

**DMPQ BLA Review Memo BLA 125731/0 20-valent Pneumococcal Conjugate Vaccine
[Diphtheria CRM₁₉₇ Protein]**

CBER CMC and Facility BLA Review Memorandum

BLA STN 125731/0

**Product Name: 20-valent Pneumococcal Conjugate Vaccine [Diphtheria CRM₁₉₇
Protein]**

Wei Wang, Ph.D./Microbiologist/CBER/OCBQ/DMPQ

**DMPQ BLA Review Memo BLA 125731/0 20-valent Pneumococcal Conjugate Vaccine
[Diphtheria CRM₁₉₇ Protein]**

1. BLA#: STN 125731/0

2. APPLICANT NAME AND LICENSE NUMBER

Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer Inc, abbreviated as Pfizer, U.S.
License Number: 0003

3. PRODUCT NAME/PRODUCT TYPE

20-valent Pneumococcal Conjugate (20vPnC) Vaccine [Diphtheria CRM₁₉₇ Protein].

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

Pfizer is developing 20vPnC to expand serotype coverage for the prevention of pneumococcal disease beyond that of the currently registered 13-valent pneumococcal polysaccharide conjugate vaccine (13vPnC, serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F). 20vPnC contains the same capsular polysaccharide conjugate serotypes in 13vPnC and 7 additional serotypes (7vPnC, serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F) with each serotype saccharide individually conjugated to diphtheria CRM₁₉₇ protein. The conjugates induce serotype-specific responses to the capsular polysaccharides contained in the vaccine (and within-serogroup for certain serotypes, e.g. serotype 15C) intended to protect against disease due to the vaccine serotypes.

The 20vPnC vaccine is a single dose (0.5mL) supplied as a sterile liquid suspension (which contains no preservatives) in a single-use 1 mL glass pre-filled syringe (PFS) with a (b) (4) elastomeric plunger stopper and a Luer lock closure.

5. MAJOR MILESTONES

6. CMC/Facility REVIEW TEAM

| Reviewer/Affiliation | Section/Subject Matter |
|----------------------------------|---|
| Wei Wang, Ph.D., OCBQ/DMPQ/B1 | <ul style="list-style-type: none">• Module 1• Module 3:<ul style="list-style-type: none">○ 3.2.S Drug substances<ul style="list-style-type: none">▪ Pneumococcal Polysaccharide (PS) of 20 serotypes▪ Diphtheria cross reactive material (CRM-CY and CRM-DM)▪ PS-CRM conjugates (20 serotypes)○ 3.2.P Drug product○ 3.2.A Facilities and Equipment |
| | |

7. INTER-CENTER CONSULTS REQUESTED

**DMPQ BLA Review Memo BLA 125731/0 20-valent Pneumococcal Conjugate Vaccine
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| Reviewer/Affiliation | Section/Topic | In agreement with consult recommendations (Yes/No) |
|----------------------|---------------|---|
| | | |

8. SUBMISSION(S) REVIEWED

| Date Received | Submission | Comments/ Status |
|---------------|-----------------|---|
| 9/3/2020 | STN 125731/0 | Module 1/reviewed |
| 10/8/2020 | STN 125731/0.1 | Modules 1, 2.2, 2.3, 3.2.S, 3.2.P, 3.2.A and 3.2.R reviewed |
| 2/2/2021 | STN 125731/0.12 | Module 1 reviewed |
| 4/14/2021 | STN 125731/0.27 | Module 1 reviewed |
| 5/21/2021 | STN 125731/0.36 | Module 1 reviewed |

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

Not applicable

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Pfizer submits this BLA, STN 125731/0, for its new 20-valent Pneumococcal Conjugate (20vPnC) vaccine with serotype coverage for prevention of pneumococcal disease beyond that of currently licensed Prevnar 13® (13vPnC) in adult and pediatric populations. The 20vPnC vaccine is modeled after the current Prevnar 13® and contains capsular polysaccharides of *Streptococcus pneumoniae* serotypes, each covalently linked to a nontoxic variant of diphtheria toxin, also known as the cross reactive material 197 (CRM₁₉₇) protein. The 20vPnC vaccine contains capsular polysaccharide conjugates of the serotypes present in 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) and seven additional serotypes (abbreviated as 7vPnV, serotypes 8, 10A, 11A, 12F, 15B, 22F and 33F). The excipients (polysorbate 80, succinate buffer, sodium chloride) and aluminum phosphate components have been conserved between Prevnar 13 and 20vPnC.

The drug substance intermediates (b) (4)

(b) (4) drug product are manufactured in three current manufacturing sites (including Pfizer (b) (4) site, FEI (b) (4), Pfizer (b) (4) site, FEI (b) (4), and Pfizer (b) (4) site, FEI (b) (4)). CBER waived the pre-license inspections of these three manufacturing facilities based on outcomes of the recent FDA (ORA and Team Biologics) surveillance inspections of these facilities involved with the manufacture of drug substances and drug product of 20vPnC.

This review memo covers areas including Chemistry and Manufacturing Controls (CMC) with focus on microbial controls, Facility and Equipment with focus on facility and major equipment qualification.


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Based on review of this BLA submission and amendments which addressed the DMPQ information requests, approval of this BLA is recommended with following Inspectional Consideration items.

Inspectional Consideration Items:

CBER recommends following items may be followed up in a next FDA inspection. CBER understands that this recommendation may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion.

(b) (5), (b) (7)(E)



B. RECOMMENDATION

I. APPROVAL

Based on information reviewed in this submission, approval is recommended

II. COMPLETE RESPONSE (CR)

III. SIGNATURE BLOCK

| Reviewer/Title/Affiliation | Concurrence | Signature and Date |
|--|-------------|--------------------|
| Wei Wang, Ph.D., Microbiologist OCBQ/DMPQ/Branch 1 | Concur | |
| Lori Peters Acting Branch Chief, OCBQ/DMPQ/Branch 1 | Concur | |
| John A. Eltermann, Jr., R.Ph., M.S., Diversion Director, OCBQ/DMPQ | Concur | |

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Module 3

3.2.S DRUG SUBSTANCE

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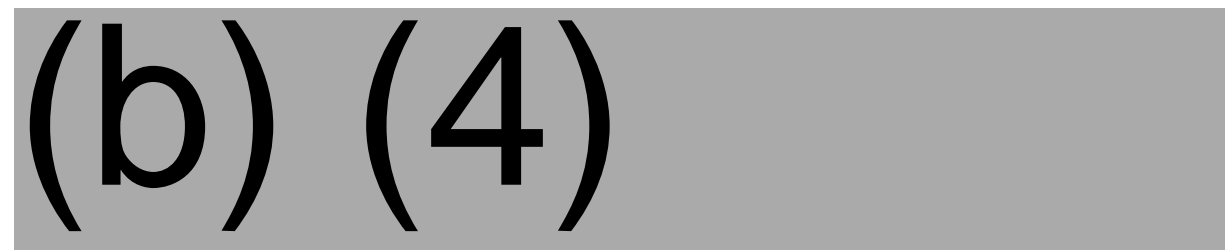
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above described 2L FC closure system for all MCB serotypes in 20vPnC. No objectionable issues were identified. No new container closure integrity test (CCIT) data is required.

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.2.P DRUG PRODUCT

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

The 20-valent Pneumococcal Conjugate (20vPnC) vaccine is a sterile liquid suspension for intramuscular administration of capsular polysaccharide antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F with each saccharide individually conjugated to diphtheria cross reactive material (CRM₁₉₇).

Each prefilled syringe of 20vPnC vaccine is designed to deliver 2.2 µg of each conjugate serotype (except serotype 6B) and 4.4 µg of conjugate serotype 6B in 0.5 mL dose of vaccine. The vaccine is formulated in (b) (4) succinate buffer containing (b) (4) sodium chloride (NaCl) and (b) (4) polysorbate 80, at (b) (4), and containing aluminum phosphate at (b) (4) aluminum as an adjuvant. Each 1 mL syringe contains a 0.5 mL dose of vaccine, supplied as a single-dose injection for parenteral administration, with no preservative.

The 20vPnC vaccine is formulated on the basis of the saccharide content, and the amount of protein is dependent on the saccharide/protein ratio of each conjugate.

To ensure that a 0.5 mL nominal volume can be administered, there is an overfill of (b) (4). There is no manufacturing overage.

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Review Comments: *Beside the new 20vPnC vaccine consists of the 7 additional conjugate serotypes (7vPnC), the manufacture of the new 20vPnC vaccine drug product use the same formulation and syringe-filling equipment located in the same manufacturing areas which are used for the manufacture of the licensed Prevnar 13.*

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The names, addresses, and responsibilities of each aluminum phosphate (AlPO₄) suspension and 20-valent Pneumococcal Conjugate (20vPnC) vaccine manufacturing site and contract laboratories are provided in Table 81.

Table 81. Manufacturing Responsibilities for AlPO₄ Suspension and 20vPnC Vaccine

| Name and Address | Responsibilities | Quality System Provisions |
|---|---|--|
| Pfizer (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) | AlPO₄ Manufacture Testing 20vPnC Vaccine Formulation and syringe filling Primary packaging release testing | 21 CFR 210, 211, 600-680 21 CFR 4.4(b)(1) 21 CFR 820.30 Design Controls 21 CFR 820.50 Purchasing Controls 21 CFR 820.100 Corrective and Preventive Action |
| Pfizer (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) | AlPO₄ (b) (4) testing 20vPnC Vaccine Labelling Secondary packaging | 21 CFR 210, 211, 600-680 21 CFR 4.4(b)(1) 21 CFR 820.20 Management Responsibility 21 CFR 820.30 Design Controls 21 CFR 820.50 Purchasing Controls 21 CFR 820.100 Corrective and Preventive Action |
| Additional Storage Site: (b) (4) (b) (4) (b) (4) (b) (4) | 20vPnC Vaccine Backup sample storage | N/A |

3.2.P.3.2 Batch Formula

The target drug product batch sizes are (b) (4). Table 82 presents the drug product unit formula for (b) (4) of formulated bulk vaccine, as well as the batch formula for representative batch sizes of (b) (4).

