

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Date	6/28/2021		
To:	Andrea Gray		
Requesting Center/Office	CBER	Clinical Review Division	FDA/OC/CBER/OTAT/DCGT/CTB/
From	Sreya Tarafdar OPEQ/OHT3/DHT3C		
Through (Team)	Suzanne Hudak, Acting Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Rumi Young, Acting Assistant Director OPEQ/OHT3/DHT3C GHDB		
Subject	BLA 125740, FSME-IMMUN/TicoVac ICC2100494 00723776		
Recommendation	<p>Filing Recommendation Date: Click or tap to enter a date.</p> <p><input checked="" type="checkbox"/> CDRH did not provide a Filing Recommendation</p> <p><input type="checkbox"/> Device Constituent Parts of the Combination Product are acceptable for Filing.</p> <p><input type="checkbox"/> Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A</p> <p><input type="checkbox"/> Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5 for Deficiencies</p> <p>Mid-Cycle Recommendation Date: 06/30/21</p> <p><input type="checkbox"/> CDRH did not provide a Mid-Cycle Recommendation</p> <p><input checked="" type="checkbox"/> CDRH has no approvability issues at this time.</p> <p><input type="checkbox"/> CDRH has additional Information Requests, See Appendix A</p> <p><input type="checkbox"/> CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.</p> <p>Final Recommendation Date: 7/13/2021</p> <p><input checked="" type="checkbox"/> Device Constituent Parts of the Combination Product are Approvable.</p> <p><input type="checkbox"/> Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3</p> <p><input type="checkbox"/> Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies</p>		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 125740
Sponsor	Pfizer Ireland Pharmaceuticals
Drug/Biologic	FSME-IMMUN/TicoVac
Indications for Use	FSME-IMMUN/TicoVac (Tick-Borne Encephalitis Vaccine (whole virus inactivated) Active immunization to prevent tick-borne encephalitis (TBE) in individuals 1 year of age and older.
Device Constituent	Pre-Filled Syringe
Related Files	BLA125740.BSME-Immun.TicoVac.CDRH-OPEQ Review.ICC2100122.Final.pdf

Important Dates	
Filing	n/a
74-Day Letter	n/a
Midcycle Meeting/IRs due	06/30/2021
Final Lead Device Review Memo Due	07/13//2021
PDUFA Date	8/13/2021

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

- ☒ Approvable – the device constituent of the combination product is approvable for the proposed indication.
- ☐ Approvable with PMC or PMR, [See Section 2.3](#)
- ☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, [see Section 2.2](#).

2.1. Comments to the Review Team

- ☒ CDRH does not have any further comments to convey to the review team.
- ☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

- ☒ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
- ☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	<input type="checkbox"/>
CDRH does not have Post-Market Commitments or Requirements	<input checked="" type="checkbox"/>

3. PURPOSE/BACKGROUND

3.1. Scope

Pfizer Ireland Pharmaceuticals is requesting approval of FSME-IMMUN/TicoVac. The device constituent of the combination product is a Pre-Filled Syringe.

CBER has requested the following consult for review of the device constituent of the combination product:

BLA 125740 describes a vaccine intended to prevent tick-borne encephalitis (TBE), supplied as a pre-filled borosilicate glass syringe with rubber tip cap (needle is supplied by the end user). The dosage is 0.5 mL or 0.25 mL, administered by intramuscular injection into the upper arm. Shawn Shermer in CDRH/OHT3 provided a consult review (ICCR#00058730/ICC2100122) for the pre-filled syringe on May 25, 2021 (attached) and identified three (3) CR deficiencies (see consult memo). However, as this BLA is considered DOD high priority and urgent, these comments will be communicated by CBER to the applicant (Pfizer Ireland) interactively in an information request. Please review the responses to IR comments and determine whether the applicant provided sufficient information to resolve the deficiencies. Please also advise on where there is flexibility to request certain information as post-approval commitments.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product by determining whether the applicant has provided sufficient information in response to the identified CR deficiencies. In this memo, I will review the responses from the sponsor to the IR issued by Shawn. This current memo is an updated version of Shawn's previous memo. I will update relevant sections below with the Sponsor's response and my review/recommendation.

This review will not cover the following review areas:

- Compatibility of the drug with the device materials (deferred to CDER)
- Biocompatibility of the primary container closure, including needle (deferred to CDER)
- Sterility (primary container closure sterility deferred to CDER)
- Human Factors (deferred to DMEPA)

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

Shawn Shermer from CDRH reviewed the application for BLA125740 under ICC2100122 and identified 3 CR deficiencies (listed below) which was communicated by CBER to the sponsor on June 3, 2021. Major Deficiencies issued as an IR on 06/03/2021:

1. *On April 1, 2021, we stated that you have not addressed all of the essential performance requirements (EPRs) for your device constituent. We requested that you provide the specification, verification, validation, stability/aging, shipping/transportation for each PFS EPR (dose accuracy/extractable volume, (b) (4) and that you provide your quality control strategy that explains how EPRs for your combination product are controlled. In your response dated 4/15/2021, you indicated that you will monitor dose accuracy and (b) (4) over the proposed shelf life. You also stated that (b) (4) is a critical to quality attribute.*

Your response does not include the data that was requested. EPRs may be stability indicating because these factors can be impacted by external stressors, including aging and environmental/shipping conditions. Though you indicate that you will monitor dose accuracy, (b) (4) over the proposed shelf life, it

is unclear what exactly your monitoring includes. Please see deficiency 2 for further comments related to stability of your drug product.

Additionally, you indicate that (b) (4) is identified as a device critical to quality attribute, but you do not include (b) (4) in your testing plan.

Provide the specification, verification, validation, stability/aging, shipping/transportation for each PFS EPR (dose accuracy/extractable volume, (b) (4) Additionally, provide your quality control strategy that explains how EPRs for your combination product are controlled. This information is necessary to ensure the device functions through the entire shelf life.

