Excipients

Excipient	Bacterial (b) (4)	Total Aerobic (b) (4)	Quality Specification
Disodium Phosphate Dihydrate*	(b) (4)		
Potassium Dihydrogen Phosphate*			
(b) (4)			
Sodium Chloride*			

Human Serum Albumin
Aluminum Hydroxide*

(b) (4)

*Additional tests are performed for these excipients.

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

Review of this section is deferred to DBSQC.

3.2.P.4.4 Justification of Specifications

All excipient specifications comply with the (b) (4) at the minimum.

3.2.P.4.5 Excipients of Human or Animal Origin

Excipient Human Serum Albumin used in the manufacture of FSME-IMMUN is of human origin while the remaining excipients are not of human or animal origin. To minimize the risk, the applicant has been vigilant in assuring proper use and control of animal derived materials by:

- Working with suppliers to collect the most up-to-date information on animal derived materials used in the process.
- Working with the United States Food and Drug Administration (US FDA) for updates on regulations and practices to control TSE in the US
- Working with other agencies worldwide, including the Committee for Medicinal
- Products for Human Use (CHMP) when needed, to keep abreast of any changes in compliance expectations.

Firm has conducted a detailed adventitious agents safety evaluation for virus seed lots and materials of animal or human origin including its source and preparation used in the manufacturing process.

Reviewer's comment:

Review of this section is deferred to product office.

3.2.P.4.6 Novel Excipient

No novel excipients are used in the formulation of FSME-IMMUN.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

The release and stability testing specifications for FSME-IMMUN are provided in the following tables.

(b) (4)

(b) (4)

Table 3.2.P.5.1-3. Drug Product Specifications, Final Drug Product

Quality Attribute	Analytical Procedure	Acceptance Criteria	
		Release	Stability
Identity	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sterility	(b) (4)	Sterile	Sterile
Extractable Volume for FSME-IMMUN 0.5 mL	(b) (4)	0.50 (b) (4)	Not Performed
Extractable Volume for FSME-IMMUN 0.25 mL	(b) (4)	0.25 (b) (4)	Not Performed
Visual Inspection (appearance)	(b) (4) : no extraneous matters, (b) (4) the vaccine is an off-white, homogenous, opalescent suspension	Complies	Complies
Endotoxin	(b) (4)	(b) (4)	Not Performed
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

Review of this section is deferred to product office.

3.2.P.5.4 Batch Analyses

An overview of (b) (4) batch analysis data from FSME-IMMUN lots produced since 1996 manufactured in Pfizer (b) (4) facility is provided including the results from antigen content and potency determinations. The results demonstrated consistency for the manufacturing process since all lots met specifications for antigen content and potency over the years.

To support the transfer of DP manufacturing into Pfizer, (b) (4) process validation lots and (b) (4) confirmatory lot were manufactured. Table 3.2.P.5.4-56 gives an overview

of the genealogy of these lots of FSME-IMMUN manufactured at commercial scale. Analytical release testing results for all these lots of FSME-IMMUN are presented in table Table 3.2.P.5.4-57 up to Table 3.2.P.5.4-59. All results are within the pre-defined acceptance criteria.

Table 3.2.P.5.4-56. FSME-IMMUN lots 0.5 mL and 0.25 mL Manufactured at Pfizer,
(b) (4)

(b) (4)

All (b) (4) PPQ lots covering both 0.5 mL and 0.25 mL fill volumes were tested sterile, and endotoxin results were all (b) (4) (Acceptance (b) (4) Other tests included (b) (4) were within specification. Review of these results is deferred to product office.

3.2.P.5.5 Characterization of Impurities

Review of this section is deferred to product office.

3.2.P.6 Reference Standards or Materials

Review of this section is deferred to product office.

3.2.P.7 Container Closure System

The TBE vaccine in a prefilled syringe (PFS) is defined as a single-entity

(biologic/device) combination product under 21 CFR Part 3.2(e). The primary container closure system of FSME-IMMUN vaccine consists of the following components:

- (b) (4) syringe barrels are composed of (b) (4) borosilicate glass.
- The plunger stopper is composed of (b) (4) Gray latex-free chlorobutyl rubber. The stopper is (b) (4)
- The tip caps are composed of (b) (4) Gray latex-free isoprene bromobutyl rubber.
- As a part of the finished product, a polystyrene plunger rod is included.

