

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: STN 125324/0 (Amendment 3.0) (Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein) (13vPnC))

Wyeth Pharmaceuticals, Inc. (License #0003)

From: Nancy Waites, Reviewer, DMPQ/OCBQ/CBER, HFM-675
CAPT Martha O’Lone, BSN, Reviewer, DMPQ/OCBQ/CBER, HFM-675
Nicole Trudel, Reviewer, DMPQ/OCBQ/CBER, HFM-675

Through: Carolyn Renshaw, Branch Chief, Manufacturing Review Branch I,
DMPQ/OCBQ/CBER, HFM-675

Subject: DMPQ Review of BLA, received 03 March 2009, for the manufacture of 13vPnC.

Cc: Julienne Vaillancourt, Ph.D., Chair, OVRP/DVRPA/CMC1, HFM-481
Michael Smith, RPM, OVRP/DVRPA/CMC3, HFM- 481

Recommendation: We recommend approval of this BLA if the other review offices do not have any issues with it.

Review Summary and Comments

The purpose of this electronic BLA is for the manufacture of 13vPnC, a second generation pneumococcal conjugate vaccine that will replace Prevnar to expand the vaccine’s serotype coverage for the prevention of pneumococcal disease worldwide. The manufacturing occurs in a total of five different facilities – 4 Wyeth facilities and 1 Contract Filling Facility -(b)(4)- Information for all five facilities was reviewed and found to be acceptable. Pre-license inspections were performed at Wyeth Pearl River, -----(b)(4)----- . The pre-license inspection at -(b)(4) was waived.

Food and Drug Administration 1
 Center for Biologics Evaluation and Research 1
 Office of Compliance and Biologics Quality 1
 Division of Manufacturing and Product Quality 1
General Overview (written by NW) 6
Manufacturing Overview 7
 Supply Strategy 7
 Initial Commercial Production Plan 7
 Manufacturing and Testing Sites Addresses and Responsibilities 8
 Manufacturing Responsibilities for Pneumococcal Polysaccharides 8
 1 page determined not to be releasable; (b)(4)..... 9
 Manufacturing Responsibilities for Pneumococcal Saccharide-CRM₁₉₇ Conjugates 9
 Manufacturing Responsibilities for AlPO₄ –(b)(4)--- and 13vPnC Drug Product 10
Process Improvements 10
 Cell Bank Improvements..... 10
 ------(b)(4)----- 10
 ------(b)(4)----- 11
 ------(b)(4)----- 11
 11 pages determined not to be releasable; (b)(4) 12
 ---(b)(4)--- 12
Drug Product 12
 Container Closure..... 12
 1 page determined not to be releasable; (b)(4)..... 13
Shipping 15
 Qualification For Shipping 13vPnC Drug Product Syringes From Pearl River To US Distribution Centers and -(b)(4)- to US Distribution Centers or From –(b)(4)- to Pearl River..... 15
 --(b)(4)----- **Details (written by MO’L) 18**
 -----(b)(4)----- 18
 8 pages determined not to be releasable; (b)(4) 19
 -----(b)(4)----- 20
 -----(b)(4)----- 20
 Environmental Monitoring 20
 --(b)(4)-- HVAC/EM- *BLA Section 3.2.1A.1* 20
 10 pages determined not to be releasable; (b)(4) 21
 Contamination and Cross-Contamination 22
 Facility/Equipment Cleaning 23
 2 pages determined not to be releasable; (b)(4) 24
 Container Closure..... 26
 Shipping 26
 --(b)(4)--- **Details (written by NT) 27**
 Drug Substance 27
 ------(b)(4)----- 27

-----~~(b)(4)~~----- 27
1 page determined not to be releasable; (b)(4)..... 28
----~~(b)(4)~~---- **Details (written by NW)**..... 29
----~~(b)(4)~~---- **Facility Overview** 29
Area Classifications 29
Differential Pressure..... 29
Flow Diagrams 30
 Personnel Flow 30
 Material Flow 30
 Equipment Flow 30
 Waste Flow 30
Environmental Qualification and Monitoring 30
 Environmental Qualifications Overview 31
 -----~~(b)(4)~~----- 31
Contamination and Cross Contamination Controls..... 31
 -----~~(b)(4)~~----- 32
 -----~~(b)(4)~~----- 32
 -----~~(b)(4)~~----- 32
 -----~~(b)(4)~~----- 32
Utilities 32
 Water for Injection (WFI)..... 32
 Clean Steam 33
 Compressed Air..... 34
 Heating, Ventilation and Air Conditioning (HVAC)..... 35
 1 page determined not to be releasable; (b)(4)..... 36
Equipment and Cleaning..... 37
 Description of Critical Equipment 37
 ----~~(b)(4)~~----- 38
 6 pages determined not to be releasable; (b)(4) 39
 ---~~(b)(4)~~--- 40
 -----~~(b)(4)~~----- 40
 -----~~(b)(4)~~----- 40
 -----~~(b)(4)~~----- 40
Equipment Cleaning 40
 Overview of Equipment Cleaning Validation 40
 2 pages determined not to be releasable; (b)(4) 42
Pearl River Details (written by NW)..... 43
 Overview of Pearl River Facilities..... 43
 Building ~~(b)(4)~~ Description..... 43
 Building ---~~(b)(4)~~--- 43
 Building ~~(b)(4)~~ – Flows 44
 ----~~(b)(4)~~----- 44
 Material Flows..... 44
 Equipment Flows 44
 Waste Flow 44
 Building ~~(b)(4)~~ – Utilities..... 45