2. *You provided stability data from multiple sites though the drug product was transferred to Pfizer, (b) (4). However, the stability data did not include data from testing of the device EPRs. If you have data demonstrating that the device EPRs were tested, provide the data. It is possible that the stability data generated from sites other than Pfizer, (b) (4) may be acceptable if you confirm what the differences are between materials, DP, and manufacturing materials/process. If there are no differences, then please provide a comparison of the performance data between the two sites.*

Additionally, the stability data from Pfizer, (b) (4) is inadequate to support the shelf life of your drug product. At the time of submission, you had 18-months long term data and (b) (4) days of accelerated data. Based on calculations performed per (b) (4), it does not appear that your (b) (4) days accelerated aging testing correlates to your proposed shelf life of (b) (4) months; (b) (4) days will support a (b) (4)-year (b) (4) month) shelf life. Provide shelf-life testing demonstrating that your EPRs are maintained through the proposed shelf-life (b) (4) months). Clearly specify storage conditions and assumptions made when applying (b) (4) for accelerated aging. Additionally, provide the complete test report which should include the objective, the acceptance criteria with a justification, the test method, including sample size, and the test results with a discussion of any deviations, and a conclusion.

3. *Based on the information provided in your submission, it does not appear as though your PFS has been tested to (b) (4) Requirements and test methods for finished prefilled syringes. Without this testing, it is not clear whether you have evaluated all of the design inputs, not just the essential performance requirements, of your combination product. Provide evidence of verification per the relevant sections of (b) (4) Your response should include a complete test report, containing the objective, the acceptance criteria with a justification and sampling rationale, the test method, the test results with a discussion of any deviations, and a conclusion. If you plan to leverage any of this information from your respective DMFs, clarify where in the DMF(s) this information is located and provide a discussion on why the evaluation of performance at the sub-assembly level is representative of your final finished combination product. This information is necessary to ensure your device meets basic performance requirements.*

The Sponsor responded to the above CR deficiencies on 06/10/2021. For detailed review and analyses of the Sponsor's response please refer to corresponding sections below.

3.3. Indications for Use

Combination Product	Indications for Use
FSME-IMMUN/TicoVac	FSME-IMMUN/TicoVac (Tick-Borne Encephalitis Vaccine (whole virus inactivated) Active immunization to prevent tick-borne encephalitis (TBE) in individuals 1 year of age and older.
Pre-Filled Syringe	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
0013	1.11.4
0012	1.11.1
0001	2.3.P, 2.3.R, 3.2.P
Amendment 21 (125740/0/21), Seq 22	

4. DEVICE DESCRIPTION

4.1. Device Description

The FSME-IMMUN drug product 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 0.1% human albumin and bound to aluminium 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 composition of both dosage forms are identical, but the nominal volume of the pediatric dosage form is half of the nominal volume of the 0.5 mL dosage form.

The syringe container closure system consists of (b) (4) 1 mL Luer Cone barrels or (b) (4) 1 mL Luer Cone barrels, (b) (4) tip caps and (b) (4) plunger stoppers. The barrels are sealed with the tip cap and plunger and a plunger rod is assembled. The plunger rod does not have direct contact with the drug product. The components, their description and their DMF reference are shown in Table 3.2.P.7-1. letter of authorization (LoA) to reference the DMF is received for each component and is provided in Module 1 Section 1.4.2.

Safety data for the syringe barrel and rubber formulations are provided in Section 3.2.P.2.4 Container Closure System.

Tip cap and plunger stopper are provided sterile, clean and ready-to-use from the component manufacturer. Validation studies, as appropriate, have been conducted on primary packaging components to demonstrate that they are suitable for use (see section 3.2.P.2.4 Container Closure System). A drawing of the container closure used for FSME-IMMUN drug product is provided in Figure 3.2.P.7-1

Figure 3.2.P.7-1. Drawing of FSME-IMMUN Container Closure System

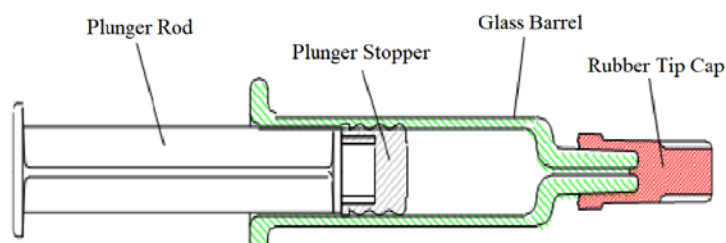


Table 3.2.P.7-1. Syringe Container Closure Components

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

3.2.P.7.1. Syringe with Tip Cap

The container described in this document is a ready-to-use syringe with a filling volume of 1 mL for parenteral administration of suspensions. The barrel is (b) (4) as described in Section 3.2.P.7.1.1.3. The plunger stopper and tip cap are (b) (4) by the supplier.

3.2.P.7.1.1. Glass Barrels

The glass barrels are supplied from (b) (4) and consist of clear and colourless 1 mL (b) (4) borosilicate glass. The glass barrels meet (b) (4) requirements for (b) (4) borosilicate glass containers, as well as (b) (4) requirements for glass barrels for injectables and sterilized sub-assembled syringes ready for filling. To improve the gliding properties, the syringe barrel is siliconized. The barrel supplier sites are listed in Table 3.2.P.7-2 The (b) (4) syringe is illustrated in Figure 3.2.P.7-2 and the (b) (4) syringe is illustrated in Figure 3.2.P.7-3.

4.2. Design Requirements

Basic Syringe Description/Requirements

Requirement	Reviewer Comment
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Health care provider
Injection Site	Upper arm (deltoid muscle) ¹
Injection tissue and depth of injection	Intramuscularly ¹
Type of Use (e.g. single use, disposable, reusable, other)	Single use
Environments of use (e.g. home, clinic)	clinic
Storage conditions and expiry	5 ± 3 °C; 30 months shelf life
Needle connection (e.g. Luer, slip tip, staked)	Luer Cone
Syringe Volume	1 mL
Device materials including lubricant	See table 3.2.P.7-1 above

1. Sequence 0001, 2.2 introduction, page 4

Additional Syringe Description/Requirements

Requirement	Reviewer Comment
Hypodermic Needle: length, gauge, and configuration of the tip.	Needle not provided with PFS
Markings (graduated scale, position of scale, length of scale, numbering of scale, and legibility)	There are no markings on the syringe barrel

criteria (for insulin syringes). Insulin Syringes: The scale on the barrel should be in units of insulin.	
Reuse Durability (for reusable piston syringes): number of times the device can be sterilized and still meet specifications (using sterilization method indicated in the labeling).	n/a
Safety Features (e.g. Needle safety component/device)	n/a
Automated Functions	n/a
Sterilization method	<p>(b) (4)</p> <p>Sterilization validation is being reviewed by CBER/OCBQ/DMPQ.</p>