Table 53. Syringe Container Closure Components

Component Type	Description	DMF Reference
Barrel	(b) (4) 1ml (b) (4) borosilicate glass barrel with Luer cone.	(b) (4)
	(b) (4) 1ml (b) (4) borosilicate glass barrel with Luer cone	
Tip Cap	(b) (4) latex-free bromobutyl and synthetic polyisoprene rubber Tip Cap	
	Siliconized (b) (4)	
Plunger stopper	(b) (4) latex-free styrene-butadiene-bromobutyl rubber plunger stopper	
	Siliconized (b) (4)	
Plunger rod	(b) (4) Polystyrene plunger rod	

Design Verification

Attributes included in the design input requirements have been verified. FSME-IMMUN vaccine prefilled syringes have undergone design verification in accordance with 21 CFR Part 820.30(f). Additional document review and bench-top lab tests demonstrated that the FSME-IMMUN prefilled syringe meets all design input requirements necessary for safe and effective drug administration at the point of use by the intended users. The tests included:

- Leachables from drug product contact materials
- Drug product quality attributes
- (b) (4)
- Deliverable volume (extractable volume)

Analysis of the design and functional attributes tested during design verification was performed to determine which functional performance tests are considered essential and would therefore be routinely tested as part of release or stability.

Reviewer's comment

The suitability and biocompatibility review of the container system is deferred to product office. Container Closure System Delivery Performance is reviewed by consult reviewer from CDRH.

Container Closure Integrity

The integrity of the syringe container closure systems used for FSME-IMMUN was demonstrated by (b) (4) studies performed with syringes filled at

Pfizer (b) (4) on Washing and Sterilization Line (b) (4)

Both combinations of the barrels (b) (4) tip cap (b) (4) and plunger stopper (b) (4) were tested. Testing is planned through 30 months, with testing of (b) (4) syringes at each time point that has completed through the 0, 3, 6, 9, 12 and 24 months storage points to date.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's comment

Both (b) (4) tests were performed, and firm stated all results met acceptance criteria. But there is limited information for the CCIT provided. An IR was sent to the firm on March 28, 2021.

DMPQ IR Question #1:

1. You have performed Container Closure Integrity Testing (CCIT) using both (b) (4) tests. Please provide the following:
 - Types of positive controls used in both CCIT methods for the final drug product.
 - The critical defect size(s), numbers of positive controls used in each test and results.
 - The sensitivities of your CCIT methods.

The response was received on April 12, 2021 in Amendment STN125740/0.11

Firm's response:

(b) (4)

Reviewer's comment:

Firm provided the number and (b) (4) for the positive controls used in both

CCIT. These positive controls are adequate for the relevant tests used. The response is acceptable.

SHIPPING VALIDATION

A temperature-controlled vehicle (TCV) was chosen for transport from Pfizer, (b) (4) to (b) (4). Active temperature-controlled (b) (4) (b) (4) were chosen for shipment to US distribution centers in (b) (4). The established shipping temperature range for FSME-IMMUN is $5 \pm 3^{\circ}\text{C}$.

The TCV OQ studies were performed with a maximum load over a period of (b) (4) under (b) (4) external conditions. The OQ results showed that the full load with set point of (b) (4) had a temperature range of (b) (4) with a mean of (b) (4) under the (b) (4) external condition and had a temperature range of (b) (4) with a mean of (b) (4) under the (b) (4) external condition. Both results met the study acceptance limit of $5 \pm 3^{\circ}\text{C}$.

TVC PQ was conducted with (b) (4) runs by (b) (4). Shipment was qualified between two Pfizer sites, from (b) (4). A summary of the results from this study is shown in Table 56. All temperatures recorded were within the range of $2-8^{\circ}\text{C}$, meeting the shipping temperature requirement of TicoVac.

Table 56. Results of Temperature-Controlled Vehicle Study from (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data Stability Study

The TicoVac DP shelf life is 30 months when stored at the recommended temperature of $5 \pm 3^\circ\text{C}$. Stability study for TicoVac DP stored under the recommended long-term condition and accelerated condition of (b) (4) as well as (b) (4) conditions are ongoing with up to (b) (4) stability data available for DP produced at (b) (4) facility.