Heating, Ventilation and Air Conditioning 45

Clean Steam 50

Compressed Air 52

Validation of the Processed Compressed Air System 52

Monitoring of the Processed Compressed Air System 54

Water for Injection 54

Contamination and Cross Contamination Controls..... **56**

Contamination Controls..... 56

Cross Contamination Controls 56

-----**(b)(4)**----- 57

-----**(b)(4)**----- 57

-----**(b)(4)**----- 57

-----**(b)(4)**----- 57

7 pages determined not to be releasable; (b)(4) 58

Equipment Cleaning Procedures and Cleaning Validation..... **59**

Document # 476-0128-VS-04D Cleaning Validation Summary Report..... 61

11 pages determined not to be releasable; (b)(4) 62

Routine Cleaning Monitoring 63

Overview of Pearl River Facility Building (b)(4) **64**

-----**(b)(4)**----- 64

Building ---(b)(4)--- Floor Aluminum Phosphate and 13vPnC Bulk Formulation 65

Environmental Qualification and Monitoring **66**

Environmental Qualifications..... **66**

Routine Environmental Monitoring..... 67

Flows..... **68**

Flows for Component Preparation Area 68

Flows for Aluminum Phosphate and Formulated Bulk Vaccine Manufacturing 68

Contamination and Cross-Contamination Controls – Building 215..... **69**

Contamination Controls..... 69

Cross-Contamination Controls..... 69

-----**(b)(4)**----- 69

Building (b)(4) Utilities..... **70**

Clean Steam..... 70

1 page determined not to be releasable; (b)(4)..... 72

Process Compressed Air..... 73

Heating, Ventilation and Air Conditioning **75**

HVAC Qualification 76

-----**(b)(4)**----- 77

Water for Injection System..... **78**

-----**(b)(4)**----- 78

Routine Monitoring of the WFI System..... 80

Equipment and Cleaning..... 80

Critical Process Equipment – Building (b)(4) 80

1 page determined not to be releasable; (b)(4)..... 82

1 page determined not to be releasable; (b)(4)..... 86

Equipment Cleaning Validation 87

Cleaning Validation 87

 3 pages determined not to be releasable; (b)(4)..... 89

Overview of Pearl River Facilities – Building (b)(4)..... 90

Building (b)(4) Complex..... 90

Building ---(b)(4)--- Floor Component Preparation Area..... 90

 ------(b)(4)-----..... 90

Flows..... 91

Building –(b)(4)-- Floor Component Preparation Area 91

Equipment and Material Flow..... 91

Soiled Equipment/Waste Material Flow 91

Building ---(b)(4)--- Floor Syringe Filling Suite 91

Personnel Flow 91

Component/Material Flow 92

Product Flow 92

Soiled Equipment/Waste Material Flow..... 92

Contamination and Cross-Contamination Controls..... 92

Contamination Controls..... 92

Cross-contamination Controls..... 92

 ------(b)(4)-----..... 93

 ------(b)(4)-----..... 93

 ------(b)(4)-----..... 93

 ------(b)(4)-----..... 93

 ------(b)(4)-----..... 93

Environmental Qualification and Monitoring – Building (b)(4) 94

 1 page determined not to be releasable; (b)(4)..... 95

Building (b)(4) – Utilities..... 96

Water for Injection (WFI) System 96

 1 page determined not to be releasable; (b)(4)..... 97

Clean Steam System..... 98

Heating, Ventilation and Air Conditioning 100

 1 page determined not to be releasable; (b)(4)..... 103

Process Compressed Air..... 104

 ------(b)(4)-----..... **106**

 ------(b)(4)-----..... **106**

 9 pages determined not to be releasable; (b)(4)..... 107

Autoclaves..... 108

Fill/Finish Product Contact Equipment and Parts Cleaning Validation..... 110

 -----(b)(4)-----..... 110

 -----(b)(4)-----..... 110

 1 page determined not to be releasable; (b)(4)..... 112

Overview of (b)(4) Facilities (written by NW)..... 113

 ---(b)(4)--- **113**

Area Classifications 113

Differential Pressure..... 113

Component Preparation Area 113
 -----(b)(4)-----
 -----(b)(4)----- 113
 -----(b)(4)----- 114

