

CBER CMC BLA Review Memorandum

BLA STN 125740

Tick Borne Encephalitis Vaccine (Whole Virus, Inactivated)

**Tony Wang, PhD
CBER/DVP**

1. BLA#:

STN 125740

2. APPLICANT NAME AND LICENSE NUMBER

Pfizer Ireland Pharmaceuticals

3. PRODUCT NAME/PRODUCT TYPE

Proper name: Tick Borne Encephalitis Vaccine

Proprietary name: TICOVAC

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

Pfizer Ireland Pharmaceuticals submitted the original Biologics License Application (STN #125740/0) on December 15, 2020 to seek approval of their Tick-Borne Encephalitis Vaccine (Whole Virus, Inactivated) (FSME-IMMUN) for active immunization to prevent tick-borne encephalitis (TBE) in individuals 1 year of age and older. The proposed trade name for the vaccine is TICOVAC. In this review, the vaccine is referred to as TICOVAC, FSME-IMMUN, FSME-IMMUN (CC) without thiomersal and FSME-IMMUN "NEW." TICOVAC 0.5 mL is an inactivated vaccine for immunization against tick-borne encephalitis (TBE) in individuals 16 years of age and older. TICOVAC 0.25 mL is an inactivated vaccine for immunization against tick-borne encephalitis (TBE) in individuals from 1 to 15 years of age. TICOVAC is produced by propagation of a TBE virus seed (strain Neudörf) in chick embryo fibroblast cells, formaldehyde-inactivation, and sucrose gradient purification of the TBE virus harvest. The drug product (DP) ^{(b) (4)} is formulated to a target 2.40 µg for TICOVAC 0.5 mL and 1.19 µg for TICOVAC 0.25 mL adsorbed to aluminum hydroxide adjuvant (0.35 mg Al₃₊ for TICOVAC 0.5 mL and 0.17 mg Al₃₊ for TICOVAC 0.25 mL ^{(b) (4)} containing human serum albumin (0.5 mg for TICOVAC 0.5 mL and 0.25 mg for TICOVAC 0.25 mL). The vaccine is thiomersal-free. The inactivated whole virus vaccine is delivered as a sterile suspension for injection in a prefilled syringe of either 0.5 mL or 0.25 mL and administered intramuscularly (IM) into the upper arm (deltoid muscle). In both adults and children, the vaccine is to be given based on official recommendations regarding the need for and timing of vaccination against TBE. The first dose should be given on an elected date and the second dose should be given between 1 and 3 months later. ^{(b) (4)}

^{(b) (4)} The third dose should be given between 5 and 12 months after the second vaccination. A booster dose (i.e., 4th dose) may be given 3 years after the third dose, if ongoing exposure or re-exposure to TBEV is expected.

5. MAJOR MILESTONES

Filing meeting: January 28, 2021

Advisory Committee meeting: March 6, 2019

Action date: August 15, 2021

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Tony Wang, CBER/OVRR/DVP	Modules 3 (except for facilities and equipment information), 4, and 5 (assays used to assess clinical endpoints), Module 1 (labeling)
Jie He, CBER/OCBQ/DMPQ/MRB2	Modules 3 (facilities and equipment information) and manufacturing records
Debra Vause, CBER/OCBQ/DMPQ/ARB	Establishment Inspection Report
Anil Choudhary, CBER/OCBQ/DBSQC	Release assays
Hsiaoling Wang, CBER/OCBQ/DBSQC	QC, Test Methods,
Simleen Kaur, CBER/OCBQ/DBSQC	QC, Test Methods,
Marie Anderson, CBER/OCBQ/DBSQC/QAB	Lot Release Protocol
Ruoxuan Xiang, CBER/OBE/DB/VEB	Potency assay validation

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
Shawn Shermer, FDA/OC/CDRH/OPEQ/OHTIII/DHTIIC/ ICCR# 00058730 2/1/2021	Delivery devices (b) (4)	Yes
Sreya Tarafdar OPEQ/OHT3/DHT3C ICCR# 00723776 6/3/2021	(Section 3.2.P.7)	Yes

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
December 15, 2020	STN 125740/0	Reviewed
April 07, 2021	STN 125740/10(response to FDA March 24, 2021 IR)	Reviewed
April 9, 2021	STN 125740/11 (response to FDA March 26, 2021 IR)	Reviewed
May 14, 2021	STN 125740/16 (response to FDA April 30, 2021 IR)	Reviewed

May 17, 2021	STN 125740/17 (response to April 27, 2021 manufacturing record request)	Reviewed
June 7, 2021	STN 125740/21 (response to May 24, 2021 FDA IR regarding lot release protocol template)	Reviewed
June 29, 2021	STN 125740/25 (response to FDA June 15, 2021 IR)	Reviewed
July 6, 2021	STN 125740/26 (response to June 21, 2021 IR regarding labeling comments)	Reviewed
July 15, 2021	STN 125740/30 (response to July 13, 2021 IR regarding manufacturing process)	Reviewed

9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments
DMF (b) (4)	Pfizer	The entire master file	No	Information pertinent to the development of this vaccine

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Pfizer Ireland Pharmaceuticals submitted the original Biologics License Application (STN #125740/0) on December 15, 2020 to seek approval of their Tick-Borne Encephalitis Vaccine (TICOVAC) for active immunization to prevent tick-borne encephalitis (TBE) in individuals 1 year of age and older. I reviewed the CMC section and assays used in clinical studies.

The active substance of TICOVAC is a (b) (4)

(b) (4)

The (b) (4) DS is manufactured by Pfizer (b) (4). The manufacturing process of FSME-IMMUN DS (b) (4) consists of the following stages: (b) (4)

(b) (4)

TICOVAC drug product (DP) is a sterile, off-white, homogenous, opalescent suspension for intramuscular injection. It is prepared through (b) (4) onto Al(OH)₃. Each 0.5 mL adult dose is formulated to contain 2.4 µg TBE virus, 0.5 mg human serum albumin (HSA), 0.35 mg Al(OH)₃, 3.45 mg of sodium chloride, 0.22 mg of dibasic sodium phosphate, and 0.045 mg of monobasic potassium phosphate. From the manufacturing process, each 0.5 mL also contains formaldehyde (≤5 µg), protamine sulfate (≤0.5 µg), chick protein (b) (4) and trace amounts of chick protein and host DNA of CECs, neomycin and gentamicin. The pediatric 0.25 mL dose of FSME-IMMUN contains the same components as the 0.5 mL dose in half of the quantities. The vaccine contains no preservative (e.g., thiomersal). The dating period for TICOVAC is 30 months from the date of manufacture when stored at 5 ± 3 °C. The date of manufacture is defined as the date of (b) (4)

The sponsor performs in-process and release testing of the vaccine and its intermediates at different stages of manufacturing to ensure that the product meets specifications and manufacturing is consistent. The master virus seed and working virus seed were qualified for the absence of detectable extraneous agents. The final vaccine formulation does not contain any new or known hazardous excipients. The final vaccine does contain HSA as a stabilizer. HSA is derived from plasma sourced from the United States according to the current plasma sourcing guidelines. The sponsor presented information ensuring safety from BSE/TSE concerns.

Release testing for final DP includes: appearance, identity, sterility, extractable volume, endotoxin. The acceptance specification for the potency of the vaccine is a minimum of (b) (4) relative to standard. Because the potency test is performed on (b) (4) vaccine, the sponsor also includes a potency (b) (4) that is performed on final DP as part of product stability testing.

Overall, the information provided in the BLA and amendments demonstrates that the manufacturing process is well-controlled with appropriate validations and in-process control testing. Moreover, adequate quality control testing has been conducted and stability data have been accrued with the DS and DP. Therefore, I recommend approval of the product.

B. RECOMMENDATION

I. APPROVAL

a. List of Drug Substance (DS) and Drug Product (DP) manufacturing facilities:

- Manufacture of DS: Pfizer (b) (4) [redacted]
- Manufacture of DP: Pfizer (b) (4) [redacted]

b. List of approvable Comparability Protocols:

- Not applicable

c. List of Post-Marketing Commitments (PMCs)/Post-Marketing Requirements (PMRs):

- Not applicable

d. Consideration for Inspectional Follow-up (e.g., flagging inspectional issues for future surveillance inspections)

Note: Due to the COVID-19 pandemic and travel restriction, CBER is unable to conduct on-site inspection during the review of the BLA. With its authority under Section 704(a)(4), CBER requested manufacturing site records from Pfizer (b) (4) [redacted] Jie He from DMPQ and I jointly reviewed the records and found the information to be acceptable. Details can be found in a joint records review memo. The following items may be considered for inspectional follow-up:

- (b) (4) [redacted]

e. Lot release requirements

The lot release protocol (LRP) is provided (original submission and amendment 21) and is acceptable.

f. Established Conditions (ECs).