(b) (4)



3.2.P.3.3 Description of Manufacturing Process

Buffer preparation: In the 20vPnC drug product (DP) manufacturing process, (b) (4) succinate, (b) (4) sodium chloride (b) (4)) is prepared (b) (4)

Formulation process: (b) (4)



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- For sterile filtration, (b) (4)

AlPO₄, (b) (4)

Formulation is operated under the process controls outlined in Table 83. The in-process tests for control (IPT-C) performed during formulation process are summarized in Table 84.

Table 83. Process Parameters for Formulation Process

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

Table 84. In-Process Tests for Formulation Process

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

(b) (4)

Filling process: The formulated bulk vaccine is then filled into syringes to deliver a nominal dose of 0.5 mL, and the syringes are stoppered. The filling of syringes is performed with a syringe filling machine housed in a Grade (b) (4) with a Grade (b) (4) background. The filler is (b) (4) syringe filling machine with a nominal filling speed of (b) (4) syringes (b) (4)

. The syringes are visually inspected using an automated visual inspection machine or manual visual inspection. The filled DP syringes are stored at 2-8 °C until ready to be shipped from (b) (4), where the syringes are packaged and labeled.

See Section 3.2.P.3.3 *Description of Manufacturing Process and Process Controls Filling* for more information regarding syringe filling process.

Syringe filling is operated under the process controls outlined in Table 85. The in-process tests for syringe filling process are summarized in Table 86.

Table 85. *Process Parameters for Syringe Filling Process*

(b) (4)

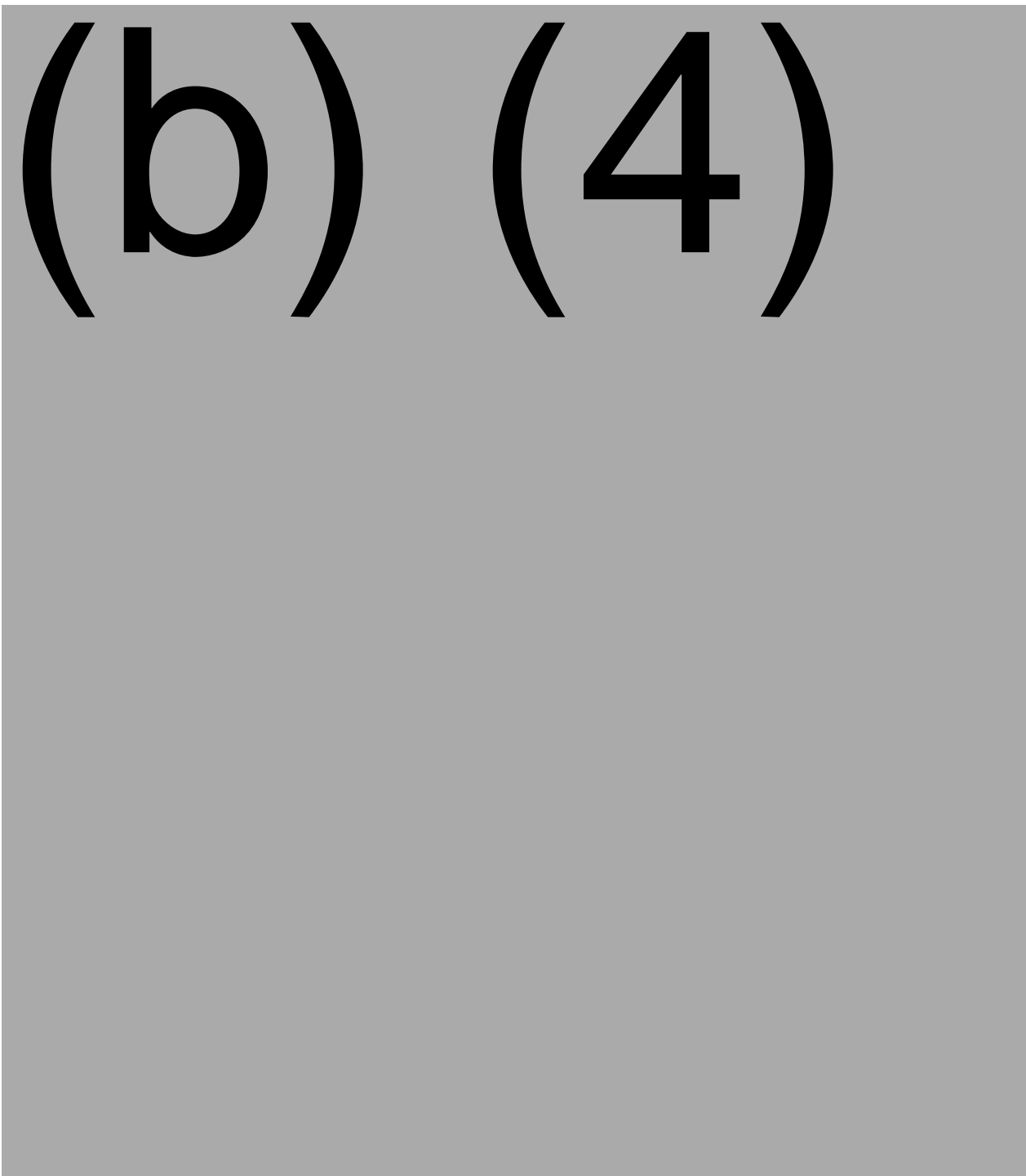


Table 86. In-Process Tests for Syringe Filling Process

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

(b) (4)

A flow diagram of the 20vPnC vaccine drug product manufacturing process is depicted in Figure 38.

Figure 38. Flow Diagram of Overall Manufacturing Process and Process Controls

(b) (4)

Review Comments: *The drug product manufacturing process for the 20vPnC vaccine uses the same formulation and filling equipment, and the same drug product container closure system which are used for the licensed Prevnar 13.*

Noted, the sponsor recently submitted a Prior Approval Supplement under BL 125324 for the addition of the (b) (4)) as an additional Prevnar 13 DP manufacturing facility for DP formulation and fill/finish (STN 125324/1941, approved by FDA on March 4, 2021). The review of the DP filling process leveraged the current licensed syringe filling process of Prevnar 13.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Review Comments: *The process parameters and IPT-C for formulation and filling process were provided above in Tables 83-86. (b) (4) tests and acceptance criteria (Table 84) for the (b) (4) appear acceptable. DMPQ defers to the Product Office reviewers to further evaluate the adequacy of process parameters and IPT-Cs.*

Process Hold Times and Time Out of Refrigeration

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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3.2.P.3.5 Process Validation and/or Evaluation

Drug Product Process Validation Lots

The information of drug product validation lots is summarized in Table 87.

(b) (4)

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(b) (4)

(b) (4)

3.2.P.4 Control of Excipients [Compendial] and [Non-Compendial]

DMPQ defers to the Product Office to evaluate this section.

3.2.P.5 Control of Drug Product

3.2.P.5.4 Batch Analyses

Review Comments: In 3.2.P.5.4 Batch Analyses, the sponsor provided batch analyses data for 20vPnC drug product lots, including pre-phase (b) (4) lots, phase (b) (4) clinical lots, and (b) (4) PV lots (b) (4).

All test results of the PV lots met acceptance criteria, including Endotoxin test results (b) (4) for all (b) (4) PV lots (acceptance criteria (b) (4) and sterility test results “Pass” for all (b) (4) PV lots (acceptance criterion: confirm to compendia requirement). In addition, the Visual Inspection (appearance) results were all Pass (Homogeneous, white suspension). DMPQ defers to the Product Office reviewers to evaluate the release testing results of other product quality attributes.

3.2.P.7 Container Closure System

The components of the primary container closure system for the 20vPnC vaccine are listed in Table 92.

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Table 92. Components of Primary Container Closure System for the 20vPnC vaccine

| Component | DMF Reference |
|---|--|
| Syringe: 1 mL (b) (4) borosilicate glass with Plastic Rigid Tip Cap (PRTC) tip cap assembly that includes a Luer lock adapter, a rigid cap, and a tip cap. Syringe barrel is (b) (4). Tip cap is composed of gray (b) (4) rubber). | DMF (b) (4) STN (b) (4) (Syringe tip cap) |
| Syringe: 1 mL (b) (4) borosilicate glass with (b) (4) tip cap assembly that includes a Luer lock adapter, a rigid cap, and a tip cap. Syringe barrel is (b) (4). Tip cap is composed of gray (b) (4) elastomer (b) (4) rubber). | DMF (b) (4) STN (b) (4) (Syringe tip cap) |
| Plunger Stopper: (b) (4) plunger stopper composed of gray (b) (4) elastomer (b) (4) rubber). Plunger stopper is (b) (4). | STN (b) (4) (Plunger stopper) |

a. (b) (4) is compliant with (b) (4).

Review Comment: The same container closure system (single use, disposable 1mL syringe) is used for the licensed Prevnar 13 and the new 20vPnC vaccine with the same presentation (i.e. 0.5mL fill volume/1mL syringe).

The syringes are received at the drug product manufacturing site ready-to-use, (b) (4). 20vPnC assembled drug product syringes are placed into sealed thermoformed trays (secondary packaging). The carton is constructed of paperboard. Each tamper-evident carton contains the drug product syringe(s) in a sealed thermoformed tray(s) and the package insert or instructions for use that fit inside the outer carton

3.2.P.8 Stability

Review Comments: Overall, the review of stability is mainly the PO's responsibility, because the PO reviews all the product quality attributes, including the results of endotoxin and sterility, to evaluate whether the overall product quality remain within the acceptance criteria through the defined expiry period under the defined storage conditions.

The DMPQ reviews results of endotoxin, sterility and CCIT (if any). The DMPQ defers to the PO reviewers to evaluate whether the sponsor provided sufficient stability data to support the proposed shelf-life. DMPQ also defers to the PO reviewers to evaluate

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whether the submitted Post-Approval Stability Protocol and Stability Commitment in Section 3.2.P.8.2 is acceptable.

In Section 3.2.P.8.1 *Stability Summary and Conclusion*, the sponsor stated that (b) (4) Phase 3 clinical lots (b) (4) of the 20vPnC vaccine are placed on formal/primary stability studies to establish a shelf life and to demonstrate product stability through the defined expiry period when stored under the recommended storage conditions of 5±3°C (2 – 8°C). The sponsor also included additional lots (e.g. PV lots and engineering lots) on supportive stability to support the justification of specifications, and to further support product stability and shelf life.