(b) (4) PPQ DP lots consisted of both 0.5 mL and 0.25 mL presentations manufactured at (b) (4) at Pfizer. (b) (4) were enrolled in a stability program. (b) (4) lot (b) (4), referred to as a confirmatory lot) of TicoVac was manufactured and placed on a long-term stability study, as well as a (b) (4) study in accordance with (b) (4)

Table 59. Pfizer, (b) (4), Drug Product Stability Program

(b) (4)

(b) (4)

The BLA submission contained stability data for all (b) (4) lots in the program as shown in the table below:

Table 60. Long Term Stability TicoVac DP batches used in the Stability Study

(b) (4)

The batch samples that were stored at 5 ± 3 °C with samples tested at the 0, 3, 6, 9, 12 and 18 months all remained sterile and met acceptance criteria. The batch samples

that were stored at (b) (4) for the accelerated studies with samples tested at the (b) (4) all remained sterile and met acceptance criteria.

The stability study report reviewed also included (b) (4) studies for these PPQ lots. The (b) (4) stability study is to (b) (4) for the duration of the study. The purpose of the (b) (4) study is to evaluate stability to support processing (inspection, packaging, transport) on site. There are up to 18 months data made available for the (b) (4) study, and all PPQ lots tested were sterile.

Reviewer's comment

The validation of the manufacturing process for TicoVac DP was done with (b) (4) PPQ DP lost produced and (b) (4) lot used for additional stability study batch. All (b) (4) PPQ lots passed sterility test at time zero and during long term stability test for up to 18 months with available data. These PPQ batches showed the consistency for the manufacturing process. Review of other IPC and final release test data is deferred to product office.

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

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

Table 3.2.P.8.2-1. Post-Approval Commercial Stability Protocol for FSME-IMMUN DP Stored at 5 ± 3 °C

(b) (4)

(b) (4)

In the BLA submission, firm did not provide FEI number for the DS manufacturing facility in (b) (4) . Firm provided the FEI number in their response to February 2, 2021 IR in Amendment STN125740/0.3 received on February 12, 2021.

DRUG SUBSTANCE

1. FACILITIES for DS MANUFACTURING

The manufacturer for TicoVac DS is at the Pfizer's (b) (4) facility. All facilities involved in TicoVac DS manufacturing and testing are summarized in Table 62.

Table 62. Sites and Responsibilities for Manufacture and Testing of TicoVac DS

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(b) (4)

DRUG PRODUCT

The sites that have responsibilities in the production of TicoVac DP and their specified functions are shown in the table below:

Table 105. Sites and Responsibilities for Manufacture and Test for TicoVac DP

Name and Address	FEI and/or DUNS Number	Responsibilities and Quality System Provisions
Pfizer (b) (4) (b) (4) (b) (4)	(b) (4) 	Quality Control Testing <ul style="list-style-type: none"> • (b) (4) Formaldehyde Content • Antigen Content • Extraneous Agents • Sucrose Content • Potency • (b) (4) • Sterility
Pfizer (b) (4) (b) (4) 	(b) (4) 	Formulation and Filling (Primary Packaging) Quality Control Testing <ul style="list-style-type: none"> • Sterility • Protein Content • (b) (4) • Endotoxin • Sodium Content • (b) (4) • Aluminum Content • Identity • Extractable Volume • Visual Inspection Labelling and Secondary Packaging
(b) (4) 	 	

Name and Address	FEI and/or DUNS Number	Responsibilities and Quality System Provisions
(b) (4)		

The Pfizer, (b) (4) Manufacturing Site is located at (b) (4)
 The manufacturing areas at (b) (4) are located in several buildings: (b) (4)

The (b) (4) Building is a dedicated facility used for manufacturing of multiple vaccines. It is a (b) (4) structure, (b) (4) manufacturing area (b) (4) technical area (b) (4) used for TicoVac manufacture where formulation of TicoVac DP is performed.

The (b) (4) Building is a multi-product building for manufacturing of sterile solutions, suspensions, gels and lyophilized products. The building is a (b) (4) structure, (b) (4) manufacturing area (b) (4) technical area (b) (4) multiple suites are used for TicoVac filling operations. The inspection operation for TicoVac syringes is performed in the (b) (4) Building.