Environmental Qualifications and Monitoring..... 114
 Environmental Qualifications..... 114
 Environmental Monitoring 114
 2 pages determined not to be releasable; (b)(4) 115
 ----(b)(4)-- **Flows..... 116**
 Personnel Flow 116
 Material and Component Flow 116
 Product Flow 116
 Waste Flow 116
 -----(b)(4)----- 116
 ----(b)(4)----- 116
 9 pages determined not to be releasable; (b)(4) 117

Equipment Cleaning Validation 119
 -----(b)(4)----- 120
 Cleaning Validation 120

Contamination and Cross-Contamination Controls – (b)(4) 122
 Contamination Controls..... 123
 Cross-Contamination Controls..... 123
 ----(b)(4)----- – **Utilities 124**
 Heating Ventilation and Air Conditioning 124
 HVAC Qualification 125
 1 page determined not to be releasable; (b)(4)..... 126
 Water for Injection System 128
 ----(b)(4)----- 130
 Clean Steam Validation 130
 Routine Clean Steam Monitoring..... 130

Process Compressed Air System..... 132
 Qualification of the Process Compressed Air System 132
 Routine Process Compressed Air Monitoring..... 133

Process Validation for 13vPnC Syringe Filling at (b)(4)..... 134

General Overview (written by NW)

13vPnC is a second generation pneumococcal conjugate vaccine that will replace Prevnar to expand the vaccine’s serotype coverage for the prevention of pneumococcal disease worldwide.

Proprietary Name: Prevnar 13

Generic Name: Pneumococcal saccharide conjugated vaccine adsorbed, 13-valent

Company Name:

Wyeth Pharmaceuticals, Inc.
401 N. Middletown Road
Pearl River, NY 10965

Dosage form: Suspension for Injection

Dosage Strength:

Each 0.5 mL dose is formulated to contain approximately:
2.2 µg of saccharide for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F
4.4 µg of saccharide for serotype 6B
Each saccharide is conjugated to CRM197 carrier protein.

Route of Administration: Intramuscular Use

Proposed Indication: Active immunization for the prevention of disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (including sepsis, meningitis, bacteremia, pneumonia and acute otitis media) in infants and children from 2 months to 5 years of age.

Manufacturing Overview

Supply Strategy

The manufacture of the 13vPnC vaccine consists of:

1. ----(b)(4)-----
2. -----(b)(4)-----
3. -----(b)(4)-----
4. -----(b)(4)-----
5. -----(b)(4)-----
6. -----(b)(4)-----
7. -----(b)(4)-----

For commercial manufacturing these activities will be distributed among Wyeth manufacturing facilities in the United States (at ---(b)(4)----- Pearl River, NY, and --(b)(4)--), and at -----(b)(4)----- In addition, Wyeth has contracted with -----(b)(4)--- ----- for formulation and filling of Drug Product syringes. The commercial manufacturing and supply scheme is depicted in Figure 2-1 of the submission.

Initial Commercial Production Plan

The manufacturing sites for each polysaccharide and subsequent conjugate are summarized in the tables below. Initially, there will be redundant manufacturing capacity for polysaccharide serotypes --(b)(4)--.

Commercial Polysaccharide Manufacturing Sites

[(b)(4)]

Commercial Conjugate Manufacturing Sites

[(b)(4)]

Manufacturing and Testing Sites Addresses and Responsibilities

The names, addresses and responsibilities of each pneumococcal polysaccharide, conjugate and formulation and filling manufacturing sites, as well as contract laboratories are provided in the tables below.

Manufacturing Responsibilities for Pneumococcal Polysaccharides

Name and Address

Responsibilities

[(b)(4)]

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

Manufacturing Responsibilities for Pneumococcal Saccharide-CRM₁₉₇ Conjugates

[(b)(4)]

Manufacturing Responsibilities for AlPO₄ –(b)(4)--- and 13vPnC Drug Product	Responsibilities
Name and Address	

Wyeth Pharmaceuticals Inc
 401 N. Middletown Rd.
 Pearl River, NY 10965
 United States
 Tel: + 1 (845) 602 5000
 Fax: + 1 (845) 602 7833

[(b)(4)]

Process Improvements

All aspects of Prevnar drug substance manufacturing processes were reviewed and, where appropriate, have been modified and improved. Several specific improvements that warrant particular mention have been implemented as part of the 13vPnC program including:

- Cell bank improvements
- Polysaccharides improvements
- Drug substance (conjugate) improvements
- Drug product improvements

Cell Bank Improvements

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

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

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

 • -----

 • -----

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

- -----

- -----

- -----

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

- -----

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

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

- -----

- -----

11 pages determined not to be releasable; (b)(4)

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

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

**Drug Product
Container Closure**

The syringe container closure system used for the drug product final container is the exact same at -(b)(4)- and Wyeth Pearl River and it is the currently licensed syringe container closure for Prevnar (7v). All raw material specifications and testing are the same.