The sponsor provided stability protocols and available stability data under each storage condition (data under the DMPQ purview is noted), and stated that the shelf life of 20vPnC drug product is 24 months when stored at the recommended temperature of 2 – 8°C:

- under the long term condition of 5±3 °C.
- under accelerated condition of (b) (4) *Noted, there was no data under the DMPQ purview.*
- (b) (4)
- under photostability conditions. *Noted, there was no data under the DMPQ purview.*

The stability attributes under the DMPQ purview are the following:

- Endotoxin (Compendial, (b) (4) method, Acceptance Criteria: (b) (4) proposed test interval of 0, 24, (b) (4) months.
- Sterility (Compendial, Acceptance Criteria: No growth detected), proposed test interval of 0, 24, (b) (4) months.
- Container Closure Integrity (Compendial, Acceptance criteria: pass), proposed test interval of 12, 24, (b) (4) months.

Review Comments: *The sponsor described a CCIT (compendial, (b) (4) detection) procedure in 3.2.P.5.2 Analytical Procedures Container Closure Integrity. It appeared that the sponsor included adequate controls, such as Positive Control (a syringe with a certified (b) (4) Negative Control (a syringe without exposure to (b) (4), and (b) (4) Positive Control (a syringe with (b) (4) to*

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verify LOD at the day of testing). The assay acceptance criteria include: the Negative Control displays no evidence of (b) (4), the Positive Control displays a visible (b) (4), and the (b) (4) Positive Control displays a visible (b) (4). For Tested Syringes (TS), and evidence of (b) (4) into the syringe (b) (4) shall constitute a test failure. The sponsor described CCIT procedure appeared acceptable.

3.2.P.8.3 Stability Data

The following two documents contained stability data under the DMPQ purview:

- 3.2.P.8.3 Stability Data Long Term Stability Data
- 3.2.P.8.3 Stability Data (b) (4) Stability Data – (b) (4)

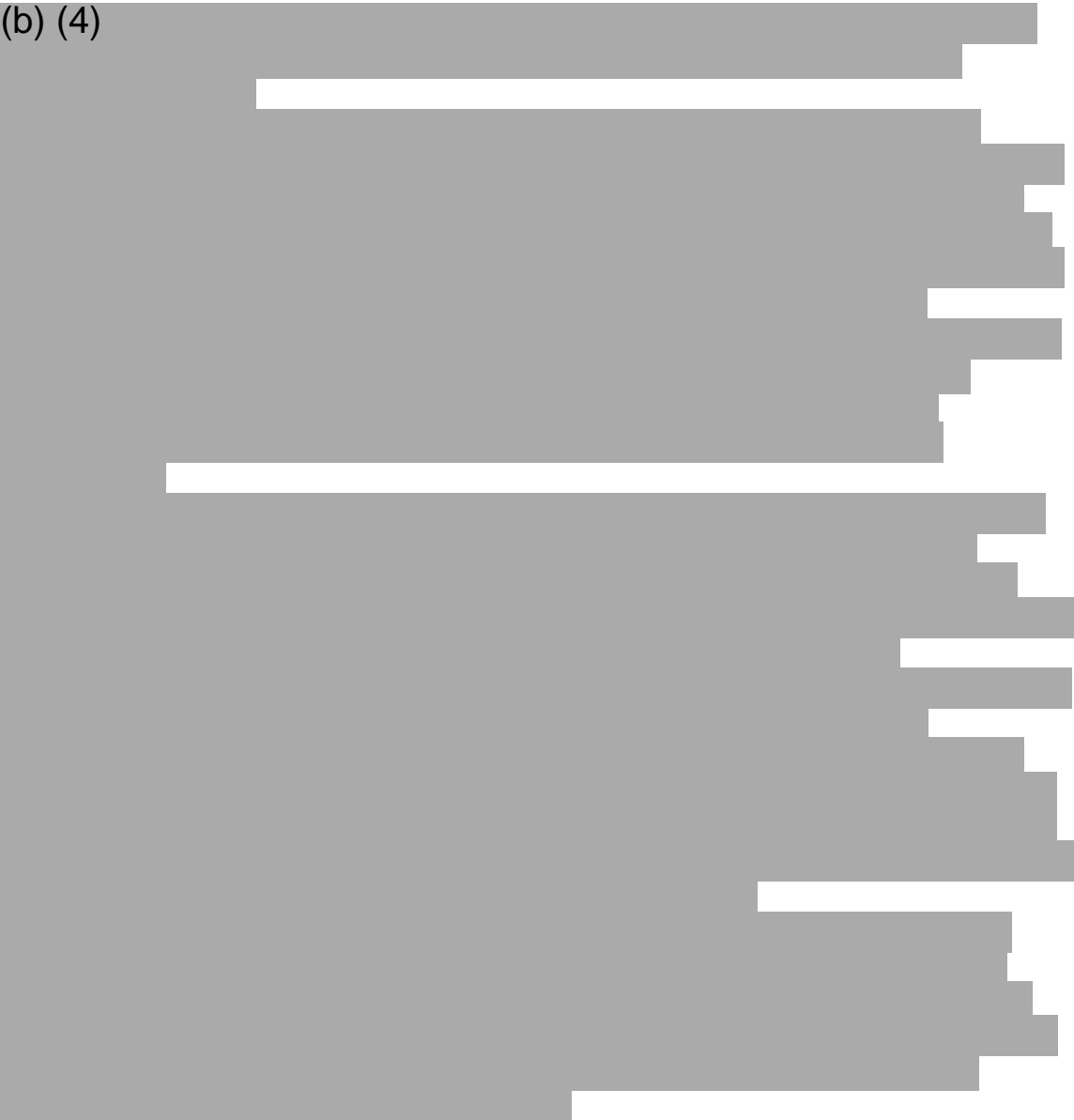
Review Comments: DMPQ reviews the submitted stability data for endotoxin, sterility and CCIT. For the primary stability lots (b) (4) only up to 18 months stability results were provided, the T0 time point endotoxin and sterility data were from batch release testing (reviewed above in Section 3.2.P.5.4 Batch Analyses), and the CCIT results at the T12 were all “Pass”. For Supportive Stability lots, up to (b) (4) months results were available, and all available Endotoxin, Sterility, and CCIT data met acceptance criteria. DMPQ defers to the Product Office to review additional product quality attributes to evaluate the adequacy of product stability.

3.2.A.1 Facilities and Equipment (DMPQ)

Pfizer (b) (4) Site

(b) (4)

(b) (4)

- (b) (4)
- 

Pfizer (b) (4) site

Review Comments: The Pfizer (b) (4) facility (FEI: (b) (4)) has been approved for (a) the manufacture of drug substances (DS), including pneumococcal polysaccharide-CRM₁₉₇ conjugate serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (i.e. the 13 serotypes pneumococcal polysaccharide conjugates, DS, in Prevnar 13, and (b) the manufacturing of the drug product (including formulation and syringe-filling) of Prevnar 13. The same 13 serotypes of pneumococcal polysaccharide conjugates will be manufactured at the Pfizer (b) (4) site for both the licensed Prevnar 13 and the new 20vPnC vaccine. The sponsor stated that there are no changes to the manufacturing process and manufacturing equipment for pneumococcal polysaccharide conjugate serotypes in 13vPnC (Prevnar 13). The sponsor indicated

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that the same drug product manufacturing equipment, including the formulation equipment and the syringe filling line, are used for manufacturing the licensed Prevnar 13 and the new 20vPnC vaccine.

The Pfizer (b) (4) site has been regularly inspected by FDA. The manufacture of Prevnar 13 was covered by the last ORA inspection (classified as VAI) in (b) (4). The review of the Pfizer (b) (4) facility is leveraged based on the review of Prevnar 13, BL 125324. The documents submitted in Section 3.2.A.1 (b) (4) Site] were reviewed below and were found acceptable:

General Information and Flows (b) (4) Site)

- 3.2.A.1 Facilities and Equipment (b) (4)] Manufacturing Suite (MS) (b) (4) – Drug Substance and Drug Product General Information. The sponsor stated that the Pfizer (b) (4) facility is comprised of (b) (4) main buildings connected by enclosed corridors for utilities, warehouse facilities, production facilities, office space, laboratory testing and process and laboratory development. The sponsor provided a (b) (4) site plan in section 3.2.A.1 Facilities-and-equipment-drw-00-rd-0001-(b) (4) Site Plan.

The manufacture of pneumococcal saccharide-CRM conjugate serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (13vPnC, DS) is conducted in (b) (4). The drug product manufacturing process steps (including formulation and syringe filling) are conducted in (b) (4).

- 3.2.A.1 Facilities and Equipment (b) (4)] Manufacturing Suite (b) (4) – Drug Substance Flows. The manufacture of pneumococcal saccharide-CRM conjugate serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F are performed in Grade (b) (4) areas in the manufacturing suites, (b) (4).

The sponsor summarized personnel flow and gowning procedures as follows:

- All personnel flow and gowning requirements are described in site procedures.
- All personnel working in Manufacturing Suite areas are trained in accordance with these procedures. In addition, to minimize contamination and maintain the integrity of the clean room classifications, doors of air locks to classified areas are interlocked. All entries to personnel locks are clearly identified and badge-controlled.

The sponsor provided following diagrams indicating personnel flow into and out of the (b) (4) manufacturing areas:

- 3.2.A.1 Facilities-and-equipment-drw-03-rd-0001-(b) (4) Floor Personnel Flow

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- 3.2.A.1 *Facilities-and-equipment-drw-03-rd-0003-(b) (4) Floor Personnel Flow*
- 3.2.A.1 *Facilities-and-equipment-drw-03-rd-0012-(b) (4) Floor Personnel Flow*
- 3.2.A.1 *Facilities-and-equipment-drw-03-rd-0014-(b) (4) Floor Personnel Flow*
- 3.2.A.1 *Facilities-and-equipment-drw-03-rd-0017 (b) (4) Floor Personnel flow*
- 3.2.A.1 *Facilities-and-equipment-drw-03-rd-0019 (b) (4) Floor Personnel Flow*

The sponsor stated that general material flow is described in site procedures for material transfer from different air quality levels. Personnel working in Suite (b) (4) and Suite (b) (4) manufacturing areas are trained in accordance with these procedures. All entries to material/equipment locks are clearly identified and badge-controlled.