- Established conditions were not defined and do not apply to this BLA

g. List approvable ECs and associated reporting categories at the end of the Review Memo.

- Not applicable

II. COMPLETE RESPONSE (CR)

NONE.

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Primary Level Review including all CMC reviewers	Concur	
Secondary Level Review (e.g., Branch/Lab Chief)	Concur	
Tertiary Level Review (e.g., Division Director)	Concur	

Review of CTD

Module 3

3.2.S DRUG SUBSTANCE

(b) (4) [Redacted text block]

[Redacted text block]

[Redacted text block]

(b) (4) [Redacted text block]

[Redacted text block]

[Redacted text block]

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

Overall Reviewer's Assessment of Section 3.2.S.7:

The information provided is acceptable.

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product The FSME-IMMUN drug product (DP) is a sterile, non-pyrogenic suspension of formaldehyde-inactivated and sucrose gradient purified Tick-Borne Encephalitis (TBE) virus harvest, diluted in phosphate buffered saline solution containing (b) (4) human albumin and bound to aluminum hydroxide. FSME-IMMUN 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 DP contains no preservative. The composition of both dosage forms is identical, but the nominal volume of the pediatric dosage form is half of the nominal volume of the 0.5 mL dosage form. The composition of FSME-IMMUN is shown in Table 26.

Table 26 – Composition of FSME-IMMUN 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) 1.19 µg (target)	(b) (4) 2.40 µg (target)
Aluminum hydroxide, hydrated	(b) (4)		0.17 mg (Al ³⁺)	0.35 mg (Al ³⁺)
Human Serum Albumin	(b) (4)	Stabilizer	0.25 mg	0.5 mg
Sodium Chloride	(b) (4)		1.725 mg	3.45 mg
Disodium Phosphate Dihydrate	(b) (4)		0.110 mg	0.22 mg
Potassium Dihydrogen Phosphate	(b) (4)		0.0225 mg	0.045 mg
Sucrose	(b) (4)		max 7.5 mg	max. 15 mg
Formaldehyde	(b) (4)		Max 2.5 µg	Max 5 µg
Protamine sulfate	(b) (4)		Max 0.25 µg (traces)	Max 0.50 µg (b) (4)
Neomycin	(b) (4)		Trace	Trace
Gentamicin	(b) (4)		Trace	Trace

Water for injection	(b) (4)				
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Abbreviation: (b) (4)

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

The DP contains the active ingredient, which is a sterile, non-pyrogenic suspension of formaldehyde-inactivated and sucrose gradient purified TBE virus harvest (b) (4) and excipients that are widely used in the manufacturing process of vaccines (see above Table 26).

3.2.P.2.1.1 Drug Substance – (b) (4)

3.2.P.2.1.2 Excipients– Excipients include (b) (4) of Disodium Phosphate Dihydrate, (b) (4) of Potassium Dihydrogen Phosphate, (b) (4) of Sodium Chloride, (b) (4) of Human Serum Albumin as a stabilizer, (b) (4) (Al³⁺) Aluminum Hydroxide as adjuvant. Disodium Phosphate Dihydrate and Potassium Dihydrogen Phosphate are (b) (4)

The concentration of the excipients has been found effective during the wide-spread use of the vaccine and has also been corroborated in large-scale pivotal clinical trials.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

In the initial vaccine, the virus seed inoculum was prepared by passage of the master virus seed into mouse brain. The final filled vaccine contained human albumin as a stabilizer and thiomersal as a preservative.

The TBE vaccine that was investigated in clinical trials from 1993 to 1997, contained antigen derived from chick embryo cell (b) (4) (chick-chick (CC) derived production virus). There were no other changes to the vaccine formulation process compared to the initial vaccine.

In the subsequent CC TBE vaccine, the preservative thiomersal was omitted. The omission of thiomersal was originally evaluated in the clinical trial IMAG 062, where the FSME-IMMUN CC TBE vaccine with, and without, thiomersal was first evaluated against the initial TBE (working virus seed propagated in a mouse brain system) vaccine. It should be noted that omission of the preservative (thiomersal) was encouraged both in the Monograph for TBE Vaccines (European Pharmacopoeia 1999/1375, TBE vaccines and European Pharmacopoeia 1998/0153 vaccines for

human use) as well as by various regulatory agencies during licensing of the vaccine. At this stage, it was also decided to reduce the vaccine formulation to its essential components, leading to the removal of the stabilizer (human serum albumin, HSA). However, administration of this thiomersal-free and HSA-free vaccine during the 2000 vaccination season resulted in increased fever reactions, particularly in children below the age of three years. Subsequent research supported the conclusion that the increased reactogenicity of the vaccine was linked to the absence of HSA. This study showed that the presence of HSA in the vaccine prevents a rise in pro-inflammatory cytokines, which are associated with induction of fever. The vaccine formulation was consequently modified to contain HSA at a concentration of (b) (4).

The current formulation of FSME-IMMUN 0.5 mL vaccine is identical to the CC TBE vaccine but without thiomersal that was included in the large-scale pivotal clinical trial (IMAG 062).

Following the licensure of FSME-IMMUN 0.5 mL for adults (2.4 µg antigen) in 2001, a pediatric vaccine with a reduced amount of antigen (half the adult dose: 1.2 µg antigen/0.25 mL) was developed in collaboration with the Austrian Health Authority and the Austrian Vaccination Council. Based on clinical study results and post-marketing surveillance, the 0.25 mL dose was licensed in Austria in December 2001 under the name FSME-IMMUN 0.25 mL Junior for all three vaccination doses in children aged 1-16 years. For pediatric use, the composition and primary container of FSME-IMMUN 0.25 mL is identical to that of FSME-IMMUN 0.5 mL with the sole exception that the FSME-IMMUN 0.25 mL vaccine is filled with half the volume. Thus, the pharmaceutical development and the production process up to the (b) (4) vaccine is identical, the only difference being the filling amount.

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) µg antigen per mL. There are no significant losses during the formulation process or on stability.

3.2.P.2.2.3 Physicochemical and Biological Properties– All analytical tests for biological, immunological, and physico-chemical characterization are performed on each vaccine lot.

3.2.P.2.3 Manufacturing Process Development

Background: The initial vaccine was Baxter FSME-IMMUN inactivated tick-borne encephalitis (TBE) virus vaccine, developed in the 1970s by Baxter, Vienna, which is no longer a registered DP manufacturing site for FSME-IMMUN. The development of the vaccine is discussed in detail in 3.2.P.2.2. A detailed tabular overview on the formulations used during clinical trials for FSME-IMMUN 0.5 mL is provided in Section 3.2.P.2.3-1. In addition, for each DP lot used, the DS batches from which the DP lots were derived, use of the DP, the DP dose, DP and DS manufacturing site and the (b) (4) used in DS manufacture are listed in Section 3.2.P.2.3-2. All DP lots used in the clinical studies were commercial lots. A detailed tabular overview on the

formulations used during clinical trials for FSME-IMMUN 0.25 mL is provided in Table 3.2.P.2.3-3 and Table 3.2.P.2.3-4 of the submission.

The FSME-IMMUN DP manufacturing process has since been transferred from the registered manufacturing site at Baxter, Vienna to the manufacturing site at Pfizer, (b) (4). The manufacturing process is shown in Figure 3.2.P.2.3-1 of the submission and summarized in 3.2.P.3.3 of this memo.

Main manufacturing process changes since manufacturing at Pfizer, (b) (4) affected the following activities: manufacturing site, (b) (4)

Processing and storage times. Section 3.2.P.2.3. (Table 3.2.P.2.3-1 of submission) provides a comprehensive comparison of the changes to the manufacturing process between the two sites. To support these changes and the transfer to Pfizer, (b) (4) FSME-IMMUN development lots were manufactured at Pfizer, (b) (4) using commercial scale equipment. (b) (4) of the formulated development lots were subsequently filled as both FSME-IMMUN 0.5 mL and FSME-IMMUN 0.25 mL. (b) (4) formulated development lot was filled completely as FSME-IMMUN 0.25 mL. The effect of each change on product quality was evaluated. The results from the DP development lots at Pfizer (b) (4) demonstrate that:

- The (b) (4) calculation does not affect the final product composition
- The preparation of a (b) (4) is effective and does not impact the product quality attributes
- The (b) (4) process of DS is effective and has no impact on DP quality attributes
- The sterile filtration of the (b) (4) is effective
- (b) (4) is effective without impacting the quality of the product
- The (b) (4) of aluminum hydroxide is effective
- (b) (4) is effective
- The final bulk vaccine meets all in-process criteria
- (b) (4) filling are effective
- The filling process is effective and demonstrated consistent quality attributes and (b) (4) throughout filling
- Process parameters and holding times for the FSME-IMMUN manufacturing process which result in a DP that meets the in-process acceptance criteria and release specifications were successfully defined.