Syringe Container Closure System

The syringe container closure system consists of -----(b)(4)-----

The syringes include plastic rigid tip cap overseal (PRTC), plunger rod and backstop.

Safety data for the syringe barrel and rubber formulations are provided within the submission in Section 3.2.P.2. Pharmaceutical Development: Description and Safety of the Syringe Container Closure System.

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

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

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

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

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

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

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

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

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

Container Closure Integrity Testing

The container closure is the exact same as the licensed Prevnar (7v) product. Wyeth provided the following documents to show that the 1 mL syringe container closure system retained integrity when exposed to a stressed environment or with a high concentration of -----**(b)(4)**----- organisms. All acceptance criteria set forth in the protocols were met.

- Document SR0708022 Container Closure Integrity Testing – ---**(b)(4)**----- Challenge Summary Report Version 2.0
- Document # SR0708023 Container Closure Integrity Testing –Microbial Challenge Summary Report Version 2.0

I reviewed 3.2.P.3.5 Process Validation and/or Evaluation – Pearl River, SR 06-2109 – Summary Report: Qualification Studies for Shipping Syringes in Temperature-Controlled Trailers to US Distribution Centers and 3.2.P.3.5 Process Validation and/or Evaluation – (b)(4)- SR 06-2109 – Summary Report: Qualification Studies for Shipping Syringes in Temperature-Controlled Trailers to US Distribution Centers and found them to be acceptable. The (b)(4) shipping studies performed with minimum and maximum number of pallets, during ---(b)(4)----- qualify the use of temperature-controlled trailers for shipment of Drug Product syringes. The studies demonstrated that both the measured and mathematically predicted temperatures were within the acceptance criterion of the study protocol, and support the shipping of 13vPnC syringes at the required shipping temperatures of ---(b)(4)--- The results also demonstrated that shipment conditions are properly monitored using -----(b)(4)----- For single-pallet shipments, (b)(4) temperature monitors should be placed on the pallet to protect against monitor failure. I do not have any questions or comments.

SR 06-2109 Summary Report: Qualification Studies for Shipping Syringes in Temperature Controlled Trailers to US Distribution Centers

(b)(4) studies were performed with temperature-controlled trailers loaded with a minimum of a ---(b)(4)--- or with a maximum capacity of pallets, -----(b)(4)----- . Electronic temperature monitors were placed at appropriate positions --- (b)(4)--- pallet to obtain thermal exposure data during transport. The trailers were set to an appropriate temperature between 2°C and 8°C during loading. The transports were performed for -----(b)(4)--- to support the longest time period for transport within the continental United States. One transport study each was done with minimum and maximum pallet numbers during -----(b)(4)----- shipping seasons. Temperature data from each of the (b)(4) studies was analyzed statistically to measure pallet surface uniformity within the load space.

Results and Discussions

The results obtained for the (b)(4) trailer shipments are detailed within this summary report in Table 3-1 located within the submission. All monitored temperatures were within the range of -(b)(4) meeting the acceptance criterion of the study. Additionally, the results demonstrate that the interior cargo areas of refrigerated trucks during -----(b)(4)- ----- shipping conditions are appropriately monitored by the placement of a ----- (b)(4)-----

Deviations

There were two deviations during execution of the qualification studies. The deviations, resolutions and impacts are detailed within the submission in Table 4-1. I reviewed the deviations and found the investigations and closeout of the deviations to be acceptable.