*See [Design Verification Section](#) for verification of design requirements

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A	Mid-Cycle Deficiencies: <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Final Deficiencies: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A
<u>Reviewer Comments</u>		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		

	Date Sent: 4/1/2021	Date/Sequence Received: 4/15/2021
Information Request #1	You reference multiple DMFs in your submission. For each DMF, you have not specifically indicated where the data is located that will be used in support of your submission. Provide specific references to how and where the referenced data will be used in support of your device's adequate verification and validation.	
Sponsor Response	<p><i>The Applicant would like to clarify that an authorization letter of each Drug Master File (DMF), referenced in Section 3.2.P.2.4 Container Closure System and Section 3.2.P.7 Container Closure System, is provided in Module 1.4.2 Statement of Right of Reference and in Table 1.</i></p> <p><i>These authorization letters provide an overview of the DMF sections containing the relevant information related to the safety of material of construction including biocompatibility. No other device performance data is being leveraged from these DMFs. All relevant performance data for the final, assembled prefilled syringe (PFS) is within the BLA, Section 3.2.P.2.4 Container Closure System.</i></p>	

	<p>Table 1. DMF Letters of Authorization – Module 1.4.2 Statement of Right of Reference</p> <div style="text-align: center; background-color: #cccccc; padding: 50px;"> (b) (4) </div>
<p>Reviewer Comments</p>	<p>The letter of reference for DMF (b) (4) states that relevant information for the tip caps (b) (4) can be found in 3.2.P.3.1 and 3.2.P.3.3; manufacturers, manufacturing process and controls.</p> <p>The letter of reference for DMF (b) (4) states that relevant information for the tip caps (b) (4) can be found in 3.2.P.3.3.1 and 3.2.A.1.6; (b) (4) list of inaccessibility indexes.</p> <p>The letter of reference for DMF (b) (4) states that the relevant information for the tip caps (b) (4) for sterilization and validation are found in 3.2.P.3.3.3, 3.2.P.3.5.1 and Chapter 4.1.2.2.7, p 69 – Determination of the maximum acceptable dose – Results for formulation (b) (4) and conclusion (paper version).</p> <p>The letter of reference for DMF (b) (4) states: “Please refer to the Table of Contents in 3.2.P.7 and the LOA attachment document(s) for details regarding components used by the applicant, including the (b) (4) sterilization of (b) (4) products.”</p> <p>The letter of reference for DMF (b) (4) is for compound (b) (4) and the (b) (4) process.</p> <p>The letter of reference for DMF (b) (4) does not provide any information as to what exactly is being reference in this DMF.</p> <p>The letter of reference for DMF (b) (4) is for the packaging material.</p> <p>The sponsor provided the requested information for all of the DMF except for DMF (b) (4) However, this has not hindered the review of this submission; so, a follow up IR will not be issued.</p>
<p>Response Adequate:</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No, See IR # Sent on Click or tap to enter a date.</p>

5. FILING REVIEW

CDRH performed Filing Review	<input type="checkbox"/>
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CDRH was not consulted prior to the Filing Date; therefore, CDRH did not perform a Filing Review ☒

5.1. Facilities & Quality Systems Triage Inspection Recommendation Information

CDRH completed a review of the Facilities	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
Inspection Recommendation	<input type="checkbox"/> Pre-Approval Inspection (PAI) <input type="checkbox"/> Post-Approval Inspection <input type="checkbox"/> Routine Surveillance <input type="checkbox"/> No Inspection Needed <input checked="" type="checkbox"/> N/A
CDRH completed a review of the Quality Systems	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A

*If a Facilities and/or Quality Systems Review is completed, the review is located in [Appendix B](#)

5.2. Filing Recommendation

FILING REVIEW CONCLUSION	
Acceptable for Filing: <input type="checkbox"/> Yes <input type="checkbox"/> No (Convert to a RTF Memo) <input checked="" type="checkbox"/> N/A	
Facilities Inspection Recommendation: <input type="checkbox"/> (PAI) Pre-Approval Inspection <input type="checkbox"/> Post-Approval Inspection <input type="checkbox"/> Routine Surveillance <input type="checkbox"/> No Inspection <input type="checkbox"/> N/A Site(s) needing inspection:	
Reviewer Comments	
Refuse to File Deficiencies : <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
74-Day Letter Deficiencies: <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

6. DEVICE PERFORMANCE REVIEW

6.1. Design Verification/Validation

6.1.1. Device Specification Standards and Guidance Documents

Syringe		Data Adequate		
		Yes	No	N/A
Pre-filled Syringe	(b) (4) (b) (4) Requirements and test methods for prefilled syringes	<input checked="" type="checkbox"/> *** see below	<input type="checkbox"/>	<input type="checkbox"/>
Co-packaged Syringe	ISO 7886-1, Sterile Hypodermic Syringes for Single Use—Part 1: Syringes for Manual Use	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Insulin Syringe	ISO 8537, Sterile single-use syringes, with or without needle, for insulin	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Needle/Sharps		Data Adequate		
		Yes	No	N/A
Needle	ISO 7864, Sterile Hypodermic Needles for Single Use	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Needle	ISO 6009, Hypodermic needles for single use – Color coding for identification	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Sharps Injury Prevention Feature	ISO 23908 - Sharps injury protection - Requirements and test methods - Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Luer Lock		Data Adequate		
		Yes	No	N/A
Connection	(b) (4)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Other		Data Adequate		
		Yes	No	N/A
[Other]	[Other]	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

*** Please refer to the Sponsor response to (Follow on) CR Deficiency # 3 listed in Section 6.2. The following table was provided by the Sponsor in their response document demonstrating that PFS has been tested to (b) (4) Requirements and test methods for finished prefilled syringes.