A summary report about these changes is provided in Section 3.2.P.2.3 and a process control strategy is described in Section 3.2.P.2.3.2 of the submission.

3.2.P.2.4 Container Closure System

The primary container closure system of FSME-IMMUN vaccine consists of syringe barrels (1 mL (b) (4) borosilicate glass), polystyrene plunger rods, rubber plunger stoppers (latex-free bromobutyl chlorobutyl) and tip caps (latex-free isoprene bromobutyl rubber). The glass meets the (b) (4) requirements, including (b) (4) requirements. The rubber stopper and the tip-cap meet (b) (4) requirements for physicochemical testing for elastomeric closures. The tip cap and plunger stopper are provided sterile, clean and ready-to-use from the component manufacturer. The plunger stopper and tip cap rubber insert elastomers comply with (b) (4). In addition, both components meet specified requirements for (b) (4) levels and are not manufactured from dry natural rubber (latex). The plunger rod is a component of the delivery device with limited duration of skin contact (b) (4). The component manufacturer certifies the plunger rod fulfills the biological requirements of (b) (4) including (b) (4). The barrel is classified per (b) (4) as an Externally Communicating Device, Circulating Blood, Limited Duration of Contact (b) (4).

(b) (4) Glass Vials are tested for (b) (4), visual inspection, dimensional checks, and functional checks. Tests for stopper are: Physicochemical, Visual inspections, and Dimensional checks. Tests for the cap are: Visual inspections, Dimensional checks, and Functional checks.

3.2.P.2.5 Microbiological Attributes

The FSME-IMMUN DP is presented in prefilled syringes as a single dose sterile suspension which contains no antimicrobial preservative. Product sterility and stability were demonstrated through the stability programs (3.2.P.8.1 Stability Summary and Conclusion). The integrity of the syringe container closure systems was demonstrated by (b) (4) studies performed with syringes filled at Pfizer (b) (4). Both combinations of the barrels (b) (4) tip cap (b) (4) and plunger stopper (b) (4) have been tested by (b) (4) testing. All syringes tested were (b) (4).

3.2.P.2.6 Compatibility

The compatibility of FSME-IMMUN with the container closure system was determined based on the formal stability studies detailed in 3.2.P.8.3 Stability Data – Baxter, Vienna and 3.2.P.8.3 Stability Data – Pfizer, (b) (4). In both stability studies, FSME-IMMUN quality attributes remained within established specifications during storage at the recommended storage conditions of 5 ± 3 °C.

Overall Reviewer's Assessment of Section 3.2.P.2:

- Because TICOVAC is supplied as a pre-filled borosilicate glass syringe with rubber tip cap (needle is supplied by the end user), CBER submitted an ICCR (# 00058730) on 02/01/2021 to CDRH. The ICCR supplied information on Section

3.2.P.7 Container Closure and 3.2.P.1 Description and Composition of the Drug Product to CDRH. Since the sponsor cross referenced the following DMFs (LOAs in 1.4.2) for the syringe components: (b) (4) (tip cap), (b) (4) (tip cap), (b) (4) (tip cap), (b) (4) (plunger rod), (b) (4) (plunger stopper), (b) (4) (barrel), (b) (4) (barrel), all of which reside in CDER's databases. The stability information in 3.2.P.8 does not appear to include any syringe-related specifications. CBER requested CDRH to review and provide a recommendation on whether the syringe constituent information is adequate to support approval of the BLA. Please note the device cGMPs and syringe sterilization validation are being reviewed by CBER/OCBQ/DMPQ. Shawn Shermer, FDA/OC/CDRH/OPEQ/OHTIII/DHTIIC, reviewed the container closure system and identified three major deficiencies. On June 10, 2021, Pfizer provided a response to this IR (dated 06/03/2021) and a second ICCR (ICCR# 00723776) was submitted to CDRH. The response was reviewed by Sreya Tarafdar (OPEQ/OHT3/DHT3C) and was deemed acceptable. For details, please refer to memos from CDRH.

The information provided is adequate.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Pfizer (b) (4)

Responsibilities: Quality Control Testing

- (b) (4) Formaldehyde
- Content
- Antigen Content
- Extraneous Agents
- Sucrose Content
- Potency
- (b) (4)
- Sterility

Pfizer (b) (4)

Responsibilities: Formulation and Filling (Primary Packaging)

Labelling and Secondary Packaging

Quality Control Testing

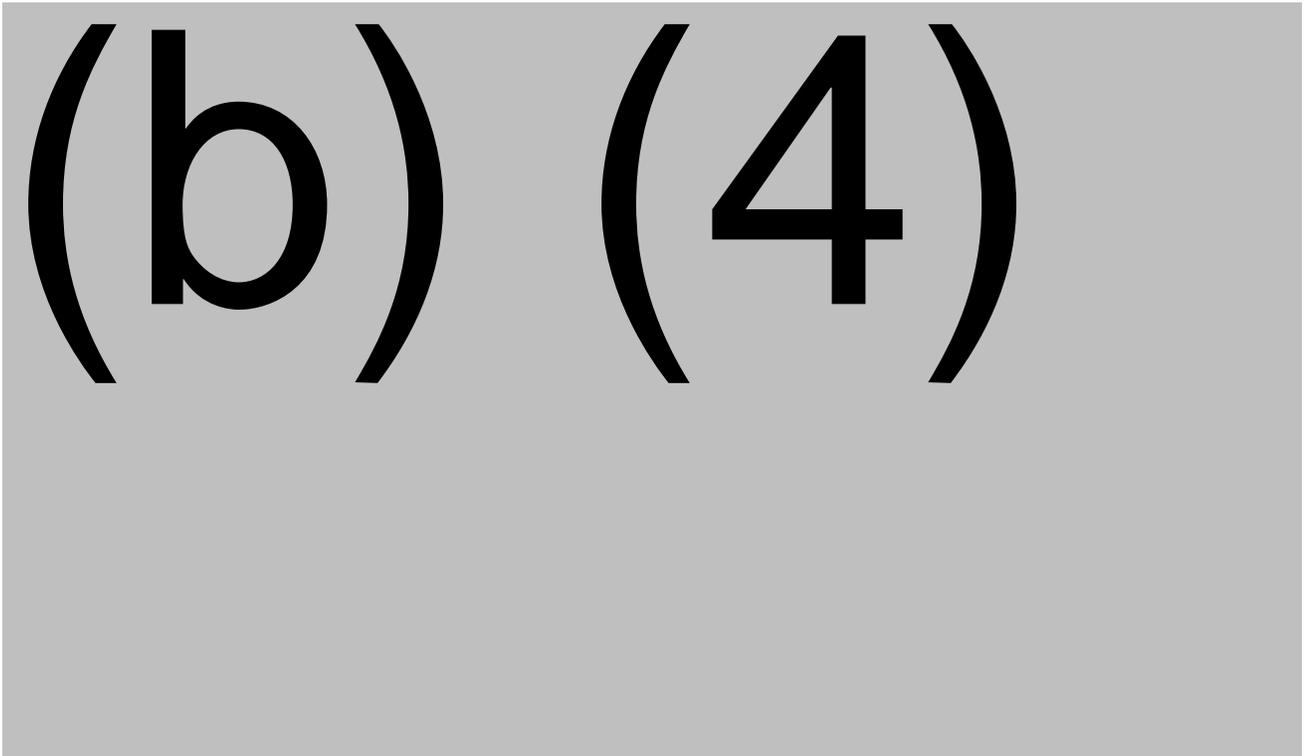
- Sterility
- Protein Content
- (b) (4)

- Endotoxin
- Sodium Content
- (b) (4)
- Aluminum Content
- Identity
- Extractable Volume
- Visual Inspection

(b) (4)

3.2.P.3.2 Batch Formula

Preparation of FSME-IMMUN 0.25 mL and 0.5 mL presentations involves the formulation of the FSME-IMMUN^{(b) (4)} lot with the formula shown in Tables 27 &28.