Material flow for each pneumococcal conjugate can vary across Suite (b) (4) and Suite (b) (4) (b) (4)

The sponsor provided following diagrams indicating material and waste flow into and out of the (b) (4) manufacturing areas:

- 3.2.A.1 *Facilities-and-equipment-drw-03-rd-0002-(b) (4) Floor Material Flow*
- 3.2.A.1 *Facilities-and-equipment-drw-03-rd-0004-(b) (4) Floor Material Flow*
- 3.2.A.1 *Facilities-and-equipment-drw-03-rd-0013 (b) (4) Floor Material Flow*
- 3.2.A.1 *Facilities-and-equipment-drw-03-rd-0015 (b) (4) Floor Material Flow*
- 3.2.A.1 *Facilities-and-equipment-drw-03-rd-0018 (b) (4) Floor Material Flow*
- 3.2.A.1 *Facilities-and-equipment-drw-03-rd-0020 (b) (4) Floor Material Flow*

Utilities (WFI, and Clean Steam and HVAC, (b) (4) Site))

The validated utility systems at the Pfizer (b) (4) site include WFI systems, Clean Steam (CS) systems and HVAC systems.

Water for Injection (WFI)

The sponsor stated follows:

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- WFI is generated in the manufacturing suites building from reverse osmosis (RO) water using (b) (4) distillation units in a (b) (4) arrangement. Each WFI distillation unit has the capacity to generate approximately (b) (4) of WFI per hour. The WFI distillation units supply hot WFI at a minimum temperature of (b) (4). WFI storage in the manufacturing suites building is maintained hot at (b) (4).
- Storage and distribution systems are designed with the following design components: (b) (4) piping, fully drainable, absence of dead legs, recirculating turbulent flow, low-point drains, sample valves, and critical alarms including (b) (4)
- The manufacturing suites building has (b) (4) WFI distribution systems: (b) (4) (which is not used for the manufacture of DS or DP of the Pevnar 13 or the new 20vPnC). WFI is distributed to manufacturing suite (b) (4) through a re-circulating WFI distribution loop where the use temperatures are (b) (4). All manual use points have (b) (4)
- WFI is used for the preparation of (b) (4) as well as for (b) (4) and process-related water needs. WFI quality is continuously monitored for (b) (4); and is also routinely monitored by Quality Control (QC). Samples are tested for compliance with WFI microbiology and chemistry acceptance criteria per current compendia guidelines

The sponsor provided following documents, including diagrams of WFI system flows and summaries of WFI system validations.

- 3.2.A.1 *Facilities-and-equipment-drw-03-rd-0022* (b) (4) *WFI and Clean Steam System*
- 3.2.A.1 *Facilities-and-equipment-drw-03-rd-0011* (b) (4) *WFI System Flow*
- 3.2.A.1 *Facilities-and-equipment-drw-03-rd-0023* (b) (4) *WFI and Clean Steam Flow*
- 3.2.A.1 *Facilities and Equipment* (b) (4) – (b) (4) *Validation of WFI Systems*. The parameters tested (including (b) (4) and specifications for WFI qualification are summarized in Table 125. All test results met specifications.
- 3.2.A.1 *Facilities and Equipment* (b) (4) – (b) (4) *Validation of WFI Systems*. The parameters tested and the specifications for validation of WFI system in (b) (4) are summarized in Table 125. All validation test results met specifications.

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- 3.2.A.1 Facilities and Equipment (b) (4) – Drug Product Validation of Water Systems. The parameters tested and the specifications for validation of WFI system in (b) (4) are summarized in Table 125. All validation test results met specifications.

(b) (4)

(b) (4)

Clean Steam (CS)

The sponsor provided following documents:

- 3.2.A.1 Facilities and Equipment (b) (4) Validation of the Clean Steam (CS) Systems.
- 3.2.A.1 Facilities and Equipment (b) (4) Validation of the Clean Steam Systems.
- 3.2.A.1 Facilities and Equipment (b) (4) – Drug Product Validation of the Clean Steam Systems.

In addition to the parameters summarized in Table 125, parameters including (b) (4) (acceptable criteria: (b) (4)) (acceptable criteria: (b) (4)) and (b) (4) were tested per (b) (4) for the validation of CS systems. The sponsor provided validation test results and showed that all specifications were met. The sponsor summarized addendum CS qualifications and concluded that the Clean Steam system is qualified. The sponsor indicated that a routine monitoring program for the clean steam system was established and is currently ongoing.

Heating, Ventilation and Air Conditioning (HAVC) Systems

Review Comments: *The following documents in Section 3.2.A.1 were reviewed and found acceptable.*

- *Facilities-and-equipment-drw-03-rd-0008-(b) (4) Pressurization and Classification Plan*
- *Facilities-and-equipment-drw-03-rd-0016 (b) (4) Pressurization and Classification Plan*
- *Facilities-and-equipment-drw-03-rd-0021 (b) (4) Pressurization and Classification Plan. The filling (b) (4) are located inside filling rooms (Grade (b) (4)).*
- *3.2.A.1 Facilities and Equipment (b) (4) – Drug Substance Validation Summary of the HVAC Systems*
- *3.2.A.1 Facilities and Equipment (b) (4) – Drug Substance Validation Summary of the HVAC Systems*
- *3.2.A.1 Facilities and Equipment (b) (4) – Drug Product Validation Summary of the HVAC Systems*

The sponsor stated that HVAC systems serving the manufacturing suites, (b) (4), are designed to meet the environmental requirements for the activities performed in the specific process areas and to provide environmental, product and personnel protection. HVAC systems are located in the manufacturing suites building mechanical (b) (4).

The HVAC systems serving (b) (4) include air-handling units (AHU) and distributed ductwork servicing controlled environments. (b) (4)

(b) (4)

The HVAC system serving (b) (4)

(b) (4)

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The qualified building management system (QBMS) automatically controls and monitors the HVAC systems. Temperature is monitored and controlled by sensors located in the (b) (4). Based on the feedback signal provided by the humidity control sensor, the HVAC can (b) (4).

The HVAC units maintain a target room temperature of (b) (4) and the relative humidity operating specification is (b) (4).

Classified HVAC systems are certified (b) (4). The certification includes HEPA (b) (4).

Routine sampling sites were determined based on hazard analysis critical control point analysis and risk assessment. Types of sampling include non-viable particulate, viable air particulate, and surface sampling. Sampling is performed as per frequency listed in site procedures. Grade (b) (4) area rooms are monitored not less than (b) (4) and grade (b) (4) area rooms are monitored not less than (b) (4). Sampling is performed under in operation conditions to ensure areas are adequately evaluated.

Review Comments: *In the HVAC validation documents, the sponsor showed that the HVAC action levels under dynamic conditions for non-viable air, active viable air and surface viable limits are the same as at the Pfizer (b) (4) sites (Table 98). The sponsor provide passing results for manufacturing suites, (b) (4) (Grade (b) (4) Grade (b) (4) areas).*

In addition, for validation of HVAC systems in (b) (4), the sponsor provided passing results of (b) (4) for viable air (b) (4), with acceptance criteria of (b) (4) for Grade (b) (4) area, (b) (4) for Grade (b) (4) area, (b) (4) for grade (b) (4) area, and (b) (4) for grade (b) (4) area).

The sponsor provided a summary report, Validation of the (b) (4) Surface Decontamination Cycle of the Filling (b) (4), (reviewed below) for the filling (b) (4) (Grade (b) (4) and (b) (4) areas) in (b) (4).

Environmental Qualification and Monitoring ((b) (4) Site)

Review Comments: *The following documents summarizing the Environmental Qualification and Routine Environmental Monitoring for the manufacturing suites, (b) (4), were reviewed and were found to be acceptable:*

- 3.2.A.1 Facilities and Equipment (b) (4) – Drug Substance
Environmental Qualification and Monitoring
- 3.2.A.1 Facilities and Equipment (b) (4) – Drug Substance
Environmental Qualification and Monitoring
- 3.2.A.1 Facilities and Equipment (b) (4) – Drug Product
Environmental Qualification and Monitoring

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The sponsor stated that all areas within manufacturing suites (b) (4) are classified in accordance with the activities that occur within the area and the level of containment and environmental control that is required. Areas are classified per th (b) (4)

The sponsor provided information of HVAC units in different manufacturing areas (room numbers and classifications).

The sponsor stated that the environmental qualifications evaluated multiple sample sites in the various environments for viable air sampling (b) (4) and surface contact plates, and total particulates (b) (4) for each classified environment defined in the protocol.

The sponsor stated that all results of the environmental qualifications of the classified areas in (b) (4) met the environmental quality requirements defined in the protocol. During qualification, and that all media used was certified for growth promoting qualities prior to use.

The sponsor stated that the classified manufacturing areas in (b) (4) are routinely monitored for viable air and no-viable air particulates. The air samples, frequency of sampling and action levels for environmental monitoring are as summarized above in Table 102 (for Grade (b) (4) areas) and Table 103 (for Grade (b) (4) areas). In addition (b) (4) Action Level: (b) (4) are tested at the Pfizer (b) (4) site.