8 pages determined not to be releasable; (b)(4)

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

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

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

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

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

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

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

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

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

Environmental Monitoring

--(b)(4)-- HVAC/EM- *BLA Section 3.2.1A.1*

The controlled polysaccharide bulk manufacturing area in -----~~(b)(4)~~----- is a contained environment with limited access. The HVAC system of Building ~~(b)(4)~~ maintains additional segregation of the ~~(b)(4)~~ processes by use of ~~(b)(4)~~ ~~(b)(4)~~ Air Handling Units (AHU) in the HVAC system for Building. The supply air processed by the HVAC units is delivered to the terminal High Efficiency Particulate Air (HEPA) filters in classified areas, which are located in the ceilings of the -----

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

10 pages determined not to be releasable; (b)(4)

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

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

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

Contamination and Cross-Contamination

Suites ----- (b)(4) ----- and in Pearl River have been designed to minimize the potential of product contamination and personnel exposure by using primarily (b)(4) system processes, separate air handling units, pressure differential zones, air locks, gowning rooms, protective clothing and defined pathways for the flow of personnel, equipment, materials and waste. Manufacturing areas are controlled environments appropriate to the operations that take place in a particular area with pressurization, whether negative or positive, maintained in the area. Room finishes are durable, smooth and cleanable. A gowning room or airlock is located at all entry points, segregating Suite --(b)(4)-- in Building (b)(4) from the rest of the (b)(4) Manufacturing Facility (b)(4) Suites --(b)(4)-- are physically segregated from the other manufacturing areas within the same building. Suites --(b)(4)-- segregate personnel and material entry areas to reduce the opportunity for product contamination and provide personnel protection. Separation includes controlled personnel, material and equipment flows, airlocks, and environmental controls (e.g., HVAC), all of which are independent of each other. The facility is capable of manufacturing aseptically-processed drug substances and intermediates. There is no manufacture of products containing penicillin, cephalosporin, live viruses, spore-forming organisms or cytotoxic drugs. Site procedures are established to avoid any potential mix-up or cross-contamination between 13vPnC drug substances.

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

----- During routine or preventative maintenance situations, when the inactivation -(b)(4)- is not operable, alternative inactivation procedures will be utilized to inactivate all waste and materials prior to their exit from Suite (b)(4). These alternative inactivation procedures have been demonstrated to be effective for inactivating ----- (b)(4) ----- SOPs for both the --(b)(4)-- and Pearl River sites describe the flow of personnel, materials, and equipment through the facility during the manufacturing process to prevent contamination and mix-ups between serotypes. Procedures also ensure that appropriate storage conditions are met throughout the manufacturing process. Clean equipment is separated from soiled equipment. Equipment parts and materials are wiped with an

2 pages determined not to be releasable; (b)(4)

Container Closure

Please refer to Container Closure Systems in the Common Details Section of this memorandum. No deficiencies were observed during the pre-license inspection for the integrity of these (b)(4) vessels.

Shipping

Please refer to Shipping in the Common Details Section of this memorandum. No deficiencies were observed during the pre-license inspection for the integrity of these (b)(4) vessels.

References

FDA “Guidance for Industry Sterile Drug Products Produced by Aseptic Processing-Current Good Manufacturing Practice” dated November 1994.

FDA “Guidance for Industry Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product” dated January 1999.

FDA “Guidance for Industry Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products” dated February 2008.

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

----- (b)(4) ----- **Details (written by NW)**

----- (b)(4) ----- **Facility Overview**

The ----- (b)(4) ----- Wyeth Biotech facility is located at ----- (b)(4) -----
----- (b)(4) ----- The facility is located on an approximately (b)(4)-acre site
approximately 7 miles from ----- (b)(4) ----- The building arrangement on the portion of
the site currently developed is illustrated in Drawing 3.2.A.1, ----- (b)(4) ----- Drug
Substance - Manufacturing Suite (b)(4) DRW 00/RD/0001: Overall Site Plan located within
the submission. A complete description of the facility can be found within the
submission in Section 3.2.A.1 Facilities and Equipment, ----- (b)(4) ----- Drug Substance,
Manufacturing Suite (b)(4) Facility Overview.

Vaccines Conjugation, Manufacturing Suite (b)(4) located in Manufacturing Suites
Building, Building (b)(4), is dedicated to the manufacture of Monovalent Bulk Conjugates
(MBCs) for Serotypes 1, 5, 6A, 7F and 19F. The suite is provided with (b)(4) corridor
that surrounds the production area and is used for intermediate product, equipment,
materials and personnel flow. Running (b)(4) is the Clean Corridor that enables personnel
to move between the production rooms. Gown and Degown rooms are provided at the
north end of the corridor.

Area Classifications

The Manufacturing Suite (b)(4) area classifications are illustrated in the submission in
Drawing 3.2.A.1, --- (b)(4) -----, Drug Substance - Manufacturing Suite (b)(4) DRW
03/RD/0008: Pressurization and Classification (b)(4) Floor Suite (b)(4). Environmental
monitoring procedures and specifications supporting these area classifications are
detailed in the submission in Section 3.2.A.1 ---- (b)(4) ----- Drug Substance -
Manufacturing Suite (b)(4) Environmental Qualifications and Monitoring. The containment
area includes HEPA filters in the return ductwork at the containment boundary. Exhaust
fans for containment areas and hoods are on the emergency power system. Additional
discussion of EM takes place further within this review under Environmental
Qualifications and Monitoring.