(b) (4)

(b) (4)

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:

- The information provided is adequate.

3.2.P.3.3 Description of Manufacturing Process

The manufacturing of DP involves adjuvating the ^{(b) (4)} (formaldehyde-inactivated, sucrose gradient purified TBE-virus antigen) with aluminum hydroxide in a solution of phosphate buffered saline and human serum albumin (HSA). (b) (4)

The filled syringes are inspected and stored at $5 \pm 3^\circ\text{C}$ until secondary packaging, release and shipping. A flow chart of the Manufacturing Process is shown below:

(b) (4) → [redacted] → Filling → Visual inspection, labeling and packaging

Overall Reviewer's Assessment of Section 3.2.P.3.3:

- The information provided is adequate.

3.2.P.3.4 Controls of Critical Steps and Intermediates

The sponsor has identified^{(b) (4)} critical steps during manufacturing of DP (b) (4) [redacted] and established in-process control tests as well as in-process monitoring during filling. 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-process control and in-process monitoring tests for Critical Manufacturing Steps are shown in Table 29 and Table 30.

Table 29 – DP in-process controls

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.P.3.5 Process Validation and/or Evaluation

(b) (4)

[Redacted content]

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

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.3:

- The information provided is acceptable.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

Excipients used for FSME-IMMUN DP include Disodium Phosphate Dihydrate, Potassium Dihydrogen Phosphate, (b) (4), Sodium Chloride, Human Serum Albumin (HSA), Aluminum Hydroxide and comply with the (b) (4) with specifications indicated in Table 36. The excipients are accepted by Pfizer based on a certificate of analysis from a qualified supplier. Additional excipient testing is performed in accordance with the (b) (4) Pfizer, including (b) (4) Disodium Phosphate Dihydrate, (b) (4) for Sodium Chloride, (b) (4) for Potassium Dihydrogen Phosphate, and (b) (4) for aluminum hydroxide.

Table 36 (adapted from Table 2.3.P-2) – FSME-IMMUN Drug Product Excipients

Excipient	Concentration	Function
Disodium Phosphate	(b) (4)	Disodium Phosphate Dihydrate and Potassium Dihydrogen Phosphate are buffering agents ^{(b) (4)}
Potassium Dihydrogen	(b) (4)	
(b) (4)	(b) (4)	
Sodium Chloride	(b) (4)	Sodium Chloride (b) (4)
Human Serum Albumin	(b) (4)	Human Serum Albumin (b) (4)
Aluminum Hydroxide	(b) (4)	(b) (4) Al(OH) ₃ ^{(b) (4)}

Abbreviation: (b) (4)

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

All excipients used in the manufacture of FSME-IMMUN are (b) (4). All analytical procedures used for testing the (b) (4) excipients comply, at a minimum, with (b) (4). Therefore, no additional validation has been performed.

3.2.P.4.4 Justification of Specifications

All excipient specifications comply, at a minimum with the (b) (4). An overview per excipient is provided in 3.2.P.4.1.1 (Table 3.2.P.4-1) of the submission.

3.2.P.4.5 Excipients of Human or Animal Origin

The 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.

Human Serum Albumin (HSA) is added as a stabilizer (b) (4)

[Redacted]

All information about human serum albumin was provided by (b) (4)

3.2.P.4.6 Novel Excipient

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

Overall Reviewer's Assessment of Section 3.2.P.4:

- HSA is derived from plasma sourced from the United States according to the current plasma sourcing guidelines. Donor selection and plasma donation testing is described in the Plasma Master File (b) (4). However, HSA is not licensed in the U.S. Therefore, there was a lot of discussions within OVR on whether we will allow non-US-licensed HSA to be included in the product. In May 2020, Dr. Marion Gruber consulted OBE (Richard Forshee), OCBQ (Mary Malarkey), and OBRR (Nicole Verdun) on the use of HSA. After careful consideration, CBER informed Pfizer that use of non-US licensed HSA in DP of the TBE vaccine is acceptable because plasma was sourced from US donors and it is appropriately tested at a level comparable to the testing performed in US-licensed HAS. The rationale is summarized in the following bullet points:
 - Since early 2003, the plasma used to manufacture the HSA for this vaccine is sourced from US donors

- The source plasma is tested for potential adventitious viruses at (b) (4)
- Non-US Albumin has been used as excipients in previous products such as factor concentrates and a vaccine (use of recombinant HSA)
- OBRR has stated in the past that it is not an expectation that HSA used in excipients or as stabilizers be licensed in the US. The product should be reviewed within the submission. Since the albumin used in the manufacture of FSME-IMMUN is not licensed in the US, the albumin component will be reviewed for its safety and purity as part of the product application, and not as a stand-alone product. The expectation is that the albumin would be manufactured under cGMP conditions and is well characterized.

The information provided is acceptable.

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)

Release specifications for (b) (4) final DP are shown in Tables 37, 38 and 39, respectively.

Table 37 – Drug Product Specifications, (b) (4)

(b) (4)

(b) (4)

Table 39 – Drug Product Specifications, Final Drug Product

Quality Attribute	Analytical Procedure	Acceptance Criteria	
		Release	Stability
Identity	(b) (4)	Identity Confirmed	Not Performed
(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)	Complies ^a	Complies ^a
Endotoxin	(b) (4)	(b) (4)	Not Performed
Potency (b) (4)	(b) (4)	N/A ^b	Potency (b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

a. Complies: no extraneous matters, after shaking the vaccine is an off-white, homogenous, opalescent suspension

b. The potency (b) (4) is only determined as part of product stability testing

c. (b) (4)

For each quality attribute (QA), a validated analytical procedure along with corresponding acceptance criteria for FSME-IMMUN DP was historically established and approved. The specifications of (b) (4) final DP, are set to ensure the quality, purity, potency and safety of the commercial DP at release and across the product shelf life of 30 months at the recommended storage temperature of 2-8°C.

The acceptance criteria for each QA were developed based on regulatory guidelines, clinical experience, historical release data obtained from commercial DP lots, stability data, and manufacturing experience at commercial scale. Specifically, all tests required

by the (b) (4) for Tick Borne Encephalitis (TBE) vaccine (inactivated) are performed. The specifications are justified based on (b) (4) requirements for the following tests: appearance, endotoxins, extractable volume, extraneous agents, (b) (4) formaldehyde content, identity, sodium content, sterility and aluminum content. Clinical experience was used to evaluate acceptance criteria for aluminum content, (b) (4) and (b) (4). Historical data was used to evaluate the acceptance criteria for (b) (4) protein content (b) (4). Stability data were evaluated for (b) (4), appearance, sterility, and potency (b) (4). Manufacturing experience and process knowledge at commercial scale were used to determine acceptance criteria for potency, (b) (4) sucrose content.

In order to set the release acceptance criteria of final (b) (4) vaccine, the sponsor evaluated results from (b) (4) process validation lots, (b) (4) confirmatory lot, (b) (4) clinical lots, and (b) (4) commercial lots, that were manufactured between June 2006 and June 2020 (Table 3.2.P.5.6-1). Of note, (b) (4) process validation lots and (b) (4) confirmatory lot were manufactured at Pfizer (b) (4) and the rest were all manufactured at (b) (4).

For justification of the stability specifications, the sponsor evaluated (b) (4) final DP lots, including (b) (4) Process Validation lots (b) (4) manufactured at Pfizer (b) (4) confirmatory lot (manufactured at Pfizer (b) (4) clinical lots and (b) (4) commercial lots. Stability data for these lots are available for 3- (b) (4) months.

For those QAs that have a clear (b) (4) requirement, such as (b) (4) formaldehyde content, the acceptance criterion by the sponsor meets or is more stringent than the (b) (4) requirement. The acceptance criteria of other specifications are justified based on the capability and consistency of the manufacturing process.

Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:

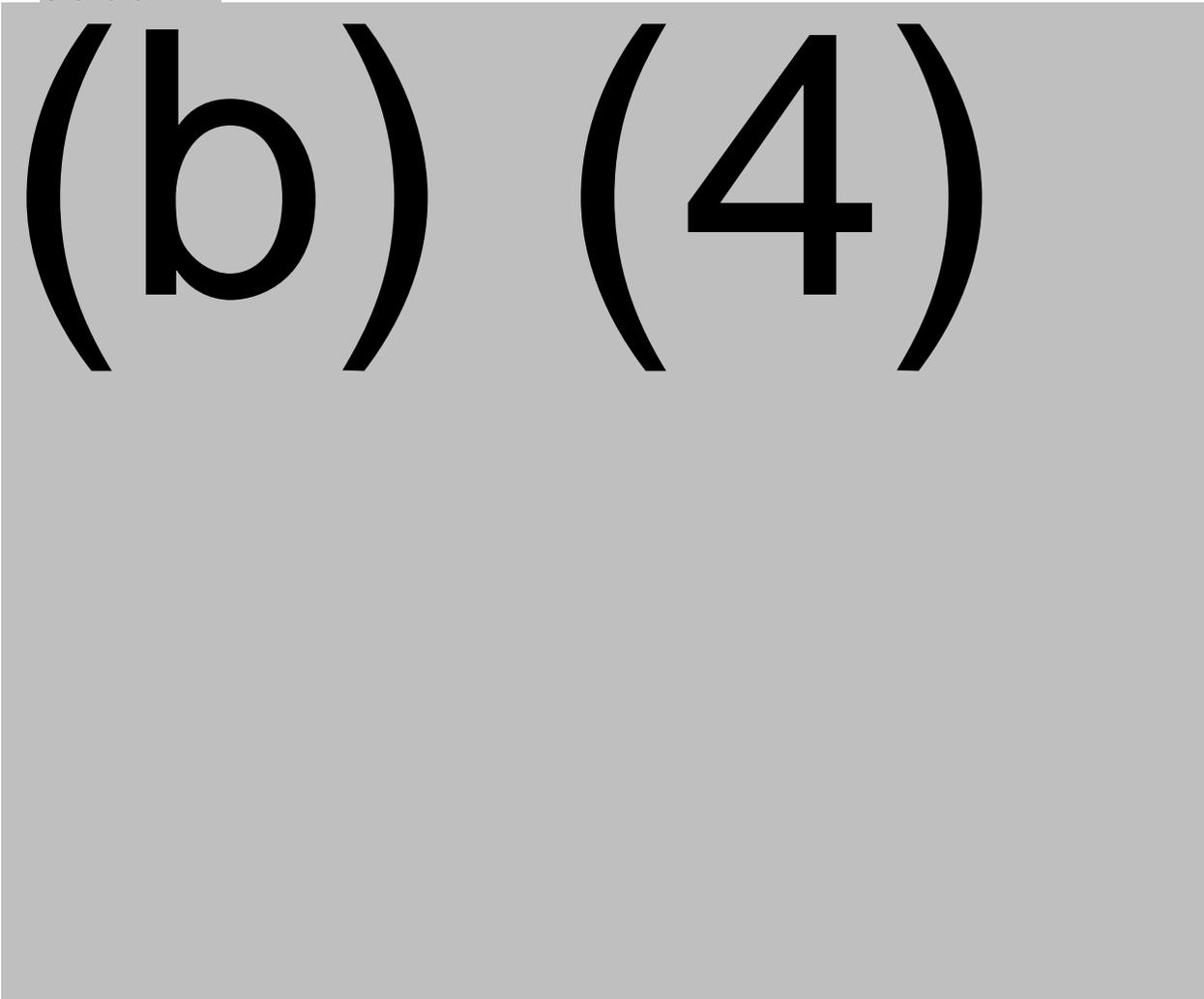
- We previously asked the sponsor to clarify how the Potency (b) (4) relates to antigen content over the proposed shelf life. The sponsor answered that FSME-IMMUN potency is determined at the process stage (b) (4). For preparation of the (b) (4), the (b) (4). Consequently, the (b) (4) is not possible. Thus, TBE (b) (4) quantification is not part of the stability testing program of the Final (b) (4) Vaccine. Consequently, a relation of TBE (b) (4) and potency over the DP shelf life cannot be determined.
- The information provided is adequate.

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

DBSQC reviewers, including Anil Choudhary (AC), Simleen Kaur (SK), Hsiaoling Wang (HW), reviewed lot release tests and method validations for the tests of DP as shown in Table 40.

Table 40 – DP Analytic testing reviewer assignments

(b) (4)



c. Final Drug Product

Test	Analytical Method	Reviewer(s)
Identity	(b) (4)	DBSQC-AC
Sterility	(b) (4)	DBSQC-SK
Extractable volume	(b) (4)	DBSQC-HW
Visual Inspection	(b) (4)	DBSQC-HW
Endotoxin	(b) (4)	DBSQC-SK

The following descriptions are my assessment on these analytic procedures from a product reviewer’s perspective. The procedures listed in Table 41 have been validated according to the relevant (b) (4). The validation/verification studies for the following analytical procedures are documented in

Section 3.2.P.5.3 Validation of Analytical Procedures: sterility, ^{(b) (4)} formaldehyde content, (b) (4), extraneous agents, protein content, (b) (4), endotoxin, sodium content, ^{(b) (4)}, sucrose content, aluminum content, potency, identity, (b) (4) extractable volume and visual inspection.

Table 41 – Analytical Procedures (Detailed procedures described in Section 3.2.P.5.2)

Test	Principle
(b) (4)	(b) (4)
Extraneous Agents	(b) (4)
Protein Content	(b) (4)
(b) (4)	(b) (4)
Endotoxin	(b) (4)

Sodium Content	(b) (4)
Sucrose Content	(b) (4)
Aluminum Content	(b) (4)
Potency	(b) (4)
Identity	(b) (4)
Extractable Volume	(b) (4)
Visual Inspection	(b) (4)

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:
 The information provided is adequate.

3.2.P.5.4 Batch Analyses
Batch Analyses – (b) (4)

Pfizer provided an overview of all batch analysis data from (b) (4) FSME-IMMUN lots produced since 1996 (Table 3.2.P.5.4-1 of the BLA) by (b) (4), which is no longer a registered DP manufacturing site for FSME-IMMUN 0.5 mL and 0.25 mL suspension for injection in pre-filled syringe. The data listed in this section is maintained for historical and supportive information on the product quality. Notably, Pfizer provided the (b) (4) and potency (in %) for these (b) (4) lots. The acceptance criteria are (b) (4) for Potency. The batch data met these specifications. The potency ranges from (b) (4) among those lots. From 1996 onward all lots were manufactured from (b) (4) FSME-IMMUN Junior was first manufactured in 2001. Also, batch data provided in Table 3.2.P.5.4-1 prior to FSME-IMMUN Final (b) (4) Vaccine (b) (4) correspond to batches manufactured using Human Serum Albumin (b) (4). Again, HSA (b) (4) is no longer used, but the batch data is maintained for historical purposes.

Pfizer then provided full batch data of (b) (4) consecutive (b) (4) vaccine lots (b) (4) along with filling indices (0.5 mL and 0.25 mL). Detailed records of these (b) (4) lots, including information on the DS batches used for manufacturing these lots (e.g. (b) (4) information on the final products (e.g. batch No., filling date, size, amount) are provided in Section 3.2.P.5.4.1.1 of the submission. Pfizer also provided results of all tests performed from DS to final DP of these (b) (4) lots. Examination of the records confirms that all test results met the criteria of all specifications.

Pfizer then provided batch analyses data of (b) (4) lots (b) (4) that were manufactured in a 2011 campaign. Testing results from the (b) (4) (b) (4) Final Drug Product of these (b) (4) lots are presented in Tables 3.2.P.5.4-34 to Table 3.2.P.5.4-38. Again, all acceptance criteria were met.

To demonstrate the consistency of the manufacturing process, comparative batch analysis data from the currently approved manufacturing site (b) (4) and the de-commissioned manufacturing site (b) (4) are provided in Tables 3.2.P.5.4-40. To Table 3.2.P.5.4-43 of Section 3.2.P.5.4.1.3 of the submission. (b) (4) lots manufactured in each site were tested and compared. The results met acceptance criteria.

Additionally, Pfizer provided batch analyzes data of (b) (4) lot filled in Tip Cap (b) (4). The data show that the product filled in the pre-filled syringes with Tip Cap meets the DP specification (Section 3.2.P.5.4.1.4 of the submission).