The (b) (4) Building area classifications are illustrated in drawing below:

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

Differential Pressure, Temperature and Relative Humidity

- 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 each manufacturing building. A minimum differential pressure of (b) (4) between adjacent rooms of different grades, and a minimum of (b) (4) between classified and non-classified areas is maintained. Room differential pressure recovery times following pressure alarm conditions were also qualified.
- Temperature: the alarm operating temperature specification is (b) (4) in Grade (b) (4) and Grade (b) (4) areas.
- Relative humidity measurements are continuously monitored (in critical rooms).

Flows for Personnel, Materials and Equipment, Product and waste

The BLA contains diagrams to show flow paths for Personnel, Materials and Equipment, Product and Wastes in the aseptic building.

Reviewer's comment

The pressure differentials between clean areas appears acceptable, where pressure cascade provides airflow from higher grade to lower grade areas with proper pressure differentials. Firm stated that procedures are in place to provide temporal and physical segregations for clean and dirty materials/equipment to prevent potential cross contamination in the facility. I reviewed the flow paths and find them acceptable.

1. HVAC SYSTEM and ENVIRONMENTAL MONITORING

HVAC

Several HVAC systems serve the (b) (4) Building and (b) (4) Building at (b) (4) facility. Each clean room has its own recirculation Air Handling Unit (AHU). (b) (4) AHU, providing fresh air and overpressure in the cleanrooms, can supply several cleanrooms.

The AHUs are located in the (b) (4) Building and (b) (4) Building that supply the (b) (4) floor production area rooms with conditioned air. The (b) (4) controls the HVAC systems. HVAC controls include startup, shutdown, room temperature, pressure, relative humidity and airflow. The (b) (4) monitors the critical clean room parameters (i.e., temperature, pressure, relative humidity). The AHUs and areas served are summarized in the table below:

Table 106. Air Handling Units and Areas Served in (b) (4) Buildings

(b) (4)

(b) (4)

IQ/OQ were performed for all AHUs to demonstrate that they operate in accordance with design requirements and that all classified environments met air quality requirements.

PQ of the HVAC systems was performed by environmental monitoring for the Grade (b) (4) Grade (b) (4) and Grade (b) (4) Areas to provide objective evidence that these controlled spaces consistently operate within defined parameters to produce the defined environmental outcome. Results of EM validation is reviewed in the section below.

Environmental Monitoring


The environmental performance qualifications (EMPQ) for the Grade (b) (4) Grade (b) (4) and Grade (b) (4) areas in the (b) (4) Building and (b) (4) Building supporting the TicoVac manufacturing, the Filling Line and the (b) (4) Grade (b) (4) systems were conducted. The controlled areas were tested during in operation conditions, to verify their performance in accordance with site procedures. For each classified area the PQ was conducted (b) (4) times. Controlled areas were monitored for (b) (4)

In operation, testing was conducted with all appropriate equipment operating and personnel presented to simulate routine production activities. Testing was performed in accordance with the acceptance criteria identified in the PQ protocol and presented in the tables below:

(b) (4)

(b) (4)