Table 10. Summary of Applicable Requirements of (b) (4)

Requirement Description	Specification Limit and Acceptance Criteria	Evidence	Result	Discussion
System characterisation				
Critical Dimension	Critical dimensions of the finished prefilled syringe are summarized	Section 3.2.P.7 Container Closure System	N/A	
Description of components and materials	Barrel	Section 3.2.P.7 Container Closure System (b) (4) - Syringe Barrel (b) (4) Syringe Barrel	PASS	Barrel specifies (b) (4) luer cone and tips that are compatible with connections that conform to (b) (4)
	Plunger stopper	Section 3.2.P.7 Container Closure System (b) (4) - Plunger stopper	PASS	The dimensions of the plunger stopper were analysed and found to comply with the nominal dimensions and tolerances of (b) (4) for a 1-3 mL plunger stopper with threads.

	Plunger rod	Section 3.2.P.7 Container Closure System (b) (4) - Syringe Plunger Rod	PASS	For the plunger stopper and plunger rod used in the manufacture of FSME Immun, the thread form and threaded depth or height, respectively, were determined from the drawing Dimensional analysis of the components determined that the plunger stopper open distal end is compatible with the corresponding proximal end of the plunger rod.
Description of the content of the finished prefilled syringe	Target fill volumes: (b) (4) mL for the FSME- IMMUN PFS 0.50mL and (b) (4) mL for the FSME- IMMUN PFS 0.25mL	Section 3.2.P.3.5 Process Validation and/or Evaluation – Summary Report – Process Validation – Pfizer, (b) (4)	PASS	FSME-IMMUN is a suspension for injection, with a target fill volume of (b) (4) mL for the FSME-IMMUN PFS 0.50mL and (b) (4) mL for the FSME-IMMUN PFS 0.25mL

Performance Requirements

(b) (4)

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

6.1.2. Device Performance Evaluation 0

Essential Performance Requirement	Specification	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy (extractable volume) ¹	FSME-IMMUN 0.5 mL = 0.50-(b) (4) FMSE-IMMUN 0.25 mL = 0.25-(b) (4)	Y	Y Test report review	N	NT
(b) (4)		NOT TESTED	NOT TESTED	NOT TESTED	NOT TESTED
		NOT TESTED	NOT TESTED	NOT TESTED	NOT TESTED
		NOT TESTED	NOT TESTED	NOT TESTED	NOT TESTED

1. Page 2 of 2 of 3.2.P.5.1 Specifications
2. Table 3.2.P.2.4-3 in Section 3.2.P.2 Container Closure System

1. Extractable volume:

➤ (b) (4)

(b) (4)

(b) (4)

Additional Information

Packaging: the sponsor completed a qualification run on the packaging process. The sponsor looked for defects after the packaging run. However, while the packaging qualification is important it does not address the EPRs listed above.
Shipping Qualification: this was also completed. The focus of this testing was the maintenance of the appropriate temperature range during shipping. This testing did not include any EPRs.

Title:	Technical Report for the Determination of Extractable Volume of (b) (4) FSME-Immun Junior/Adult Drug Product Samples Document ID: 15102-EXVOL-TRPA-A1 [found in 3.2.R of Sequence 0001]
Scope/Objective & Acceptance Criteria:	This testing was completed to validate extractable volume after moving to a different manufacturing site. “Extractable volume is verified per (b) (4)
<u>Methods</u>	(b) (4)

	<ul style="list-style-type: none"> (b) (4)
Results:	(b) (4)
Conclusions/ Reviewer Comments:	<ul style="list-style-type: none"> Study completed in 2015. There are three pages that are not readable; pdf pages 12-14. PDF pages 15-26 are not in English.
Acceptable:	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Title:	3.2.P.3.5. PROCESS VALIDATION AND/OR EVALUATION - SUMMARY REPORT – PROCESS VALIDATION – PFIZER, (b) (4)
Scope/Objective & Acceptance Criteria:	The objective of the process validation program was to demonstrate that the drug product manufacturing process could consistently produce drug product lots that meet pre-defined acceptance criteria when executed within normal operating ranges (NOR) for all product quality attributes. The results of these studies are detailed in 3.2.P.3.5 Process Validation and/or Evaluation-Summary Report – Process Validation – Pfizer (b) (4).
Methods	(b) (4)

Results:	(b) (4)
Conclusions/ Reviewer Comments:	(b) (4) For all process validation lots, all final product test results met the pre-determined acceptance criteria.
Acceptable:	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Title:	3.2.P.3.5 Process Validation and/or Evaluation Summary Report - Qualification of Labeling, Packaging and Shipping – Pfizer, (b) (4)
Scope/Objective & Acceptance Criteria:	FSME-IMMUN drug product syringes undergo labeling and final packaging at Pfizer, (b) (4) before being shipped from (b) (4) distribution centers using qualified shipping containers.
Methods	(b) (4)

	(b) (4)
Results:	(b) (4)
Conclusions/ Reviewer Comments:	This labeling, packaging, and shipping testing did not include any testing regarding the device constituent EPRs.
Acceptable:	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A

6.1.3. Stability Review Summary

Shelf-life:	30 months
Storage conditions:	$5 \pm 3^{\circ}\text{C}$
Time period and storage conditions provided for accelerated aging stress conditions	(b) (4)
Time period and storage conditions provided for real-time aging:	$5 \pm 3^{\circ}\text{C}$ (b) (4) (30 months for the
Time period and storage conditions provided for thermal cycling	(b) (4)
Time period and storage conditions provided for excursion	$5 \pm 3^{\circ}\text{C}$ (b) (4) $5 \pm 3^{\circ}\text{C}$ storage for the duration of the study (30 months)

*Endpoint evaluation is provided in [section 6.1.2.](#)

Reviewer Comments

Primary stability studies have been completed at (b) (4). Supportive studies have also been both completed at (b) (4) and are ongoing at Pfizer, (b) (4)

(b) (4) lots of final vaccine formulated and filled at the alternative manufacturing site (b) (4) also reflecting the maximum batch size of (b) (4) were placed on stability. The study comprises long-term stability testing at a temperature of 5 ± 3 °C.¹

The sponsor states: "All test results for both long term and the accelerated storage conditions met the commercial specification." (page 3 of the stability summary document)

On page 5, Table 3.2.P.8.1-1 is a summary of stability studies. It is unclear how the studies relate to the subject drug product.