Lastly, to support the introduction of Human Serum Albumin (b) (4) (HSA (b) (4) FSME-IMMUN (b) (4) was formulated with (b) (4) HSA (b) (4) Batch (b) (4)

was filled into (b) (4) Final Drug Product Batches (Indices (b) (4) Batch Analysis Data for (b) (4) Vaccine are presented in Table 3.2.P.5.4-47 and Table 3.2.P.5.4-48, respectively, of the submission. Batch Analysis Data for Final Drug Product are presented in Table 3.2.P.5.4-49, of the submission. All results meet the acceptance criteria for (b) (4) Final Drug Product testing. To follow up, the first (b) (4) commercial FSME-IMMUN (b) (4) vaccine lots manufactured using HSA (b) (4) (See genealogy in Table 3.2.P.5.4-50 of the submission) were filled into (b) (4) final DP lots. Batch analysis data for (b) (4) are presented in Table 3.2.P.5.4-51 and Table 3.2.P.5.4-52, respectively, of the submission. Batch analysis data for final DP are presented in Table 3.2.P.5.4-53 to Table 3.2.P.5.4-55 of the submission. All results meet the acceptance criteria for (b) (4) final DP testing.

Batch Analyses - Pfizer (b) (4)

In order to support the transfer of DP manufacturing into Pfizer, (b) (4) process validation lots and (b) (4) confirmatory lot were manufactured. Table 42 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 Tables 43-45. All results are within the pre-defined acceptance criteria.

Table 42 (adapted from Table 3.2.P.5.4-56) – FSME-IMMUN lots 0.5 mL and 0.25 mL Manufactured at Pfizer, (b) (4)

(b) (4)

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

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.5.4:

- The information provided is acceptable.

3.2.P.5.5 Characterization of Impurities

The sponsor listed the estimated amount of (b) (4) formaldehyde (b) (4) in the table of composition of the DP (see Table 26). One component that is not included in the table is the chick/egg protein. In a prior communication addressed by the sponsor in 2019 (page 245 of Section 1.6.3 Correspondence Regarding Meetings attached in the submission), in response to Question 7.d Pfizer stated that based on the (b) (4) results from (b) (4) lots (b) (4) into which (b) (4), it could be assumed that a very low amount of chicken protein is present in the final product (detection limit (b) (4) of protein detected by (b) (4) In a worst-case scenario, the hypothetical value of chick protein in a vaccination dose is (b) (4) vaccine. We requested that Pfizer include this theoretical value in the prescribing information. The clinical review team agreed that this information should be included in the package insert (Please see details under Module 1 Labeling).

Overall Reviewer's Assessment of Section 3.2.P.5:

- The information provided is acceptable.

3.2.P.6 Reference Standards or Materials

Table 46 lists all sources of standards which are used for the respective tests.

Table 46 (adapted from Table 3.2.P.6-1) – Reference Standards and/or Material

(b) (4)

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

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.6:

- The information provided is acceptable.

3.2.P.7 Container Closure System

Please also refer to review of 3.2.P.2.4.

Overall Reviewer's Assessment of Section 3.2.P.7:

- The information provided is acceptable.

3.2.P.8 Stability

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

FSME-IMMUN 0.5 ml and FSME-IMMUN 0.25 ml Junior have an assigned shelf life of 30 months when stored at 5 ± 3 °C. In support of this claim, stability information for FSME-IMMUN DP stored under the recommended long-term condition of 5 ± 3 °C, the accelerated condition of (b) (4) conditions were provided.

Primary stability studies have been completed at (b) (4). Supportive studies have also been completed at (b) (4) and are ongoing at Pfizer, (b) (4). Primary stability refers to the formal stability studies from which stability data are submitted for the purpose of establishing a shelf life. Supportive stability refers to additional data relevant to product stability and shelf-life support. The (b) (4) is not stored but is (b) (4). Therefore, no long-term stability testing is performed on the (b) (4).

Primary stability studies include studies on long-term storage condition, (b) (4). For primary stability study of long-term storage of DP, at the recommended temperature of 5 ± 3 °C, the shelf life is 30 months. This shelf-life claim is based on completed and ongoing stability study of (b) (4) lots of FSME-IMMUN 0.5 mL (b) (4) and (b) (4) lots of FSME-IMMUN 0.25 mL Junior (b) (4) Tip Cap) at the recommended storage condition (Section 3.2.P.8.1.3). Of note, FSME-IMMUN (b) (4) is no longer manufactured, however, the information is provided for historical purpose. Among the FSME-IMMUN 0.5 mL lots, (b) (4) lots were produced from (b) (4) lots were produced from chick-chick (CC) derived working virus seed. The stability studies show that there is no difference in stability between

syringes containing 0.5 ml and syringes containing 0.25 ml. Test results met the commercial specification. Stability data obtained from (b) (4) lots of FSME-IMMUN 0.5 mL (b) (4) under accelerated storage temperature condition of (b) (4)

(b) (4) were also presented in support of the shelf life (Section 3.2.P.8.3 Stability Data – (b) (4) The potency (b) (4) was within the specification (b) (4)

Lastly, a study was conducted to evaluate whether (b) (4) vaccine would influence potency of the vaccine. The potency of the (b) (4) did not differ significantly from that stored at 5 ± 3 °C.

Supportive stability studies (Section 3.2.P.8.1.5 of the submission) include information in support of the introduction of a (b) (4) into the filling process (3.2.P.8.3 of the submission), alternative primary packaging material – Plunger Stoppers and Tip Cap (3.2.P.8.3) and alternative manufacturing site for formulation and filling and batch size increase. Additionally, to support the introduction of HSA (b) (4) FSME IMMUN (b) (4) was formulated using (b) (4)

HSA (b) (4) was filled into (b) (4) Final Drug Product batches (Indices (b) (4)

A FSME-IMMUN 0.25 mL Junior (b) (4) batch was placed on stability for (b) (4) months at routine storage conditions of 5 ± 3 °C. The batch met stability specifications except for (b) (4) out of specification (OOS) result for sterility testing at the 24 months testing time point. An investigation (PR#2387041) could not identify an assignable root cause. A contamination during test sample transport and/or testing preparation was determined to be the most probable root cause. The impact of the OOS result for sterility on stability study for FSME-IMMUN Junior lot (b) (4) was evaluated and excluded.

Finally, (b) (4) process validation lots manufactured at commercial scale at Pfizer, (b) (4) were enrolled in a stability study at long-term, accelerated, (b) (4) conditions. An (b) (4) (referred to as the confirmatory lot) was manufactured at Pfizer, (b) (4) and enrolled on a long-term stability study and (b) (4) study.

Analytical data for all DP lots stored at the recommended conditions of 5 ± 3 °C were provided. Data for up to 24 months were provided for (b) (4) lot and for up to 18 months were provided for the other (b) (4) process validation lots. Data for up to 3 months were provided for the confirmatory lot (Section 3.2.P.8.3 of the submission). All test results met specifications. In addition, all data remain within the stability acceptance criteria in the following studies:

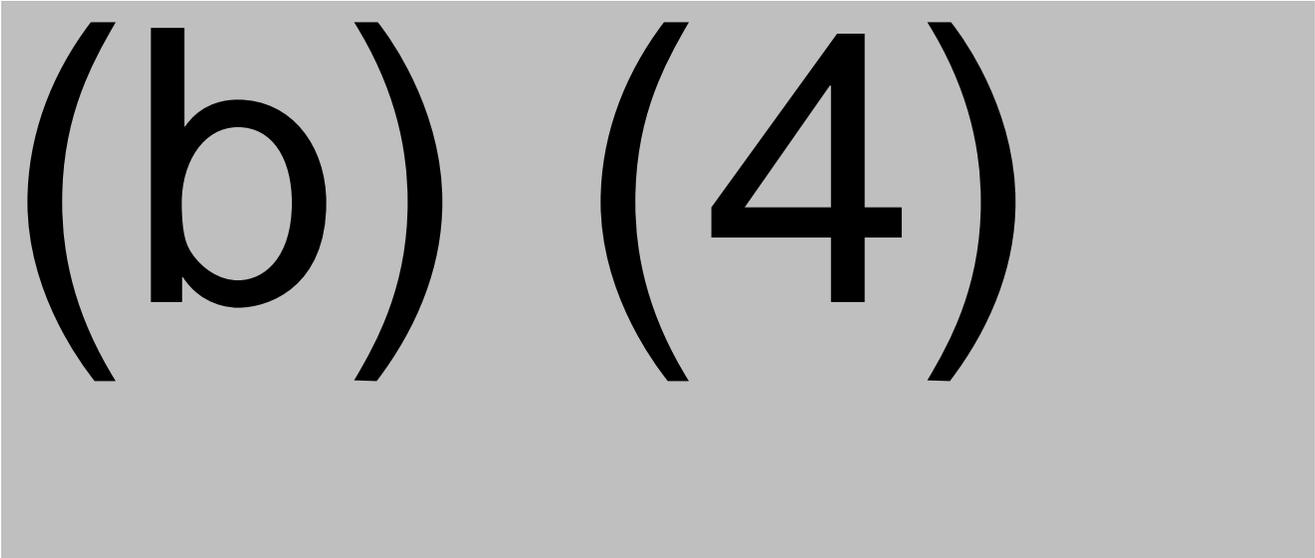
- Accelerated stability study: (b) (4)

Therefore, the product should be kept in its original secondary packaging in order to be protected from light.