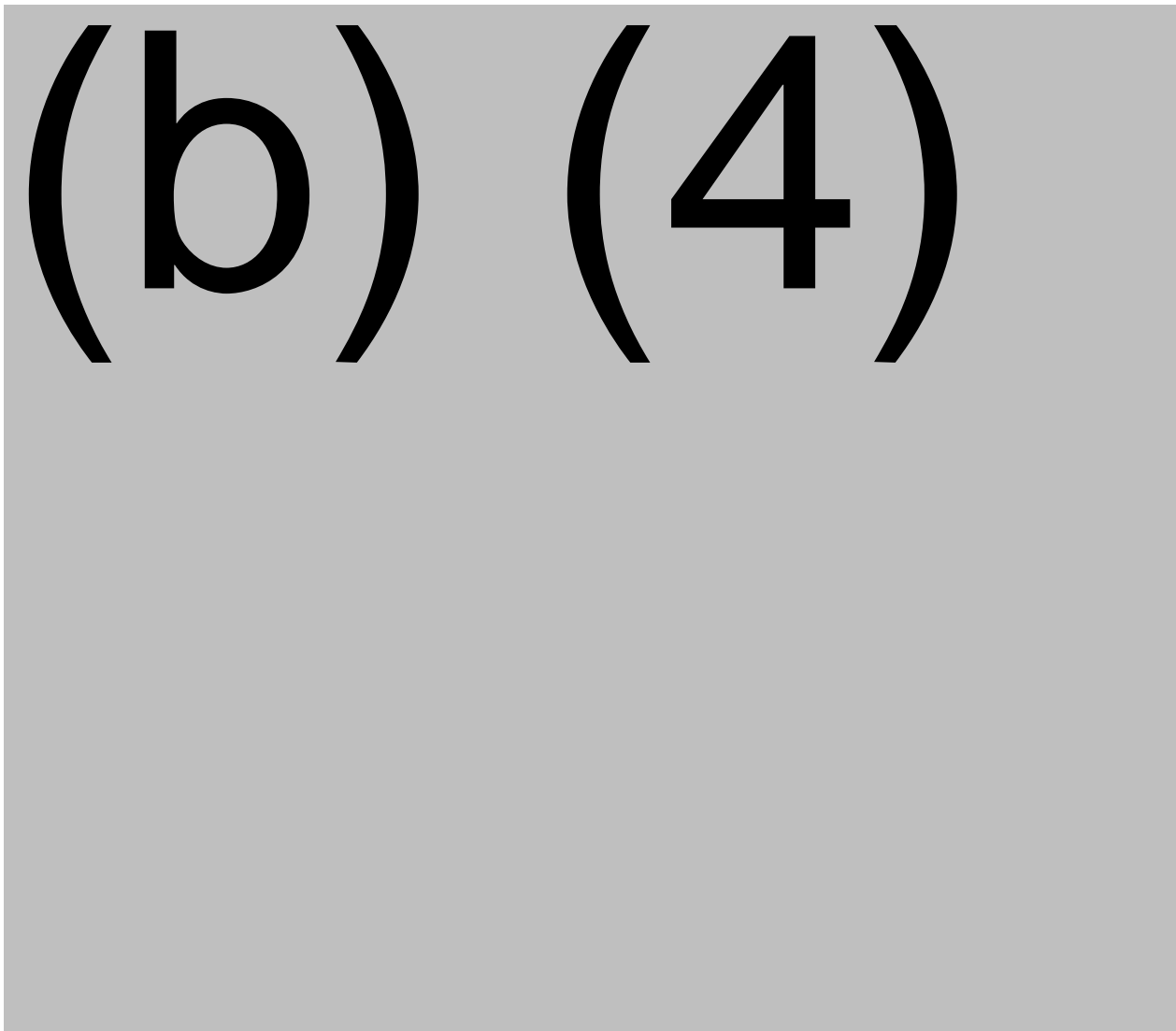
(b) (4)



(b) (4)

The sampling locations covered defined critical areas in the facility including production areas, airlocks, material locks, corridors, gowning room, locker room, storage areas and surface areas on all major equipment. The sampling plans for Grade ^{(b) (4)} (filling line), ^{(b) (4)} areas and acceptance criteria are shown in the table below:

(b) (4)



(b) (4)

All the tested samples including total particulates, air viable and surface viable levels meet the acceptance criteria during in operation conditions.

Reviewer's comment

The EM acceptance criteria for (b) (4) conform to (b) (4) cleanroom standards. There was no EM trending data submitted with the original BLA. An Information Request was sent to firm on February 2, 2021 requesting EM data during PPQ campaign at (b) (4) facility and firm provided response in Amendment 3 (STN125740.0/3) received on February 12, 2021.

DMPQ IR

Please provide the environmental monitoring reports summarizing data acquired during FSME-IMMUN PPQ campaigns at both the (b) (4) facilities.

Firm's response

Firm provided a summary report for (b) (4) facility covering the period from February 2, 2018 to July 5, 2018. The results included EM data for filling line (b) (4) Building during filling operations of all (b) (4) DP PPQ lots. The EM samples are summarized in the table below:

(b) (4)

I reviewed the EM results for the filling line where all (b) (4) DP PPQ lots were processed. There were few excursions reported during these runs and included:

(b) (4)

Reviewer's comment:

Firm stated that all deviations that occurred during EMPQ have been resolved and deemed no impact to the EMPQ as a result of these deviations. The EM data during DP PPQ campaign was requested and reviewed in the PPQ section. With very few (b) (4) excursions and only (b) (4) excursion, the filling line appears to be able to maintain a controlled aseptic environment during PPQ runs.