Support Utilities and Computer Systems (b) (4) Site)

Review Comments: *The following documents were reviewed and found acceptable:*

- 3.2.A.1 Facilities and Equipment (b) (4) – Drug Substance Support Utilities.
- 3.2.A.1 Facilities and Equipment (b) (4) – Drug Substance Support Utilities.
- 3.2.A.1 Facilities and Equipment (b) (4) – Drug Product Support Utilities. Support utilities in (b) (4) are the same, including:
 - (b) (4) systems and Process (b) (4) system, which are all controlled, monitored using a manufacturing control system (MCS).
 - Emergency Electrical Power, which is controlled and monitored using an electrical control system (ECS).
 - Plant Steam system, Chilled Water system, and (b) (4) Water system, which are all controlled, monitored using a building management system (BMS).
- 3.2.A.1 Facilities and Equipment (b) (4) Manufacturing Suite (b) (4)

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- 3.2.A.1 *Facilities and Equipment* (b) (4) Manufacturing Suite (b) (4)
- 3.2.A.1 *Facilities and Equipment* (b) (4) Manufacturing Suite (b) (4)

(b) (4)

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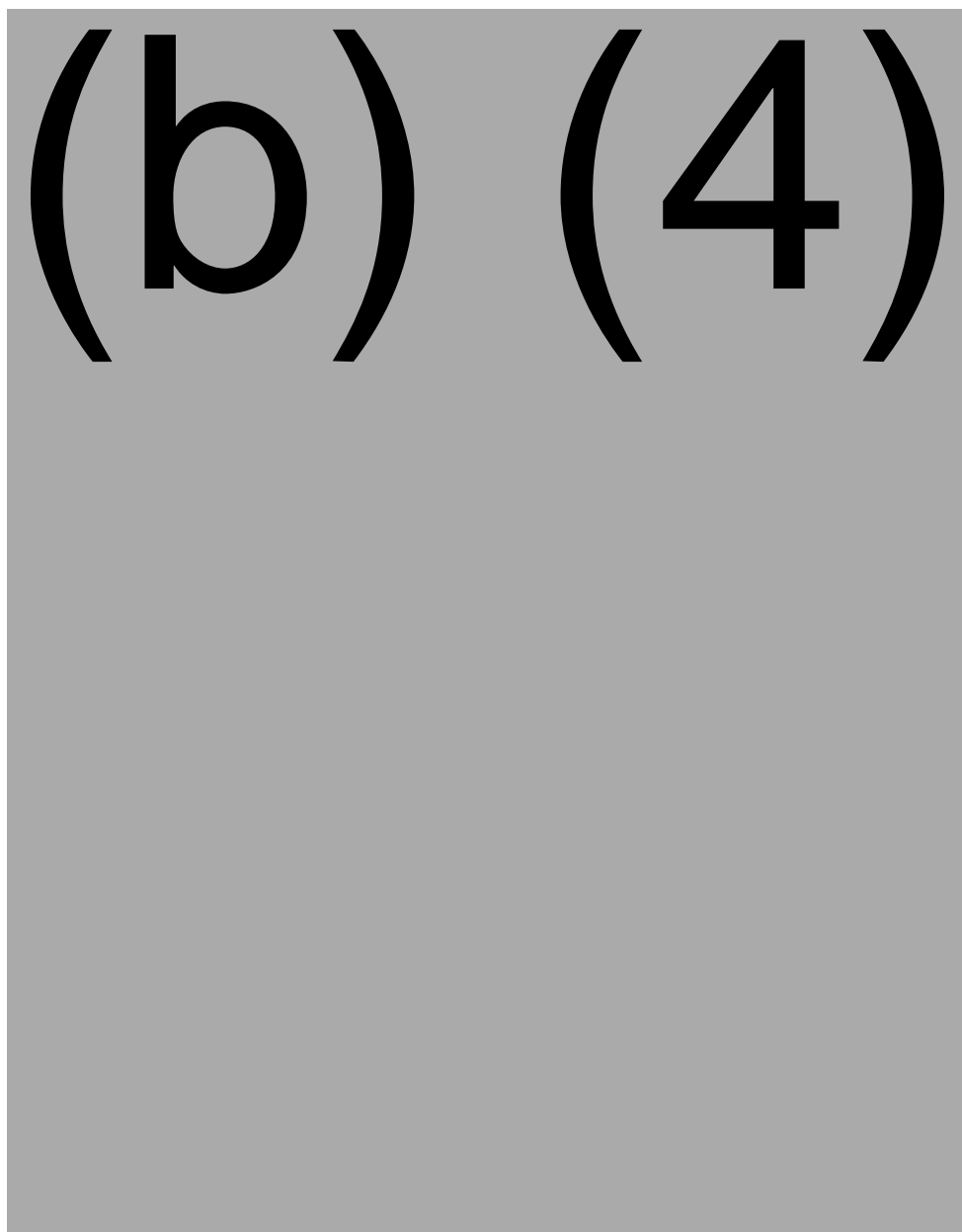
[Redacted text block]

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Manufacturing Equipment and Equipment Qualification (b) (4) Site)

Review Comments: *Following manufacturing equipment documents were reviewed and found acceptable:*

- (b) (4)



(b) (4)

- 3.2.A.1 *Facilities and Equipment* (b) (4) – *Drug Product Manufacturing Equipment.*

The sponsor stated that syringe fill finish (SFF) is designed as a (b) (4)-product facility for drug product formulation, syringe filling and inspection. SFF is currently dedicated to the production of vaccine filled syringes (Prevnar 13, 20vPnC vaccine, (b) (4)). The suite is provided with a (b) (4) and is used for intermediate product, equipment, materials and personnel flow. Gown and de-gown rooms are provided at the (b) (4) end of the corridor.

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The sponsor provided a list of the major equipment (in MS^{(b) (4)} used for the manufacture of drug product and AIPO4 in Table 3.2.A.1-1, and a list of the major MS^{(b) (4)} manufacturing equipment requiring (b) (4) in Table 3.2.A.1-2.

(b) (4)

(b) (4)

(b) (4)

Review Comments: *Following equipment qualification documents were reviewed and found acceptable. As the firm stated that there is no significant changes to the manufacturing facility and equipment at the Pfizer (b) (4) site:*

- (b) (4)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Equipment Cleaning and Sanitization (b) (4) Site)

The sponsor provided following documents to provide overview and results of cleaning validations performed in DS manufacturing suites (b) (4), and DP manufacturing suite (b) (4)

- 3.2.A.1 Facilities and Equipment [(b) (4)] Manufacturing Suite (b) (4) – Drug Substance Cleaning Validation Overview. The sponsor stated that Product contact equipment / systems used in the production of the

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pneumococcal saccharide-CRM₁₉₇ conjugates in (b) (4) are dedicated to (b) (4) manufacturing. The product contact surfaces are cleaned using validated procedures, including (b) (4) cleaning cycles include a (b) (4)

[REDACTED]

Review Comments: Overall, the equipment cleaning validation strategy, and the equipment cleaning validation parameters and acceptance criteria in (b) (4)

[REDACTED]


- 3.2.A.1 Facilities and Equipment (b) (4) J MS^{(b) (4)} – Drug Substance Cleaning Validation Summary.
- 3.2.A.1 Facilities and Equipment (b) (4) J MS^{(b) (4)} – Drug Substance Cleaning Validation Summary
- 3.2.A.1 Facilities and Equipment (b) (4) J MS^{(b) (4)} – Drug Product Cleaning Validation Overview. The sponsor stated that a (b) (4) approach was taken during cleaning validation of equipment and parts used in the manufacture of 20vPnC (20-valent pneumococcal conjugate vaccine). The product contact equipment and parts that were used in AlPO₄ were dedicated. The product contact equipment and parts that were used in 13vPnC, Trumenba and 20vPnC were dedicated with the exception of (b) (4) which were shared for the (b) (4) used in 13vPnC, Trumenba and 20vPnC manufacture. The (b) (4) were shared between 13vPnC and 20vPnC.

The equipment cleaning validation parameters and acceptance criteria in MS^{(b) (4)} summarized in Table 126. (b) (4)

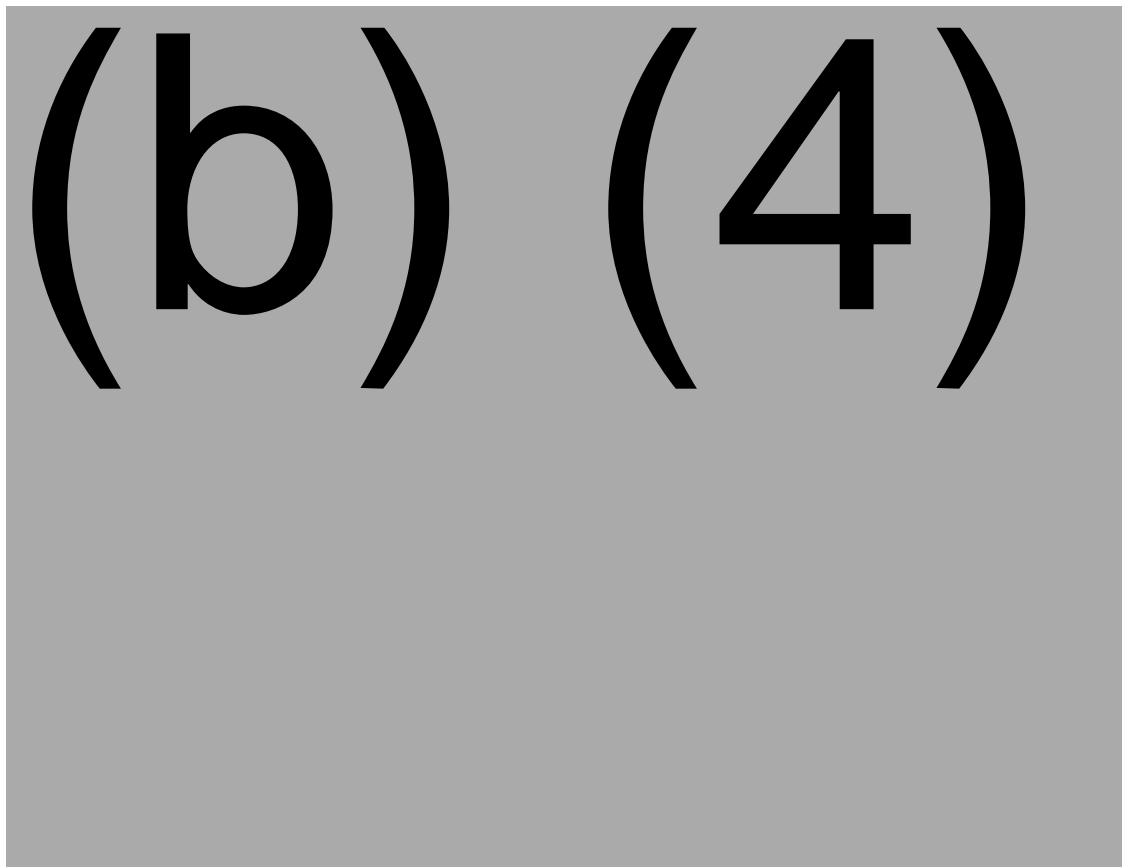
[REDACTED]

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


(b) (4)

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(b) (4)

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(b) (4)

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The sponsor concluded that the cleaning procedures/processes associated with cleaning the equipment/systems used in the production of pneumococcal conjugated vaccine have been validated, results demonstrate that the cleaning procedures are robust and reproducible, and that all cleaning procedures were validated and are suitable for their intended purposes.