Differential Pressure

The integrity of differing environmental standards is maintained by a cascade of airflow
from areas of higher classification to areas of lower classification within the
manufacturing facility.

The specified differential pressure to be maintained between areas of different
classification in this facility is ---- (b)(4) ----- Pressure differentials are also required
between some areas of the same classification to ensure airflow from clean to dirty areas.
Pressures are maintained by an active pressure control system. Each area is monitored
and controlled against a reference header to provide stable control. Temperature in all
clean rooms is maintained at ---- (b)(4) ----- during manufacturing operations. Relative
humidity is maintained at ---- (b)(4) ----- RH. Differential pressure between rooms and
temperature and humidity measurements in return ducts from critical process rooms are
continuously monitored and recorded. ----- (b)(4) ----- is monitored in cold rooms.

Environmental Qualifications Overview

The testing evaluated multiple sample sites in the various environments for viable microorganisms (air sampling, settle plates and contact plates) and non-viable particulates -----(b)(4)----- for each classified environment defined in the protocol. The results of the qualifications demonstrated that the classified areas in Manufacturing Suite (b)(4) met the environmental quality requirements defined in the protocol. During qualification, all media used was certified for growth promotion prior to use.

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

Environmental Monitoring Grade (b)(4)

[(b)(4)]

Environmental Monitoring Grade (b)(4)

[(b)(4)]

Contamination and Cross Contamination Controls

A summary of the controls used to prevent contamination and cross-contamination can be located within the submission in Section 3.2.A.1 Facilities and Equipment, ----(b)(4)-----
----- Drug Substance, Manufacturing Suite (b)(4) Contamination and Cross Contamination Controls.

I reviewed this section and found it to be acceptable. I did not have any questions or comments.

Manufacturing Suite (b)(4) has been designed to minimize the potential of product contamination and personnel exposure using separate air handling units, pressure differential zones, air-locks, gowning rooms and defined pathways for the flow of personnel, equipment, materials and waste.

The facility is capable of manufacturing aseptically-processed drug substances and intermediates. There is no manufacture of products containing penicillin, cephalosporin, live viruses, spore-forming organisms or cytotoxic drugs. Dedicated product contact equipment is labeled appropriately or controlled by a validated Manufacturing Control System (MCS) system. All portable equipment is cleaned in accordance with validated written procedures after each use. Stationary (fixed) equipment and process piping is ---(b)(4)----- using a (b)(4) system (See Section 3.2.A.1 Equipment Cleaning Procedures and Cleaning Validation, ---(b)(4)----- Drug Substance – Manufacturing Suite (b)(4) within the submission and further on in this review for additional information).

To avoid mix-ups or cross contamination between 13vPnC drug substances, -----(b)(4)----- Room clearance procedures provide assurance that no specific materials or documents remain from manufacturing of a previous batch and routine room cleaning is performed as per site cleaning procedures.

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

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

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

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

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

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

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

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

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

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

Utilities

Water for Injection (WFI)

A description of the water for injection system and qualification of the system can be found in the submission in Section 3.2.A.1 Facilities and Equipment 1 ---(b)(4)-----, Drug Substance, Manufacturing Suite (b)(4) Water System and Section 3.2.A.1, ---(b)(4)-----, Drug Substance - Manufacturing Suite (b)(4) M3-GC-1120: Water for Injection

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

1. -----

2. -----

3. -----

4. -----

Equipment and Cleaning
Description of Critical Equipment

A description of the critical equipment is located within the submission in Section 3.2.A.1 Facilities and Equipment ---(b)(4)---, Drug Substance, Manufacturing Suite (b)(4), Description of Critical Equipment.

Installation and Operational Qualifications were completed for the Activation equipment as detailed in the submission in Section 3.2.S.2.5 Process Validation and/or Evaluation, Serotypes 1, 5, 6A, 7F, 19F. A Performance Qualification (PQ) is performed for -----(b)(4)----- Vessels where ---(b)(4)--- is applied as a good manufacturing practice to control bioburden. Cleaning Validation information for the equipment is provided within the submission in Section 3.2.A.1, ----(b)(4)----, Drug Substance - Manufacturing Suite (b)(4), M3-GC-1180: Cleaning Validation Summary Report.