Deficiency 2 below

1. Stability-summary.pdf

6.1.4. Biocompatibility Evaluation

☐ Biocompatibility was **evaluated** [e.g. co-packaged syringes, co-packaged components outside of primary container closure]

☒ Biocompatibility was not evaluated **because**: PFS, including the needle are part of the primary container closure; biological safety evaluation under the purview of CBER

6.1.5. Sterility Evaluation

☐ Sterility **Evaluated** (e.g. co-packaged syringes, co-packaged components outside of primary container closure)

☒ Sterility not evaluated (syringe, including needle are part of primary container closure, sterility evaluation is under the purview of CBER)

6.2. Device Performance Review Conclusion

DEVICE PERFORMANCE REVIEW CONCLUSION		
Filing Deficiencies: <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	Mid-Cycle Deficiencies: <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Final Deficiencies: <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Reviewer Comments		
CDRH sent Device Performance Deficiency or Interactive Review Questions to the Sponsor: <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		

	Date Sent: 4/1/2021	Date/Sequence Received: 4/15/2021
Information Request #2	You provided Table 3.2.P.8.1-1 (Summary of Stability Studies) on page 5 of document "stability-summary.pdf. It is unclear how this information relates to the subject drug product. Provide clarification regarding how each study is applicable to the current subject drug product and evidence to demonstrate that all device essential performance requirements (EPRs) have been evaluated over the intended shelf life.	
Sponsor Response	Table 3.2.P.8.1-1 summarizes the available stability studies for FSME-IMMUN. Primary stability studies, used for establishing a shelf life, have been completed at (b) (4). Supportive studies, providing additional data relevant to product stability and shelf life support, have also been both completed at (b) (4) and are ongoing at Pfizer, (b) (4)	

	<i>The stability studies initiated for the drug product, manufactured at Pfizer (b) (4), are provided as from page 6 (lot (b) (4)) onwards and contain assessment of the stability indicating drug product quality attributes. The container closure integrity testing over shelf life are presented in Section 3.2.P.2.5 Microbiological Attributes. The identified EPR's for this container closure system and the control strategy are further described in response to query 3. The identified EPR's are not expected to be stability indicating and to demonstrate this we will further monitor them over the proposed shelf life.</i>
Reviewer Comments	The sponsor states that the EPRs are not expected to be stability indicating. However, these factors can be impacted by external stressors, including aging and environmental/shipping conditions. The sponsor proposes to monitor the identified EPRs over the proposed shelf life. This is appropriate; however, it should be completed prior to Approval.
Response Adequate:	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No, See IR # Sent on 6/3/2021

Follow-On Deficiency	Date Sent: 6/3/2021	Date/Sequence Received: 6/10/2021
Complete Response Deficiency #2	<p>You provided stability data from multiple sites though the drug product was transferred to Pfizer, (b) (4). However, the stability data did not include data from testing of the device EPRs. If you have data demonstrating that the device EPRs were tested, provide the data. It is possible that the stability data generated from sites other than Pfizer, (b) (4) may be acceptable if you confirm what the differences are between materials, DP, and manufacturing materials/process. If there are no differences, then please provide a comparison of the performance data between the two sites.</p> <p>Additionally, the stability data from Pfizer, (b) (4) is inadequate to support the shelf life of your drug product. At the time of submission, you had 18-months long term data and (b) (4) days of accelerated data. Based on calculations performed per (b) (4) (b) (4) it does not appear that your (b) (4) days accelerated aging testing correlates to your proposed shelf life of (b) (4) months; (b) (4) days will support a (b) (4) year (b) (4) month) shelf life. Provide shelf-life testing demonstrating that your EPRs are maintained through the proposed shelf-life (b) (4) months). Clearly specify storage conditions and assumptions made when applying (b) (4) for accelerated aging. Additionally, provide the complete test report which should include the objective, the acceptance criteria with a justification, the test method, including sample size, and the test results with a discussion of any deviations, and a conclusion.</p>	
Sponsor Response	<p><i>The applicant wants to clarify that the proposed shelf life for FSME-IMMUN PFS is 30 months and not (b) (4) months (the same as the current licensed shelf life). Additional stability data from Pfizer, (b) (4) is available. Up to (b) (4) months data is provided for (b) (4) lot (b) (4) and 30 months data is provided for the other (b) (4) process validation lots (b) (4). 12 months data is provided for the confirmatory lot (b) (4). Sections 3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data – Pfizer, (b) (4) have been updated accordingly. As such, Pfizer is not reliant on (b) (4) and accelerated aging to support the proposed shelf life. The control strategy for the two identified EPRs (delivered dose (b) (4)) over shelf life, is outlined in query response 1.</i></p> <p><i>New or Replaced Supporting Documentation</i></p>	

	<i>3.2.P.8.1 Stability Summary and Conclusion, Replaced 3.2.P.8.3 Stability Data – Pfizer, (b) (4) Replaced</i>
Reviewer Comments	<i>The sponsor has provided data from the long-term stability study covering a period of 30 months (which is the claimed shelf life) for (b) (4) process validation lots and (b) (4) months data from (b) (4) lot. Since the sponsor has performed stability study over a long term and relevant data is available, thus the accelerated aging study not aligning with (b) (4) is acceptable. Sponsor provided updated 30 months and (b) (4) months data in Seq 022 Section 3.2.P.8.3 tables 3.2.P.8.3-2 through 8. The data based on long -term/real time study provided shows that the drug product in its final product form is stable and sterile and maintains performance through its shelf life. The sponsor's response is adequate and acceptable.</i>
Response Adequate:	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No, See IR # Sent on Click or tap to enter a date.