2. UTILITIES

(b) (4)

(b) (4)

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(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3. EQUIPMENT for DP MANUFACTURING

Major process equipment used in TicoVac manufacture are in the (b) (4) Building (b) (4) the (b) (4) Building (filling), and the (b) (4)

(b) (4) Building (inspection). The critical manufacturing equipment for TicoVac are described in the Table 117 below:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

18 pages have been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

Computer System

There is minimal information for the systems provided in the BLA submission, other than stating that IQ/OQ/PQ for the computer systems were conducted. An IR was sent on Feb. 2, 2021. Firm provided their response in Amendment STN125740/0.3.

DMPQ IR Question #4:

Please provide the general descriptions of the computer systems which control critical manufacturing processes, software validation summary reports and change control procedures for automated systems at your (b) (4) facilities.

Firm's response:


All major computerized systems used in the manufacturing of TicoVac at Pfizer (b) (4) are operated and controlled by a (b) (4). For all GMP relevant processes only qualified or validated computerized systems are used.

List of Major Equipment used in the manufacturing of FSME-IMMUN at (b) (4)

(b) (4)

High level summary reports for IQ/OQ/PQ for these systems are provided.

(b) (4)

A large rectangular area of the document is redacted with a solid grey box. The redaction covers approximately the top third of the page, starting below the header and ending above the first paragraph. The text "(b) (4)" is visible at the top left of this redacted area.

Firm stated that all deviations during verification execution has been resolved. There was no impact to the verification of the equipment as a result of these deviations. Verification execution was successfully completed and established that the equipment was installed and operates in accordance with design and manufacturers specifications and is fit for intended use.

Pfizer stated any change that has the potential to impact the safety, identity, strength, purity, quality, stability or regulatory filing of products is implemented and controlled via the site (b) (4) and according to the Change Control Management as defined by local Change Control Management SOP.

Reviewer's comment

The firm's response to the computer system is acceptable.

3.2.A.2 Adventitious Agents Safety Evaluation

Firm has multiple mechanisms, procedures and assays utilized to minimize and control the potential entry of adventitious agents into the production stream of the inactivated tick-borne encephalitis (TBE) virus vaccine (FSME-IMMUN).

The adventitious agent control program includes the engineering systems of the facility and vessels, the control of the starting and raw materials used in the process, the capacity of the manufacturing process to remove or inactivate adventitious agents and in-process and environmental testing to monitor the level of adventitious agents in and around the process stream.

A virus seed lot system with known history is used as starting point for the manufacture of the vaccine. Ingredients of animal or human origin are used in the preparation of the vaccine components and during upstream and downstream processing as well as during pharmaceutical formulation.

Equipment and materials are cleaned and sterilized according to validated procedures, some steps in the production of the vaccine antigen have adventitious agent reduction capability, such as the (b) (4) in the DS formulation.

❑ **Viral Clearance Studies**

The manufacturing steps in (b) (4) have been evaluated for their viral clearance abilities. I defer review of this section to product office.

3.2.R Regional Information (USA)

❑ **Executed Batch Records**

Executed batch records (BR) are included in the BLA submission including:

One (b) (4) production BR

One DP formulation BR

One DP filling BR

BRs for all QC test method validations, including sterility, potency, identity, protein content, aluminum content *et al*

❑ **Method Validation Package**

I defer review of this section to DBSQC.

❑ **Combination Products**

Refer to Container Closure System section of the memo for review of the design control. Addition evaluation is conducted by CDRH consult for this BLA.

❑ **Comparability Protocols**

Not applicable.

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

Pfizer did not request a categorical exclusion (CE) from the requirement to prepare an environmental assessment under 21 CFR § 25.31(a) in the BLA. Review of this issue is deferred to product office.

B. Labeling Review

Full Prescribing Information (PI):

Review of this issue is deferred to product office.

Modules 4 and 5

Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

Review of this issue is deferred to product office.