Control of Cross Contamination (b) (4) Site)

The sponsor summarized controls implemented in (b) (4) to minimize and prevent cross contaminations in following documents:



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3.2.A.1 Facilities and Equipment (b) (4) – Drug
Substance Control of Cross Contamination.

3.2.A.1 Facilities and Equipment (b) (4) – Drug Product Control
of Cross Contamination.

Controls of cross contamination including follows:

(b) (4)



(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Review Comments: Overall, the aforementioned cross-contamination controls appeared acceptable. No major objectionable issues noted.

Pfizer (b) (4) site

***Review Comments:** The Pfizer (b) (4) site has been recently approved (PAS, STN 125324/1941, approved by FDA on March 4, 2021) for the manufacture of the Prevnar 13 drug product (including formulation and fill/finish). For the manufacture of the 20vPnC, the syringe labeling is performed at the Pfizer (b) (4) site. No change to the manufacturing equipment for syringe labelling of the drug product for Prevnar 13 and the new 20vPnC vaccine.*

3.2.R Regional Information (USA) Executed Batch Records (PO)

DMPQ defers to the PO reviewers to review executed manufacturing batch records of DSI, DS and DP for 20vPnC vaccine.

Combination Products (DMPQ)

Same as the licensed Prevnar 13, the new 20vPnC vaccine in prefilled syringe is regulated as a combination product of biologics and device. The new 20vPnC vaccine is filled in the same syringes which have been used for the licensed Prevnar 13 (13vPnC vaccine). The same filling equipment and manufacturing areas in Pfizer (b) (4) site are used for the approved Prevnar 13 and the new 20vPnC.

The sponsor stated that Pfizer adheres to cGMP for combination products per 21 CFR 4.4(b)(1). A streamlined approach has been established, with a quality system in accordance with 21 CFR 210, 211, 600-680 and the integration of the specific device Quality System Regulation (QSR) applicable provisions as per 21 CFR 820.20 (Management Responsibility), 21 CFR 820.30 (Design Controls), 21 CFR 820.50 (Purchasing Controls) and 21 CFR 820.100 (Corrective and Preventive Action).

In 3.2.R 21 CFR Part 4 Description, the sponsor summarized each device quality system regulation sub-system policy/procedure as follows:

Management Responsibility (21 CFR 820.20): Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer Inc. maintains responsibility and holder of information for the 20vPnC vaccine in prefilled syringe under the Quality System Regulation (QSR). Pfizer has established procedures for the application of management responsibility to combination products. The procedures define how the quality management team, with executive responsibility, establishes its policy, and that quality objectives are defined and achieved. Management has established an organizational structure with roles, responsibilities, and authorities that are defined, communicated and implemented throughout the organization. The foundation of Pfizer's QMS outlines management responsibilities starting with a quality manual followed by quality policies, operating standards, and procedures in compliance with 21 CFR 820.20. QMS requirements,

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procedures, and records are maintained in a validated document management system. The QMS is audited to assess compliance and effectiveness, and periodic management reviews are conducted at a defined frequency to ensure that the quality system is suitable and effective in meeting applicable regulatory standards and quality system requirements.

Design Control (21 CFR 820.30): Pfizer has established procedures for the application of design controls for combination products within the QMS and is a formal process that considers the product through a series of defined activities, from initiation of design requirements through design verification, design validation, design transfer, commercialization and post market surveillance. Each stage defines associated activities and deliverables that may be generated for each activity. The procedures define the processes, requirements and necessary documentation, where relevant, for: Design and Development Planning, Design Input, Design Output, Design Review, Design Verification, Design Validation, Design Transfer, Design Changes, and Design History Files (DHF).

Purchasing Controls (21 CFR 820.50): Pfizer has established purchasing control procedures to ensure that all suppliers of materials, products, and services conform to specifications and requirements. The supplier selection process ensures that Pfizer evaluates the supplier's capability to meet the purchase order or contract requirements. Records of supplier assessment and evaluations are established and maintained. Pfizer has instituted quality agreements with the constituent suppliers for part/component/subassembly. Quality agreements include provisions for Pfizer to be notified of changes to components/subassemblies, and services as defined within the Agreement. Suppliers of materials, components, and services used in the manufacture of Pfizer's combination products as well as contract manufacturing organizations and contract laboratories, are appropriately qualified consistent with 21 CFR 820.50 requirements. Once qualified, Pfizer includes the suppliers on an approved supplier list. Only approved suppliers, contractors, and consultants are used for GMP activities.

Corrective and Preventative Action (21 CFR 820.100): Pfizer has established procedures for application of corrective and preventive action (CAPA) for combination products. The procedures outline the process for identifying, initiating, implementing, verifying, and completing CAPAs. A CAPA is created for potential quality issues identified through non-conformances, complaints, returned product, risk assessments, audits, inspections, and trends. Issues are identified and investigated to determine a root cause or contributing cause, if applicable. CAPAs are defined and implemented, as needed. As appropriate, actions are either verified or validated to ensure effectiveness and assessed to confirm that changes, if implemented, do not adversely impact the safety and effectiveness of the combination product. Final approval and CAPA closure represents verification that the corrective and/or preventive actions have been effective. Periodic management reviews of CAPA trends (including deviation category and root cause) ensure effectiveness of the CAPA process and may result in continuous improvements to the existing procedures.

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The review of combination product is leveraged from the Prevnar 13, BL 125324.

Review Comments: *The DMPQ secondary reviewers request the sponsor to provide further information regarding the Combination Product (see Question 2 of IR dated 3/31/2021).*

Comparability Protocols (PO and DMPQ)

Review Comments: *The sponsor submitted (b) (4) comparability protocols (CP). DMPQ defers to the PO reviewers to review and evaluate the adequacy of (b) (4) CPs regarding preparation, qualification, storage of future working cell banks (WCBs) of *S. pneumoniae* Serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F, and renewal WCBs of *C. diphtheriae* CRM₁₉₇. In these CPs, the sponsor stated that the *S. pneumoniae* Serotypes WCB vials are shipped according to validated procedures using qualified shipping containers, and that renewal WCBs of *C. diphtheriae* CRM₁₉₇ vials are not shipped because they are manufactured and used at the (b) (4) site. DMPQ reviewed following (b) (4) CPs and found them acceptable.*

The following (b) (4) CPs were reviewed above in section of Pfizer (b) (4) Site.

- *3.2.R Comparability Protocol [Serotypes 8, 10A, 11F, 12F, 15B, 22F, 33F and CRM197] Building (b) (4) Equipment Cleaning Comparability Protocol, (b) (4)*
- *3.2.R Comparability Protocol [Serotypes 8, 10A, 11F, 12F, 15B, 22F, and 33F and CRM197] Introduction of Mammalian and Animal Derived (b) (4) and Bacterial Derived Products and Related Raw Materials into the Common Commercial Areas, (b) (4) Facility.*

DMPQ Secondary Review

Information Request (IR dated 3/31/2021) and Responses

The following information request (IR) items were raised by the DMPQ secondary reviewers and were sent to the sponsor on 3/31/2021. The sponsor's responses (received on 4/14/2021, STN 125731/0.27) were reviewed below and were found acceptable:

1. Regarding the equipment in the manufacturing areas in (b) (4) at the Pfizer (b) (4) site:
 - a. Please provide a summary of the equipment qualification information, including Operational Qualification and Performance Qualification for the

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equipment in (b) (4) used for the manufacture of pneumococcal polysaccharide serotypes 8, 10, 11A, 12F, 15B, 22F and 33F.

Sponsor's Responses: In QQR1 Table 1 of Section 1.11.1 *Quality Information Amendment* of STN 125731/0.27, the sponsor listed major equipment in (b) (4) summarized equipment OQ/PQ Testing Requirements and Cleaning Validation PQ Testing Requirements.

Review Comments: *The summarized OQ/PQ testing requirements (e.g. for (b) (4), OQ testing requirements included: (b) (4)*

And PQ testing requirement included (b) (4) Testing) appeared acceptable. The Cleaning Validation Testing Requirements for (b) (4) equipment were the same as provided in the Section 3.2.A.1 Facilities and Equipment (b) (4) Cleaning Validation Summary of the original BLA submission and were already reviewed (see Table 104 and Table 109). The sponsor's response appeared acceptable.

- b. Please provide a table of the equipment in (b) (4) and explain if the equipment is dedicated to the manufacture of pneumococcal polysaccharide serotypes used in Prevnar products (Prevnar 13, Prevnar 20) or if the equipment is shared. If shared, please identify the nature of the other products and provide applicable cleaning validation study.

Sponsor's Responses: The sponsor provided major equipment in (b) (4) in Table 2 of Section 1.11.1 *Quality Information Amendment* of STN 125731/0.27, and specified whether the equipment is dedicated to 20vPnC or shared with another product.

(b) (4)

The sponsor stated that the only product that shares equipment with 20vPnC in (b) (4) is the investigational vaccine, (b) (4) (IND

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(b) (4). The sponsor stated that all shared equipment between 20vPnC and (b) (4) in (b) (4) use the same or comparable validated cleaning cycles. The sponsor provided the (b) (4) cleaning validation (CV) study reports RPT-87439 and RPT-99562, and media preparation equipment and buffer preparation equipment CV study reports RPT-61775 and RPT-100144. For each piece of shared equipment, the section and page number associated with the (b) (4) CV study report were provided in Table 2 above.

***Review Comments:** The referenced sections showed that the (b) (4) cleaning results of (b) (4) for shared equipment, including (b) (4) Table 3-1, Table 3-3, (b) (4), Table 3-4 and (b) (4) Table 3-6, all met acceptance criteria which are the same as specifications for the 20vPnC equipment cleaning (e.g. acceptance criteria specified in Tables 105 and 106). The sponsor's response appeared acceptable.*

- c. If the same equipment was used for the manufacture of commercial scale phase 3 clinical pneumococcal polysaccharide for Prevnar 13, please provide a tabular description of major equipment modifications for the (b) (4) commercialization project which required re-qualification, and a summary of qualification report.