	Date Sent: 6/3/2021	Date/Sequence Received: 6/10/2021
Complete Response Deficiency 3	Based on the information provided in your submission, it does not appear as though your PFS has been tested to (b) (4) Requirements and test methods for finished prefilled syringes. Without this testing, it is not clear whether you have evaluated all of the design inputs, not just the essential performance requirements, of your combination product. Provide evidence of verification per the relevant sections of (b) (4) . Your response should include a complete test report, containing the objective, the acceptance criteria with a justification and sampling rationale, the test method, the test results with a discussion of any deviations, and a conclusion. If you plan to leverage any of this information from your respective DMFs, clarify where in the DMF(s) this information is located and provide a discussion on why the evaluation of performance at the sub-assembly level is representative of your final finished combination product. This information is necessary to ensure your device meets basic performance requirements. .	
Sponsor Response	<i>The FSME-IMMUN PFS presentation has been evaluated in accordance with the requirements of (b) (4) and meets all applicable requirements. In addition to information provided in query response 1 that summarized the (b) (4), the (b) (4) and the delivered dose, we deemed that (b) (4) , biological requirements and container closure integrity were applicable as a design input requirement per (b) (4) FSME IMMUN PFS is intended to deliver a single, sterile, intramuscular injection of a liquid suspension composed of inactivated Tick-Borne Encephalitis Virus (strain Neudörfl) for active immunization against tick-borne encephalitis (TBE) caused by Tick-Borne Encephalitis (TBE) Virus. It should be stored under refrigerated conditions (2°C to 8°C) and should not be frozen. FSME IMMUN PFS's intended user is a healthcare professional (HCP) in a clinical practice at a doctor's clinic (office), hospital environment, or similar setting. FSME IMMUN is intended for use in patients who are 16 years of age and older. FSME IMMUN Junior is intended for use in patients who are 1 to 15 years of age. As provided in Section 3.2.P.2.4 Container Closure System, risk management activities were performed and concluded that the overall risk profile was judged to be acceptable. In this section the design validation activities were described. All requirements were successfully met.</i>	

Reviewer Comments	<i>The sponsor has provided a table (table 10. Summary of Applicable requirements of (b) (4) in their response document) summarizing the requirement description per every clause of the standard, the acceptance criteria, location of evidence in the submission, the results and the discussion for each testing. Please refer to the table in section 6.1.1. above. The response from the sponsor is adequate and acceptable.</i>
Response Adequate:	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No, See IR # Sent on Click or tap to enter a date.

7. CONTROL STRATEGY REVIEW

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Dose Accuracy	The sponsor uses Extractable Volume for their quality attribute. The sponsor has demonstrated that Extractable Volume has met specifications for Release but has not been tested as part of Stability (3.2.5.1; table 3.2.P.5.1-3 page 2)	N Y (data provided in response to IR – Tables 1-6 below)
(b) (4)	The release and stability testing specifications, as provided in 3.2.P.5.1, do not (b) (4)	N Y (data provided in response to IR – tables 7-8 below)
		N Y (data provided in response to IR - tables 7-8 below))
		N Y (data provided in response to IR – table 9 below)

Table 1. Dose Accuracy Specifications

Essential Performance Requirement	Method	Acceptance Criteria	
		Release	Stability
Extractable volume (Dose Accuracy) for FSME-IMMUN 0.5ml	(b) (4)	0.50 (b) (4)	Not Performed ^a

Extractable volume (Dose Accuracy) for FSME-IMMUN 0.25mL	(b) (4)	0.25-(b) (4)	Not Performed ^a
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a. Dose accuracy is not considered a stability indicating parameter and past data from (b) (4) for FSME-IMMUN lots have shown no change in the extractable volume over time. Sterility and Visual (appearance) testing are performed on stability and these attributes can determine any breach in the container closure integrity.

Table 2. Summary of (b) (4) Dose Accuracy results for FSME-IMMUN 0.5mL

Parameter	Target/Acceptance Criteria	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Extractable volume (Dose Accuracy) (mL)	0.50-(b) (4)	(b) (4)	(b) (4)	(b) (4)

a. Additional significant digits provided and used for evaluation

Table 3. Summary of (b) (4) Dose Accuracy results for FSME-IMMUN 0.25mL

Parameter	Target/Acceptance Criteria	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Extractable volume (Dose Accuracy) (mL)	0.25-(b) (4)	(b) (4)	(b) (4)	(b) (4)

a. Additional significant digits provided and used for evaluation

Table 4. Dose Accuracy for FSME-IMMUN 0.25mL before assembly and packaging

Batch	Method	Acceptance Criteria	Result
(b) (4)		0.25-(b) (4)	(b) (4)
		0.25-(b) (4)	(b) (4)

Table 5. Dose Accuracy for FSME-IMMUN 0.25mL after assembly and packaging

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer Comments

The sponsor has not adequately addressed their Control Strategy for the identified EPRs. Please see the CR deficiency for IR deficiency 3 below.

Update 06/28/2021: The sponsor has provided all requested data summarized in tables in response to our IR #3 sent out on June 03, 2021.

Control Strategy Conclusion

The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.

☒ Yes

☐ No

7.1. Control Strategy Review Conclusion

CONTROL STRATEGY REVIEW CONCLUSION

Filing Deficiencies:

☐ Yes ☐ No ☒ N/A

Mid-Cycle Deficiencies:

☒ Yes ☐ No ☐ N/A

Final Deficiencies:

☒ Yes ☐ No ☐ N/A

Reviewer Comments

CDRH sent Control Strategy Deficiency or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No

	Date Sent: 4/1/2021	Date/Sequence Received: 4/15/2021
Information Request #3	You have not addressed all of the essential performance requirements (EPRs) for your device constituent. Provide the specification, verification, validation, stability/aging, shipping/transportation for each PFS EPR (dose accuracy/extractable volume, (b) (4)). Additionally, provide your quality control strategy that explains how EPRs for your combination product are controlled.	
Sponsor Response	<p>The Applicant assesses essential performance requirements in building an appropriate analytical control strategy based on analysis of the design and functional attributes tested during design verification to build the rationale as to which tests are appropriate for inclusion in release or stability testing. Section 3.2.P.2.4 Container Closure System, 3.2.P.2.4.5.1 Design Verification, has previously identified dose accuracy (deliverable volume) as an essential performance requirement (EPR). Dose accuracy is linked to (b) (4) DP manufacturing. Data presented in 3.2.P.3.5 Process Validation and/or Evaluation summary Report – Process Validation – Pfizer (b) (4) indicates this EPR is controlled by an (b) (4) . This attribute remains controlled over time as container closure integrity is tested over shelf life (See Section 3.2.P.2.5 Microbiological Attributes), which ensures that the internal volume in the syringe is maintained over the proposed shelf life. To demonstrate this, we will continue to monitor the dose accuracy over the proposed shelf life as part of the initial qualification.</p> <p>(b) (4) is a functional attribute also identified as an EPR with acceptance criterion of (b) (4) in Table 3.2.P.2.4-3 in Section 3.2.P.2.4.5.1 Design Verification. The syringe container closure components as described in Table 3.2.P.2.4-1 in Section 3.2.P.2.4.1 Description of the Container Closure System, are off the shelf components that are industry wide used for these pharmaceutical systems. The (b) (4) data referenced in Section 3.2.P.2.4.5.1.1 demonstrates that the EPR acceptance criteria were met for final assembled and packaged syringes. The data presented demonstrates the (b) (4) is controlled and indicates the incoming control on syringe components and in process controls of the siliconization of the barrel are sufficient controls of this attribute and, therefore, do not require routine testing.</p> <p>We will continue to monitor the (b) (4) over the proposed shelf life as part of the initial qualification. (b) (4) is not identified as an EPR because this has no direct impact on the dose delivery. The (b) (4) is part of the preparation of the device and identified as a device critical to quality attribute.</p>	
Reviewer Comments	The sponsor's response does not include the data that was requested. The sponsor proposes to monitor dose accuracy (b) (4) . It is unclear what it means to "monitor" these EPRs. The sponsor does not address (b) (4) appropriately. See deficiency below.	
Response Adequate:	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No, See IR # Sent on 6/3/2021	