Installation and Operational Qualifications were completed on the -(b)(4)- vessels and testing demonstrated the -(b)(4)- vessels meet user requirements as detailed within the submission in Section 3.2.A.1, ----(b)(4)---, Drug Substance - Manufacturing Suite (b)(4), M3-GC-0975: -(b)(4)- Vessels Qualification Summary Report. A Performance Qualification (PQ) is performed for the Fill Vessels where --(b)(4)--- is applied as a good manufacturing practice to control bioburden. Details on the performance of the -----(b)(4)-----systems can be located within the submission in Section 3.2.S.2.5 Process Validation and/or Evaluation, Serotypes 1, 5, 6A, 7F, 19F. Cleaning Validation information for the equipment is provided within the submission in Section 3.2.A.1, ---(b)(4)----, Drug Substance - Manufacturing Suite (b)(4), M3-GC-1180: Cleaning Validation Summary Report

6 pages determined not to be releasable; (b)(4)

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

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

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

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

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

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

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

Equipment Cleaning

A description of the Cleaning Validation can be found within the submission in Section 3.2.A.1 Facilities and Equipment -----**(b)(4)**-----, Drug Substance, Cleaning Validation. The results obtained during the cleaning validation are detailed in M3-GC- 1180 Cleaning Validation Summary Report, -----**(b)(4)**-----, Manufacturing Suite **(b)(4)**.

I reviewed the above sections and found them to be acceptable. I do not have any questions or comments.

Overview of Equipment Cleaning Validation

The product contact equipment and systems used in the production of the pneumococcal saccharide-CRM197 conjugates in ----**(b)(4)**----- are dedicated to Monovalent Bulk Conjugate (MBC) manufacturing.

The production equipment and systems are cleaned to prepare the equipment / systems for the subsequent batch. Large and fixed equipment, such as buffer vessels and dilution vessels, are -----**(b)(4)**----- . Easily removed/easy to breakdown equipment, such

as small equipment parts and hoses may be -----(b)(4)----- . Both (b)(4) and (b)(4) cleaning cycles can be generally broken up into a ----(b)(4)---- or a ----(b)(4)----- rinse. The ----(b)(4)----- cycle generally consists of: -----(b)(4)----- . The (b)(4) rinse cycle generally consists of ----(b)(4)----- rinses (depending on the equipment type). All of the steps mentioned utilize (b)(4) and the cleaning steps use a ----(b)(4)----- solution as a cleaning agent on process equipment and parts.

Cleaning validation monitoring is performed for -----(b)(4)----- in addition to visual inspection of the equipment in order to monitor the cleaning process.

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

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

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

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

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

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

2 pages determined not to be releasable; (b)(4)

Differential Pressures

Pressure differentials of------(b)(4)----- are maintained across closed doors between areas of different classifications. The pressure in the room with the more stringent classification maintains the higher pressure with the exception of the containment area, Fermentation, where pressure is lower than adjoining rooms. Temperature in all rooms is maintained at -----(b)(4)----- during manufacturing operations, except for Dispensing Room (b)(4) which is maintained at -----(b)(4)----- and the Product Transfer Area (Rooms -----(b)(4)-----) which is maintained at -----(b)(4)----- . Relative humidity is maintained between -(b)(4)---. Differential pressure between rooms and temperature and humidity measurements in return ducts from critical process rooms are continuously monitored and recorded. Sufficient air changes per hour are provided to meet the room cleanliness classification.

Building (b)(4) – Flows

Building (b)(4) segregates personnel and material entry areas to reduce the opportunity for product contamination and provide personnel protection. Details regarding personnel, material, equipment, and waste flows are located within the submission in Section 3.2.A.1 Facilities and Equipment, Pearl River, Building (b)(4) Flows.

I reviewed the following flow diagrams and accompanying description of the flow patterns, segregation procedures and gowning procedures and found them to be acceptable. I do not have any questions or comments.

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

Material Flows

Section 3.2.A.1, Pearl River, Drug Substance – Building (b)(4), DRW G-079959:
Building---(b)(4)--- Floor Material/Process Flow.

Equipment Flows

Section 3.2.A.1, Pearl River, Drug Substance - Building (b)(4), DRW G-079959:
Building ---(b)(4)--- Floor Material / Process Flow

Waste Flow

Section 3.2.A.1, Pearl River, Drug Substance - Building (b)(4), DRW G-080067:
Building ---(b)(4)--- Floor Solid Waste Flow

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

HVAC Qualification

The HVAC system servicing the production areas has been qualified. A summary of the qualifications performed is detailed in Section 3.2.A.1, Pearl River, Drug Substance - Building (b)(4), 476-0009-VS-01: HVAC Qualification Summary Report and Section 3.2.A.1, Pearl River, Drug Substance - Building (b)(4), 476-0009-VS-02: Environmental Qualification Summary Report within the submission.