Sponsor's Responses: The sponsor stated that the same equipment (b) (4) used for the manufacture of commercial scale phase 3 clinical pneumococcal polysaccharide (serotypes 3, 6A and 19A for 13vPnC, and serotypes in 7vPnC for 20vPnC) will be used for commercial production of 20vPnC pneumococcal polysaccharide serotypes 8, 10A, 11A, 12F, 15B, 22F and 33F.

In Table 3 of Section 1.11.1 *Quality Information Amendment* of STN 125731/0.27, the sponsor listed major equipment along with modifications (which required re-qualification) for the (b) (4) commercialization project. The sponsor provided a summary report for the project plan, *RPT-89942, Summary Report for (b) (4) Commercialization Project Automation, Equipment, Utilities and Facilities Project Verification Plan per CCR 2446568.*

The sponsor provided cleaning validation study reports, *RPT-103111, Final Report for the Cleaning Validation Assessment for PNG Vaccine Intermediates in Building (b) (4) Post-Commercialization, RPT-100144, Final Report for Cleaning Validation Assessment for (b) (4) Commercialization Project in the Media Prep Area, and RPT-112622, Buffer Prep and (b) (4) Strategy Cleaning Validation for (b) (4) Commercialization Project Final Report.*

***Review Comments:** For equipment requiring requalification, the effective status of each protocol final report was shown as “Effective/complete” in RPT-89942. For equipment requiring cleaning requalification, the sponsor provided cleaning revalidation results in RPT-103111 or RPT-100144, demonstrating that cleaning revalidation results all met acceptance criteria (as specified above, e.g. in Table 105). The sponsor’s responses were accepted.*

2. Regarding the Combination Product designation for your final product, please address the following items:
 - a. For the pre-filled syringe 20vPnC vaccine, please provide Quality System Regulation (QSR) data in Section 3.2.R to demonstrate the compliance with relevant 21 CFR 820 regulations for combination product, including:
 - A summary of Management Responsibility per 21 CFR 820.20.
 - A summary of Design Controls per 21 CFR 820.30. Please provide a copy of the Design History File for the pre-filled syringe supporting your new product indication.
 - A summary of Purchasing Controls per 21 CFR 820.50. Please explain the testing that is performed to ensure the sterility of the product-contact syringe components as received from the supplier(s).
 - A summary of Corrective and Preventive Actions related to the filing and components of the pre-filled syringe per CFR 820.100.

Sponsor’s Responses: In QQR2 of Section 1.11.1 Quality Information Amendment of STN 125731/0.27, the sponsor stated that a summary of Pfizer’s overarching quality system including specific device Quality System Regulations (QSR) 21 CFR 820.20 was provided in Section 3.2.R 21 CFR Part 4 Description of the initial BLA submission. The sponsor stated that information regarding Design Verification, Design Validation, and Risk Management were submitted in following sections:

- Section 3.2.P.2.4.2.3 Product Design Verification, including (a) assessing compliance of product components to acceptance criteria and design requirements through certification and technical information gathered from component manufacturers, and (b) Bench-top laboratory testing of product functional and design attributes including analysis to determine which functional performance requirements are considered essential (defined as EPRs) and would therefore be routinely tested as part of release or stability.
- Section 3.2.P.2.4.2.4 Product Design Validation, summarizing (a) User Task Summary which identifies the primary operating functions which need to be completed to safely and effectively use the product, and (b) Design Validation Summary demonstrating how user needs for the syringe were validated.

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- Section 3.2.P.2.4.2.5 Product Risk Management, including (a) assessment of the risk that the design, manufacture, and use of the 20-valent Pneumococcal Conjugate (20vPnC) prefilled syringe may pose to the patient or user, and (b) Risk analysis was performed and concluded that the overall risk profile of the 20vPnC prefilled syringe is acceptable and that the benefits of using this product outweigh the remaining, marginal risks.

The sponsor provided a traceability matrix (INX100403218) that appraises the 20vPnC design history file and demonstrates how the user needs, design constraints, design input, requirements, and design outputs for the product relate to ensure the product is safe and effective for its intended use. The sponsor stated that syringe filling and stoppering for 20vPnC is solely performed at Pfizer (b) (4) located in (b) (4). The product contacting syringe components, including the syringe barrel with a rigid plastic tip cap and the plunger stopper (as described in Section 3.2.P.7 Container Closure System), are received sterile, ready to use. Sterility of the product contacting components received at Pfizer (b) (4) is controlled through purchasing controls, which include component material specifications for all syringes and plunger stoppers. Documentation demonstrating conformance with purchasing controls is required with each supplier's shipment for every batch of components and must accompany the shipment. Materials cannot be released for production without an authorized copy of the following:

- Syringes – Certificate of Conformance (CoC)
- Plunger Stoppers – Certificate of Analysis (CoA)

Review Comments: *The Section 3.2.R 21 CFR Part 4 Description was already reviewed above in the section 3.2.R Regional Information, Combination Products, and was accepted. The examples of syringe CoCs and plunger stopper CoAs which were submitted in Section 3.2.R. Regional Information were reviewed and accepted. The sponsor's response appeared acceptable.*

- b. Please explain if you updated your Device History File for Prevnar 13 to cover the new product indication or if a new Device History File was created for your new product, 20vPnC vaccine.

Sponsor's Responses: The sponsor stated that components of syringe system are identical to the new 20vPnC vaccine and the licensed Prevnar 13, and are commercially available off-the-shelf and are managed through appropriate purchasing controls. While Prevnar 13 and 20vPnC vaccines are

closely related, having drug product manufacturing equipment of identical design, identical componentry, and processes, a new, independent Design History File was created for the new 20vPnC vaccine product. Given the similarity of the product and its use, development of 20vPnC leveraged learnings and on-market information from Prevnar 13. As such, relevant documents may appear in both Design History Files, but both files are managed and remain separate.

Review Comments: *The sponsor's response appeared acceptable.*

Information Request (IR dated 5/14/2021) and Responses

The following information request (IR) items were raised by the DMPQ secondary reviewers (LP and NL) and were sent to the sponsor on 5/14/2021. The sponsor's responses (received on 5/14/2021, STN 125731/0.36) were reviewed below:

1. In Section 3.2.P.3.5 *Process Validation and/or Evaluation Validation of Aseptic Process by Media Fills*, Table 3.2.P.3.5-2. *20vPnC Bulk Media Fill Details and Visual Inspection Results*, you did not provide media fill information regarding the filling date(s), the filling line(s), and syringe/stopper combinations used in the three runs media fills. Please provide the missing information.

Sponsor's Responses:

The sponsor stated that the media fill program for the 20vPnC vaccine leverages the media fill program previously established for Prevnar 13® for all steps common to both processes. From a media fill perspective, the only difference between the two processes is the (b) (4) step. All other processing steps, aseptic connections and interventions are shared across the processes (as shown in Figure below). To support the introduction of the 20vPnC vaccine, three bulk media fills challenged the (b) (4) operation, once in the (b) (4), the existing media fill program supports all subsequent manufacturing steps. Therefore, filling was not executed for the supplemental 20vPnC bulk media fills.



Because the (b) (4) batch sizes of 20vPnC utilize the (b) (4), only (b) (4) batch of media fills were performed to support this process difference for 20vPnC. The filling line media simulations and bulk media simulations are incorporated into the site media fill strategy.

The sponsor provided the details of the syringe and plunger stopper component combinations for the media fills reported in Table 3.2.P.3.5-4 of Section 3.2.P.3.5 Validation of Aseptic Process by Media Fills (reviewed above on page 132 of this memo), indicating (b) (4) syringes and (b) (4) syringes were used in the media fills.

Review Comments: *As stated and depicted above, to support the manufacture of 20vPnC, the sponsor performed three-run media fills to challenge the (b) (4)*

. The remaining filling steps leveraged the media fills which have been completed with pass results for Prevnar 13 because the filling process steps are the same for the new 20vPnC vaccine and the licensed Prevnar 13. The sponsor's response appeared acceptable.

2. You stated that the primary labeling of the drug product filled syringes is performed at the Pfizer Manufacturing (b) (4) facility in (b) (4).
 - a. Please clarify the facility where the quality control unit reviews and approves the production records of the finished labeled drug products for release or distribution. Please explain if this is similar or different to the oversight for Prevnar13.
 - b. Please clarify the facility that authorizes the release of the labeled drug product to the distribution centers.

Sponsor's Responses:

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- a. Batch record review and approval of the finished labeled drug products is done at the Pfizer Manufacturing (b) (4) facility in (b) (4) which is the same facility where the batch record review and approval of the finished labeled drug products is done for Prevnar 13®.
- b. Release of the labeled product to the distribution centers is done at the Pfizer Manufacturing (b) (4) facility in (b) (4) which is the same facility where the release of the labeled product to the distribution centers is done for Prevnar 13.

Review Comments: *The sponsor's responses appeared acceptable.*

3. In Section 3.2.P.7.5 Secondary Packaging Components, you provided a brief description of the secondary packaging. Please confirm if the intended secondary packaging for 20vPnC has been approved for Prevnar 13.