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

Pfizer committed to place a minimum of (b) (4) lot of DP in the commercial stability program at the long-term storage condition of 5 ± 3 °C each year that DP is manufactured. The protocol is provided in Table 48 at the long-term storage conditions of 5 ± 3 °C.

Table 48 – Long-term storage conditions



Overall Reviewer’s Assessment of Section 3.2.P.8:

- The following information request was previously issued on September 4, 2019 (when reviewing MF(b) (4)) regarding the Potency acceptance criteria in the long-term stability plan: “regarding the post approval stability protocol and stability commitment for the final DP, we note that an acceptance limit was included for Potency (b) (4) but not for Potency (b) (4)”. Please provide a lower limit for Potency that is supported by data from manufacturing and clinical experience”. Pfizer responded in December 2019 that the potency (b) (4) was set up as an attribute which characterizes the vaccine behavior over time. The acceptance limit was established based on a total of (b) (4) FSMEIMMUN lots that were produced between 1986 and 1991. Each of those lots was subjected to at least (b) (4) potency tests over a period of at least (b) (4) months, as described in Section 3.2.P.8.1 of MF(b) (4). The logarithm of the potency of each stability timepoint was compared to the timepoint (b) (4). These (b) (4) showed a (b) (4). Thus, the acceptance limit for the (b) (4) was set to (b) (4). Pfizer further noted that FSME-IMMUN potency is determined at the (b) (4).

(b) (4). Hence, (b) (4) quantification is not part of the stability testing program of the (b) (4). Instead, an acceptance limit was included for Potency (b) (4) but not for Potency because a relation of (b) (4) (b) (4) over the Drug Product shelf life cannot be determined.

- The information provided is acceptable.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

I did not review this section.

3.2.A.2 Adventitious Agents Safety Evaluation

To control the potential entry of adventitious agents into the production stream of the vaccine, viral and non-viral contamination has been assessed through the following approaches: a) the engineering systems of the facility and vessels, b) the control of the starting and raw materials used in the process, c) 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.

Pfizer uses ingredients of animal or human origin in the preparation of the vaccine. All product steps and ingredients are controlled according current cGMP principles. Raw materials of biological origin in (b) (4) manufacturing have been assessed in Section 3.2.A.2. Human serum albumin is used in the formulation of the DP. In summary, Pfizer provided the following information on characterization of adventitious agents:

- (b) (4)
- Documentation of raw materials testing
- (b) (4)
- Justification of deviations from testing currently recommended by CBER
- Source of origins of HSA (b) (4)

Of note, information on adventitious agents was not available such as virus seed testing done in 1983 at the (b) (4) and hence Pfizer included a risk analysis for viral seeds (Section 3.2.A.2.2.2.). Historically, adventitious agents testing of (b) (4) was performed in 1983 at the laboratories of (b) (4).

For both (b) (4) not all raw data will be retrievable. For example, Pfizer acknowledged that (b) (4)

However, (b) (4) Chick Embryo Cell (CEC) culture derived from (b) (4). Since then, Pfizer established consistency in the manufacturing process of (b) (4). Testing for (b) (4) is no longer needed because the viruses likely do not grow on (b) (4)

Details regarding the (b) (4) and

(b) (4) viral seeds have been reviewed in Section 3.2.S.2.3. In brief:

- (b) (4)
-
-

Besides, a detailed adventitious agents safety evaluation for materials of animal or human origin (i.e., (b) (4) protamine sulfate, (b) (4), human serum albumin (HSA), (b) (4), Polyethylene Terephthalate bottle) including their sources and preparations used in the manufacturing process is given in Section 3.2.A.2.2. Among those, HSA is added as a stabilizer (b) (4) final DP. HSA (b) (4) and has been validated for use in the formulation of FSME-IMMUN. HSA is derived from plasma sourced from the United States according to the current plasma sourcing guidelines. Donor selection and plasma donation testing is described in the Plasma Master File

(b) (4) Source plasma is tested for potential presence of the following viruses at three stages: antibody tests for HBV, HIV-1/2, and HCV; nucleic acid amplifying tests for HAV, HBV, HCV, HIV-1/2 and Parvovirus (b) (4). Only pools non-reactive for HIV, HAV, HBV, HCV and not exceeding the limit of Parvovirus B19 are accepted for further manufacturing. Baxter further investigated in (b) (4) laboratory studies the (b) (4)

(b) (4) HAS (b) (4) excipient, i.e. (b) (4)

The following Table summarizes virus reduction factors achieved by steps (b) (4) HSA (b) (4) (See section 3.2.A.2.3.1.4.3 of the submission).

Table 49 – Virus Reduction Factors for HSA (b) (4)

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

(b) (4)

[Redacted]

[Redacted]

[Redacted]

Overall Reviewer's Assessment of Section 3.2.A.2:
 The information provided is acceptable.

3.2.A.3 Novel Excipients

No novel excipients are used for the formulation of the vaccine.

3.2.R Regional Information (USA)

Executed Batch Records

The executed batch records are normally reviewed during the pre-approval inspection. Due to the COVID-19 pandemic and travel restriction, CBER requested a record review and Pfizer provided all relevant records in BLA AMENDMENT 125740/0/16. Jie He from DMPQ and I jointly reviewed the records and found the information to be acceptable. Details can be found in a joint records review memo.

Method Validation Package

Please refer to sections 3.2.S.4.2.and 3.2.S.4.3 Analytical Procedures and Validation of Analytical Procedures for Drug Substance and 3.2.P.5.2 and 3.2.P.5.3 for Drug Product.

Combination Products

TICOVAC is distributed in a pre-filled syringe (PFS) presentation. The PFS containing TICOVAC is considered as a combination product, and the Center for Device and

Radiological Health (CDRH) was consulted on the acceptability of the PFS. An information request (IR) was communicated to Pfizer with regards to essential performance requirements (dose accuracy/extractable volume, (b) (4) for the device constituent. Pfizer's responses have been reviewed by two CDRH reviewers and found acceptable and adequate. Please refer to review of 3.2.P.2.4.

Overall Reviewer's Assessment of Combination Products Section:

The information provided is acceptable.

Comparability Protocols

None.

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The request is justified as the manufacturing of this product does not significantly alter the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

B. Labeling Review

Full Prescribing Information (PI):

Dosage Forms and Strengths,

The Description in Section 11 of the Product Insert initially stated:

“TRADENAME (tick-borne encephalitis vaccine inactivated) 0.5 mL is a sterile non-pyrogenic suspension of formaldehyde-inactivated and sucrose gradient purified TBE virus antigen (2.4 micrograms target) obtained from chick embryo fibroblast cells (CEF). It is bound to an adjuvant (0.35 mg aluminum hydroxide, (b) (4) and diluted in a buffer system containing human serum albumin (HSA, 0.5 mg). Each 0.5 mL dose also contains 3.45 mg of sodium chloride, 0.22 mg of dibasic sodium phosphate, 0.045 mg of monobasic potassium phosphate, ≤15 mg of sucrose, and water for injection.

TRADENAME (tick-borne encephalitis vaccine inactivated) 0.25 mL is a sterile non-pyrogenic suspension of formaldehyde-inactivated and sucrose gradient-purified TBE virus antigen (1.2 micrograms target) obtained from CEF. It is bound to an adjuvant (0.17 mg aluminum hydroxide, (b) (4) and diluted in a buffer system containing human serum albumin (HSA, 0.25 mg). Each 0.25 mL dose also contains 1.725 mg of sodium chloride, 0.110 mg of dibasic sodium phosphate, 0.0225 mg of monobasic potassium phosphate, ≤7.5 mg of sucrose, and water for injection.”

Comments: In the Warning & Precautions section a warning of allergy “to any vaccine component” is issued. Hence, we asked Pfizer on June 21, 2021 to list all vaccine components, including impurities in Section 11. The suggested language is as follows:

“TICOVAC, Tick-borne Encephalitis Vaccine is a sterile, off-white, homogenous, opalescent suspension for intramuscular injection. TICOVAC is prepared from tick-borne encephalitis (TBE) virus propagated in chick embryo fibroblast (CEF) cells. The harvested virus suspension is inactivated by treatment with formaldehyde, purified by sucrose gradient centrifugation and adsorbed onto aluminum hydroxide. TICOVAC is available in a 0.5 mL adult presentation and a 0.25 mL pediatric presentation.