Follow-On Deficiency	Date Sent: 6/3/2021	Date/Sequence Received: 6/10/2021
Complete Request #1	On April 1, 2021, we stated that you have not addressed all of the essential performance requirements (EPRs) for your device constituent. We requested that you provide the specification, verification, validation, stability/aging, shipping/transportation for each PFS EPR (dose accuracy/extractable volume, (b) (4)) and that you provide your quality control strategy that explains how EPRs for your combination product are	

	<p>controlled. In your response dated 4/15/2021, you indicated that you will monitor dose accuracy (b) (4) over the proposed shelf life. You also stated that (b) (4) is a critical to quality attribute.</p> <p>Your response does not include the data that was requested. EPRs may be stability indicating because these factors can be impacted by external stressors, including aging and environmental/shipping conditions. Though you indicate that you will monitor dose accuracy, (b) (4) over the proposed shelf life, it is unclear what exactly your monitoring includes. Please see deficiency 2 for further comments related to stability of your drug product.</p> <p>Additionally, you indicate that (b) (4) is identified as a device critical to quality attribute, but you do not include (b) (4) in your testing plan.</p> <p>Provide the specification, verification, validation, stability/aging, shipping/transportation for each PFS EPR (dose accuracy/extractable volume, (b) (4)). Additionally, provide your quality control strategy that explains how EPRs for your combination product are controlled. This information is necessary to ensure the device functions through the entire shelf life.</p>
<p>Sponsor Response</p>	<p><i>Dose Accuracy</i> <i>Dose accuracy is part of our routine release testing described in 3.2.P.5.1 Specifications, and in Table 1. This attribute is therefore tested on every batch (see 3.2.P.5.4 Batch Analysis).</i> <i>In addition as presented in 3.2.P.3.5 Process Validation and/or Evaluation – Summary Report – Process Validation – Pfizer, (b) (4); an in process control for (b) (4) is also performed to control the dose accuracy. The data of both dose accuracy (b) (4) performed during PV is listed in Table 2 and Table 3. In order to demonstrate that the final assembly and packaging process has no impact on the EPR, samples from (b) (4) confirmatory lot of FSME-IMMUN 0.25mL (b) (4) were tested for dose accuracy as per (b) (4) Results (b) (4) are provided in Table 4 and Table 5. FSMEIMMUN 0.25mL was considered representative for FSME-IMMUN 0.5mL as both presentations are assembled by the same process and have identical components, bulk material, plunger rod insertion process, and tolerances for plunger position which allows a stable plunger rod insertion process.</i> <i>Following final assembly and packaging of the FSME-IMMUN PFS, (b) (4) testing in accordance with (b) (4) were performed. The FSME-IMMUN PFS remained intact during transport handling simulations according to (b) (4) when protected by secondary and tertiary packaging materials. The absence of visual movement of plunger rod or obvious leaks or cracks of the PFS indicates that EPR dose accuracy is unaffected by the transport simulations. Supporting data of dose accuracy over shelf life is available and provided in Section 3.2.P.8.3 Stability Data – (b) (4). Table 6 shows data from final product manufactured by (b) (4) and demonstrates that the dose accuracy does not change over the shelf life and confirms that the EPR is not stability indicating. Furthermore, the final product including container closure system manufactured by (b) (4) and Pfizer has been shown to be</i></p>

	<p><i>equivalent, therefore the data previously generated by (b) (4) is fully representative for finished product manufactured at Pfizer (refer to Section 3.2.P.3.5 Process Validation and/or Evaluation – Summary Report – Comparability – Pfizer, (b) (4). Whilst dose accuracy has not to date been tested for the lots manufactured by Pfizer, the container closure integrity of the container closure system manufactured by Pfizer is tested over shelf life as presented in Section 3.2.P.2.5 Microbiological Attributes, which ensures that the internal volume in the syringe is maintained over the proposed shelf life, and assures the dose accuracy would be met at end of shelf life.</i></p> <p>(b) (4)</p> <p>(b) (4)</p>
Reviewer Comments	<p>The Sponsor has responded stating that</p> <ul style="list-style-type: none"> • dose accuracy testing is performed on every batch during routine release • in-process control for (b) (4) in performed to control dose accuracy

	<ul style="list-style-type: none"> dose accuracy was tested (b) (4) and found to not impact the EPR (b) (4) /shipping testing on assembled and packaged products were performed and found to not impact EPR dose accuracy. Dose accuracy over shelf life was provided from final products manufactured at (b) (4). The sponsor used this data to leverage the results of products manufactured at Pfizer, (b) (4) (IR#4 sent on 07/01/2021 see below). (b) (4) will be tested further to prove that EPR is controlled during manufacture, at release and over shelf life as part of the annual stability commitment. Similar to dose accuracy, assembly packaging shipping studies had no impact on (b) (4). (b) (4) was tested per (b) (4) and (b) (4) – all results were acceptable. <p>**** All data report tables provided by Sponsor are listed in section 7.</p> <p>While the response is adequate, the sponsor has not provided any dose accuracy over shelf life data for products manufactured at their own site. IR#4 sent out to sponsor requesting relevant data. If the sponsor can provide the data now – well. If not, it can be put on as a PMC recommendation.</p>
Response Adequate:	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No, See IR # 4 Sent on 7/1/2021