Sponsor's Responses:

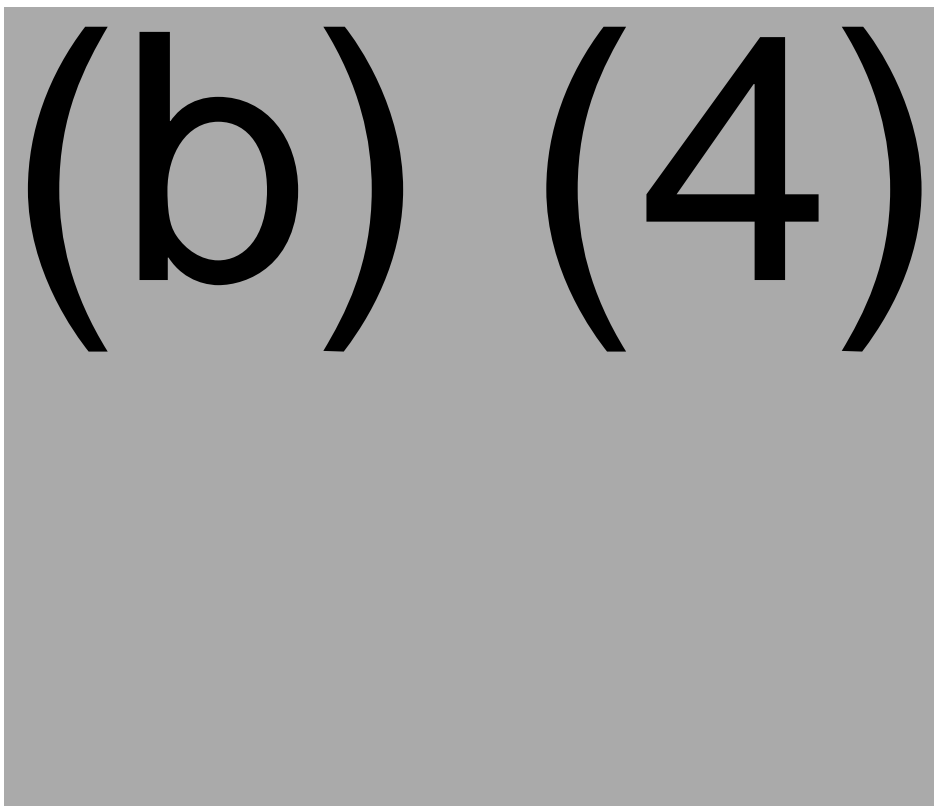
The intended secondary packaging for 20vPnC has been approved as well for Prevnar 13® and is described in the Prevnar 13 BLA (STN 125324), in section 3.2.P.3.5. Process Validation and/or Evaluation Qualification of Labeling, Packaging and Shipping – (b) (4).

Review Comments: *The sponsor's responses were accepted.*

4. In Section 3.2.A.1 Facilities and Equipment – Validation of Water Systems – (b) (4), you noted a performance qualification and addenda qualifications were performed at the Wyeth (b) (4). Facility in (b) (4). Please identify when the performance qualification and addenda qualifications were completed and clarify if you have implemented significant modifications since the last FDA surveillance inspection in (b) (4). If significant modifications were made, please describe the modifications and explain the impact to the qualification status.

Sponsor's Responses:

The dates that the performance and addenda qualifications were completed are listed in Table 1. There have not been any significant modifications to the Water for Injection (WFI) systems since the last FDA surveillance inspection in (b) (4).



Review Comments: *The sponsor's responses were accepted.*

5. You submitted the following two documents to summarize the Media Fills (MF) for the validation of the (b) (4) dispensing systems within the manufacturing suites at (b) (4), and at (b) (4) site.
- 3.2.S.2.5 Process Validation and/or Evaluation [Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F] Media Simulation
 - 3.2.S.2.5 Process Validation and/or Evaluation [Serotypes 8, 10A, 11A, 12F, 15B, 22F, 33F] Media Simulation

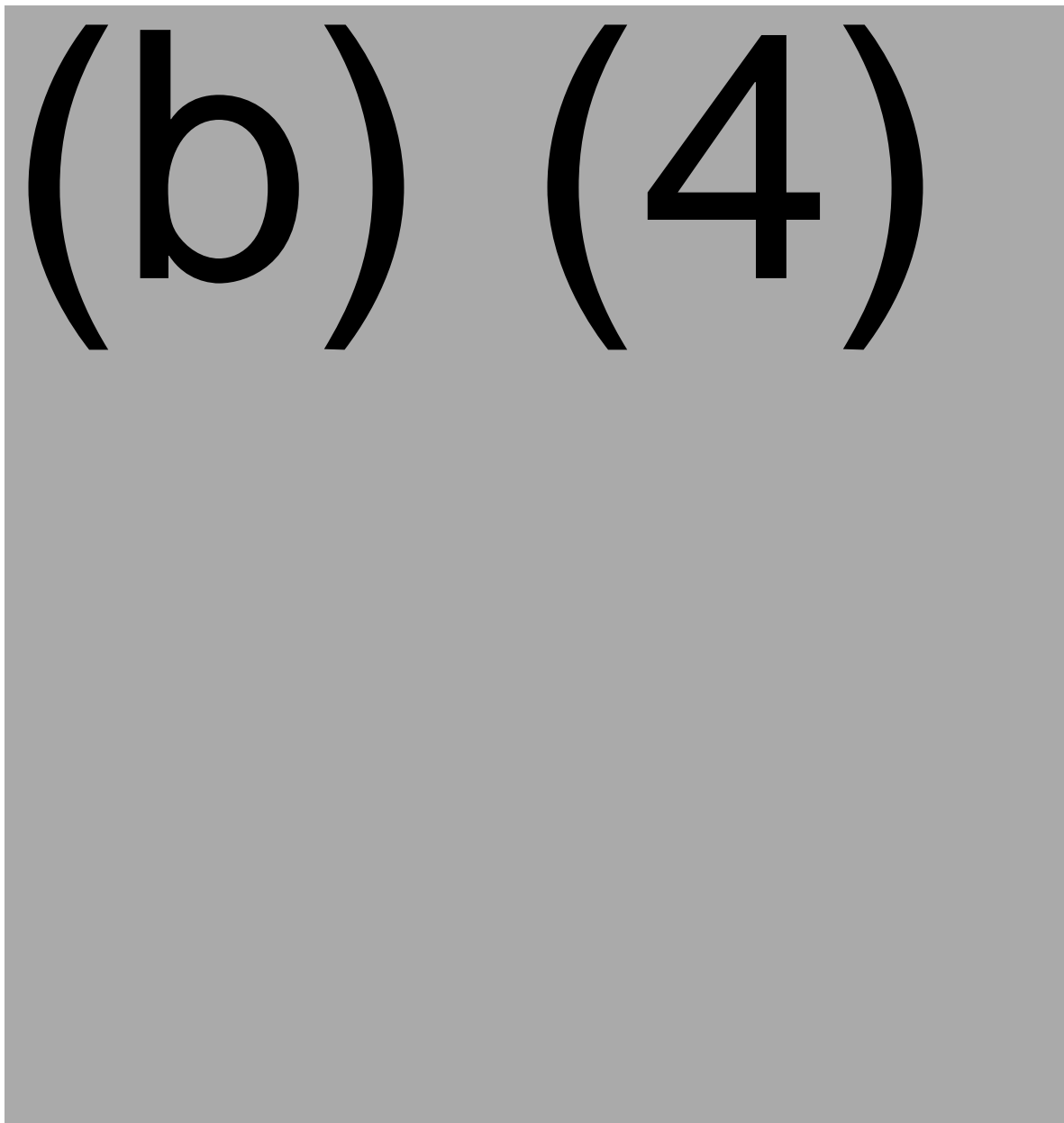
Please provide a tabular summary of information, including the date of the most recent MF qualification at each of the Drug Substance manufacturing sites, the number of MF runs performed for each MF qualification, the number of units filled for each MF qualification presented in these two document, and the results of the most recent media fills.

Sponsor's Responses:

The media fill (MF) program for the 20vPnC Drug Substances leverages the media fill program previously established for Prevnar 13® Drug Substances. A summary of media fill information for the (b) (4) dispensing systems used within the manufacturing suites at the (b) (4) and (b) (4) sites,

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including the dates, batch numbers, number of MF runs performed, the number of units filled and the results are presented for both the initial and most recent qualifications performed at each site, reference Table 1 and Table 2.



(b) (4)

Review Comments: *The sponsor's responses were accepted.*

6. Regarding your drug product syringe filling process, please provide a brief description of how the product vessel, which contains the sterile filtered formulated vaccine, is connected to the filling equipment for dispensing into the syringes.

Sponsor's Responses:

The product vessel is connected to a (b) (4)

(b) (4)

Review Comments: *The sponsor's responses were accepted.*

7. In 3.2.A.1 Facilities and Equipment (b) (4) Validation Summary, you stated that (b) (4) are identical (equipment and CRM₁₉₇ cycle) to (b) (4) in (b) (4) and can be used interchangeably to (b) (4) CRM₁₉₇.

Please clarify when the (b) (4) units (b) (4) were installed for use and qualified. Please also clarify when the (b) (4) units (b) (4) and (b) (4) were approved for use by the Agency and provide the submission tracking number.

Sponsor's Responses:

The installation verification for the (b) (4) units (b) (4) was approved on 02-Apr-2010, and the units were considered fully qualified to (b) (4) CRM₁₉₇ when the performance qualification was approved on 17-Aug-2012.

The (b) (4) units (b) (4) were approved for use by the Agency on 29-May-2013, reference Prevnar 13® Prior Approval Supplement STN 125324/912.

Review Comments: Based on the information in DocuBridge, the PAS STN 125324/912, was for the (b) (4) for CRM in (b) (4)

The sponsor's responses were accepted.

8. In Section 3.2.R.1.5.7 Cleaning Verification Sampling in the (b) (4) Cleaning Comparability Protocol, (b) (4), for equipment cleaning, you test (b) (4) only in (b) (4) samples while you test (b) (4). Please provide a justification to explain why you do not test (b) (4) in (b) (4) samples.

Sponsor's Responses:

For equipment cleaning verification and validation in (b) (4)

It is not necessary to (b) (4)

Review Comments: The sponsor's responses were accepted.

9. Please clarify if an (b) (4) test is performed on the unlabeled filled syringe at Pfizer Manufacturing (b) (4) facility in (b) (4) to ensure the drug product (b) (4) and to differentiate between Prevnar 13 and 20vPnC.

Sponsor's Responses:

As part of our compliance with the cGMP, Pfizer (b) (4) performs an (b) (4) test on unlabeled filled syringes. The acceptance criteria for the 20vPnC drug product (b) (4)

Review Comments: The sponsor's responses were accepted.

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10. In Amendment STN 125731/0.27, you stated that an investigational vaccine, (b) (4) (IND (b) (4)) shares equipment with 20vPnC in (b) (4) at the Wyeth (b) (4) facility in (b) (4)

Please provide the following information:

- a. Clarify if (b) (4) can form (b) (4)
- b. Identify the disinfectant agent(s) used.
- c. Clarify if the shared vessels are sterilized after cleaning.

Sponsor' Responses:

(b) (4)

Review Comments: *The sponsor's responses appeared acceptable. The PQ of (b) (4) were reviewed above in Section 3.2.A.1. Pfizer (b) (4) Site, Equipment Qualifications (b) (4) Equipment Qualification.*