Each 0.5 mL dose is formulated to contain 2.4 microgram (μg) TBE inactivated virus, 0.5 mg human serum albumin (HSA), 0.35 mg aluminum hydroxide, 3.45 mg of sodium chloride, 0.22 mg of dibasic sodium phosphate, and 0.045 mg of monobasic potassium phosphate. From the manufacturing process, each 0.5 mL also contains formaldehyde ($\leq 5 \mu\text{g}$), sucrose ($\leq 15 \text{ mg}$), protamine sulfate ($\leq 0.5 \mu\text{g}$), chick protein (b) (4) and trace amounts of CEF host cell DNA, Neomycin and Gentamicin. The pediatric 0.25 mL dose of TICOVAC contains the same components as the 0.5 mL dose in half of the quantities.

TICOVAC is formulated without preservatives.”

In a response dated July 6, 2021, Pfizer accepted most recommended changes. However, Pfizer removed the estimated chick protein amount and CEF host cell DNA from the section 11- Description. After a discussion CBER felt that both components should still be included in the package insert because they are potential allergens which are mentioned in Section 4 – Contraindications of the package insert. We asked to revise the language to read “Each 0.5 mL dose is formulated to contain 2.4 microgram (μg) TBE inactivated virus, 0.5 mg human serum albumin, 0.35 mg aluminum hydroxide, 3.45 mg sodium chloride, 0.22 mg dibasic sodium phosphate, and 0.045 mg of monobasic potassium phosphate. From the manufacturing process, each 0.5 mL may also contain formaldehyde ($\leq 5 \mu\text{g}$), sucrose ($\leq 15 \text{ mg}$), protamine sulfate ($\leq 0.5 \mu\text{g}$), chick protein (b) (4) and trace amounts of chick protein and DNA from CEF cells, CEF host cell DNA, neomycin and gentamicin. The pediatric 0.25 mL dose of TICOVAC contains the same components as the 0.5 mL dose in half of the quantities.”

Clinical Studies

Pfizer made a claim in Section 14.1- Immunogenicity that “TICOVAC vaccination induces equivalent titers of TBEV–neutralizing antibodies against European, Siberian, and Far Eastern TBEV strains as documented in healthy adults” and cited a reference that appeared in the Journal of Infectious Diseases, 2011, 203:1556-64 by Orlinger, et.al. After reviewing the paper and a WHO position paper dated June 10, 2011 regarding vaccines against tick-borne encephalitis, we (Tony Wang, Sara Gagneten, Marian Major and Robin Levis) felt that there is good evidence to believe the vaccine will be protective against other TBEV subgroups. However, we recommend removing

this claim from the package insert because the current indication already states “to protect against tick born encephalitis” without specifying a subgroup. We will request a qualification report of the assay that was used in the referenced study if Pfizer insists on including the claim.

Clinical Pharmacology:

Mechanism of Action: Protection against TBE is conferred mainly by TBE virus-neutralizing (NT) antibodies. The effectiveness of TICOVAC was assessed by measuring NT antibodies or total IgG antibody (ELISA) responses resulting in seroconversion after vaccination.

How Supplied:

TICOVAC is supplied in the following strengths and package configurations:

0.5 mL

Pre-filled Syringe, 1 Dose (10 per package) – NDC 0069-0411-10

Pre-filled Syringe, 1 Dose (1 per package) – NDC 0069-0411-01

0.25 mL

Pre-filled Syringe, 1 Dose (10 per package) – NDC 0069-0297-10

Pre-filled Syringe, 1 Dose (1 per package) – NDC 0069-0297-01

The tip cap and rubber plunger of the pre-filled syringe are not made with natural rubber latex.

Storage and Handling:

Upon receipt, store refrigerated at 2°C to 8°C (36°F to 46°F).

Keep the syringe in the outer carton in order to protect from light. Do not freeze. Discard if the vaccine has been frozen.

Carton and Container Label:

The current Carton states: Each 0.5 mL is a sterile non-pyrogenic suspension of formaldehyde-inactivated and sucrose gradient purified TBE virus antigen (2.4 micrograms target). It is bound to an adjuvant (0.35 mg aluminum hydroxide, (b) (4) and diluted in a buffer system containing human serum albumin (HSA, 0.5 mg). Each 0.5 mL dose also contains 3.45 mg of sodium chloride, 0.22 mg of dibasic sodium phosphate, 0.045 mg of monobasic potassium phosphate, ≤15 mg of sucrose, and water for injection.

The tip cap and rubber plunger of the prefilled syringe are not made with natural rubber latex.

See package insert for additional information including dosage and administration.

No Preservative.

Overall Reviewer’s Assessment of Module 1:

- The information provided is acceptable.
- The carton label does not mention residuals such as chick protein. However, this information is included in the prescribing information. The syringe label contains information on expiration date.

Module 4

Module 4 does not contain results from vaccine effectiveness studies. Therefore, I did not review this module.

Module 5

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

Immunological and virological assays were used to assess the TBEV vaccine performance. An overview of the immunogenicity endpoints and assay methods used in each of the clinical studies is provided in the Summary of Clinical Efficacy (SCE), Module 2.7.3, Section 2.7.3.1.2, Table 3 (for adult studies) and Table 4 (for pediatric studies). Assays that have been used in support of primary endpoints and/or have been used consistently throughout clinical development (“core assays”) include:

- Immunozygm FSME IgG ELISA (to evaluate the TBE antibody immune response).
- Adner Neutralization (NT) assay (to determine immune response to TBE vaccination overcomes the potential issue of cross-reactive (but functionally inactive) antibodies)
- *In vivo* Potency assay (to measure the potency of DP in mice).

Note: other than the *in vivo* potency assay, the above assays have not been validated.

In addition: Pfizer stated that the following assays were used in a very limited number of studies:

- Enzygnost anti-FSME-Virus IgG (to evaluate TBE antibody in studies B9371038 and 700801). This is a commercial Enzyme Immunoassay for Determination of IgG-Antibodies against TBE Virus in Animal Serum manufactured by (b) (4)
- (b) (4) Neutralization (NT) assay (to determine immune response to TBE vaccination overcomes the potential issue of cross-reactive (but functionally inactive) antibodies)

(b) (4)

[Redacted content]

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

(b) (4)

Overall Reviewer's Assessment of Module 4&5:

- Neither the Immunozygm FSME IgG ELISA nor the Neutralization (NT) assay has been validated. These two assays were used in most of the clinical studies in evaluating the TBE antibody immune response and calculating seropositivity and seroconversion rate (Section 2.7.3).
- There are (b) (4) ELISA assays and (b) (4) Neutralization (NT) assays that were used in various clinical studies. The (b) (4) Adner NT assays are quite similar except

that the Adner assay (b) (4)

The former involved a (b) (4)
(b) (4)

(b) (4) NT assay was used in adult Studies 201/202 and 213, as well as in pediatric studies 198/215, 199/206, and 205/207. The immune response determined by NT was lower than that determined by ELISA. Pfizer explained that this was caused by more stringent assay cut-off criteria and the relatively high virus concentration used in this NT assay (b) (4). Subsequently, serum samples tested by NT according to (b) (4) et al in adult Study 213 and pediatric Study 209 were reanalyzed using the Adner NT assay. The results from the neutralization test according to the Adner assay correlated well with the ELISA results, and thus the Adner assay became the method of choice for determining neutralizing antibodies in recipients of FSME-IMMUN.

- The clinical review team (Ihid Carneiro Leao and Meghan Ferris) indicated that they are selecting studies 208 and 213 as pivotal adult studies and study 209 as the pivotal pediatric study. Study 690601 may be considered as pivotal for the (b) (4) immunization schedule. Studies 209 and 213 involved Immunozygm FSME IgG ELISA and (b) (4) Adner NT assays. Study 208 is a safety study that used Immunozygm FSME IgG ELISA. Study 690601 employed Immunozygm FSME IgG ELISA and Adner NT assay.
- The *in vivo* potency assay is validated. However, there is no linearity/relative accuracy assessment. This is an *in vivo* assay that requires many live animals for a test. Pfizer explained why linearity/relative accuracy could not be assessed (see Table 50). The explanation is acceptable. However, for future studies an *in vitro* potency assay is recommended.