	Date Sent: 7/1/2021	Date/Sequence Received: 7/8/2021
Information Request #4	<p>In your response to our Query 1 in our IR dated 03 June 2021, you have provided supporting data for dose accuracy over shelf life in Section 3.2.P.8.3 Stability Data- (b) (4) (b) (4). You have also provided data from the final product manufactured by (b) (4), (b) (4) to demonstrate their dose accuracy over shelf life. However you have not provided any data from the dose accuracy testing for the final product manufactured by Pfizer at your own site. Please provide dose accuracy data for the final product manufactured at your own site.</p>	
Sponsor Response	<p><i>The Applicant would like to clarify that there is no dose accuracy stability data for the final product manufactured at Pfizer, (b) (4)</i></p> <p><i>As stated in our response to Q1 from the Response to FDA 03 June 2021 Information Request, specifically in Table 1 footnote (a), dose accuracy is not considered a stability indicating parameter and available data from (b) (4) for FSME-IMMUN lots have shown no change in the extractable volume over time. Sterility and Visual (appearance) testing are performed on stability and these attributes can determine any breach in the container closure integrity.</i></p> <p><i>Furthermore, the final product including container closure system manufactured by (b) (4) (b) (4) Pfizer, (b) (4) has been shown to be equivalent, therefore the data previously generated by (b) (4) is fully representative for finished product manufactured at Pfizer, (b) (4) (refer to Section 3.2.P.3.5 Process Validation and/or Evaluation – Summary Report – Comparability – Pfizer, (b) (4).</i></p>	

	<i>Whilst dose accuracy has not to date been tested for the lots manufactured by Pfizer, (b) (4) the container closure integrity of the container closure system manufactured by Pfizer, (b) (4) is tested over shelf life as presented in Section 3.2.P.2.5 Microbiological Attributes, which ensures that the internal volume in the syringe is maintained over the proposed shelf life, and assures the dose accuracy would be met at end of shelf life.</i>
Reviewer Comments	<p>The sponsor refers to (b) (4) sterility testing. Those methods are not in CDRH's area of expertise to determine adequacy. If the sponsor can assure by those methods that nothing is leaving the syringe/CCI system then its adequate and no PMC is needed. If those methods do not ensure that, then we recommend PMC. We defer to CDER regarding the methods they reference.</p> <p>Update from 07/09/2021: the review team from CDER confirmed upon their review of the (b) (4) sterility testing of the product/CCI system as follows: <i>In the BLA, firm provided summary reports for the CCITs for the PFS using (b) (4) test methods, (b) (4). Both combinations of the barrels (b) (4) tip cap (b) (4) and plunger stopper (b) (4) have been tested. As part of the stability program, the (b) (4) test has been planned through 30 months, with (b) (4) syringes tested at each time point completed through 0, 3, 6, 9, 12 and 24 months storage to date. All examined units are contaminant free for samples with up to 24 months in the stability program. The integrity of the PFS has been demonstrated. Both CCITs used acceptable (b) (4) that provided assurance for the sensitivity of the methods. DMPQ has no issues with the tests performed.</i></p> <p>CDRH has no further requests for PMC and is satisfied with Pfizer's response as well as product reviewer's clarification.</p>
Response Adequate:	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No, See IR # Sent on

<<END OF REVIEW>>

8. APPENDIX A (INFORMATION REQUESTS)

8.1. Filing/74-Day Information Requests

N/A

8.2. Mid-Cycle Information Requests

1. You reference multiple DMFs in your submission. For each DMF, you have not specifically indicated where the data is located that will be used in support of your submission. Provide specific references to how and where the referenced data will be used in support of your device's adequate verification and validation.
2. You provided Table 3.2.P.8.1-1 (Summary of Stability Studies) on page 5 of document "stability-summary.pdf". It is unclear how this information relates to the subject drug product. Provide clarification regarding how each study is applicable to the current subject drug product and evidence to demonstrate that all device essential performance requirements (EPRs) have been evaluated over the intended shelf life.
3. You have not addressed all of the essential performance requirements (EPRs) for your device constituent. Provide the specification, verification, validation, stability/aging, shipping/transportation for each PFS EPR (dose accuracy/extractable volume, (b) (4)
 Additionally, provide your quality control strategy that explains how EPRs for your combination product are controlled.

8.3. Interactive Information Requests

8.3.1. *Interactive Information Requests sent on* *Click or tap to enter a date.*

9. APPENDIX B: FACILITIES & QUALITY SYSTEMS REVIEW

9.1. Facility Inspection Report Review

N/A

9.2. Quality Systems Documentation Review

N/A

9.3. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	Mid-Cycle Deficiencies: <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	Final Deficiencies: <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
Reviewer Comments		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: <input type="checkbox"/> Yes <input type="checkbox"/> No		

10. Appendix C: Stability testing

Stability information for FSME-IMMUN drug product stored under the recommended long-term condition of 5± 3°C, the accelerated condition of (b) (4) as well as (b) (4)

Primary stability studies have been completed at (b) (4)
Supportive studies have also been both 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 shelf life is 30 months when stored at the recommended temperature of 5 ± 3°C.

Table 3.2.P.8.1-1 Summary of Stability Studies

Lot Number	Presentation	Manufacturing Site	Study Purpose	Study Type	Storage Condition	Data Presented
Primary Stability Studies						
(b) (4)						

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

(b) (4)

(b) (4)

stability-data-pfizer(b) (4).pdf found in sequence 0001 3.2.P.8.3

This data did not include any information regarding the device EPRs. Additionally, per the Accelerated (b) (4) (b) (4) the accelerated testing is not sufficient as the duration of testing should be at least (b) (4) days.

The sponsor needs (b) (4) months of (b) (4) to demonstrate (b) (4) months of stability for the Pfizer, (b) (4) site. If we can leverage the data from the previous sites, then extractable volume has been tested ad nauseum.

However, for all these lots that have been tested, I do not know how many samples were tested. If we cannot leverage the data from the previous sites, then the testing listed in below is not sufficient for extractable volume.

Table 3.2.P.8.3-1. Pfizer, (b) (4) Drug Product Stability Program

(b) (4)

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