I reviewed 476-0009-VS-01: HVAC Qualification Summary Report and 476-0009-VS-02: Environmental Qualification Summary Report and found them to be acceptable. I did not have any questions or comments. The qualification demonstrated that the system operates according to design specifications and maintains the facility within the design parameters. The HVAC qualification tests for the system’s ability to provide required air changes, pressurization, temperature, and relative humidity in the production areas. The controllers and building management systems (Supervisory Control And Data Acquisition (SCADA)) are qualified. The HVAC systems for the commercial manufacturing areas were designed and qualified for classified environments for temperature -----(b)(4)-----) relative humidity ---(b)(4)----- to maintain differential pressures between rooms, and sufficient air change rate to provide cleanliness. As part of the qualification of the HVAC system, all classified production areas were tested under active and inactive conditions. Rooms were monitored for total particulate levels, airborne viable particulates, surface viable levels, temperature and relative humidity. The HEPA filters are certified ---(b)(4)-----.

HVAC Qualification Summary Report 476-0009-VS-01D

This document summarizes the Installation and Operational Qualifications for the Heating, Ventilation, and Air Conditioning (HVAC) systems and associated --(b)(4)--- Flow Unit and Biosafety Cabinets serving the Polysaccharide Production Area in building (b)(4).

Installation Qualification

Per Wyeth, Installation Qualification (IQ) for the HVAC System was executed to verify that all utilities, instrumentation, and equipment were installed and documented according to engineering specifications. Critical equipment and associated devices have been inspected and tagged. Critical instruments have been calibrated. Preventive Maintenance programs have been implemented. All drawings have been verified to accurately depict as-built conditions. Verification of utilities, control systems, all applicable system documentation was completed. The IQ reports are listed in Table 3-1 within the summary report located in the submission. All deviations encountered during IQ executions were investigated and satisfactorily addressed. All IQs were successfully completed.

Operational Qualification

Per Wyeth, Operational Qualification (OQ) for the HVAC System was executed to demonstrate that all Classified Environments meet air quality requirements. Tests including air quality, HEPA filter integrity, design requirements, velocities, air changes, calibrations, alarms, and interlocks were satisfactorily completed. All OQ reports are listed in Table 4-1 in the summary located within the submission. Any deviations encountered during OQ executions were investigated and satisfactorily addressed. All OQs were successfully completed.

Per Wyeth, Installation/Operational Qualification (IO) for the HVAC System was successfully executed. All IOs are listed in Table 4-2 in the summary report located within the submission. Any deviations encountered during IO executions were investigated and satisfactorily addressed. All IOs were successfully completed.

Performance Qualification

This summary report for the PQ references Section 3.2.A.1, Pearl River, Drug Substance - Building (b)(4), 476-0009-VS-02: Environmental Qualification Summary Report for the summary report for the execution of the PQ. My review for this summary report is located below.

Environmental Qualifications

All areas within Building (b)(4) used for the manufacturing of pneumococcal polysaccharides 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 -----(b)(4)-----
-----.

The environmental qualification standard operating procedure involves sampling for -----(b)(4)----- days at rest and in operation. A summary of the qualifications is provided in 3.2.A.1, Pearl River, Drug Substance - Building (b)(4), 476-0009-VS-02: Environmental Qualification Summary Report. The testing evaluated multiple sample sites in the various environments for viable microorganisms (air sampling, settle plates, and contact plates) and non-viable particulates -----(b)(4)----- for each classified environment defined in the protocol. The results of the qualifications demonstrated that the classified areas in Building (b)(4) met the environmental quality requirements defined in the protocol. During qualification, all media used was certified for growth promotion prior to use.

I reviewed 476-0009-VS-02: Environmental Qualification Summary Report and found it to be acceptable. I did not have any questions or comments. The environmental qualifications of the facility Heating, Ventilation, and Air Conditioning (HVAC) units serving the Pneumococcal Polysaccharide Production Area in Building --(b)(4)--- Floor, demonstrated that the HVAC system met established environmental acceptance criteria for controlled spaces. All deviations associated with the qualification activities were investigated appropriately and closed out.

Environmental Qualification Summary Report 476-0009-VS-02

The rooms were tested for ----(b)(4)----- days during at rest conditions and----(b)(4)--
----- days during in operation conditions to verify their performance in accordance
with Wyeth specifications. Rooms were monitored for total particle levels, airborne
viable particulate, surface viable levels, temperature and relative humidity. At rest testing
was performed following ----(b)(4)----- operation testing. In operation testing
was also conducted with all appropriate equipment operating and personnel present to
simulate routine production activities. Routine monitoring sites were selected based on
the results of the environmental performance qualifications for the Pneumococcal
Polysaccharide Production Area, Building (b)(4).

Performance Qualification (PQ)

Performance Qualification (PQ) served as the system at rest and in operation performance
test for the graded environments. The scope of the environmental PQs included the
following verifications: Test Equipment and Instrumentation Verification, Standard
Operating Procedure (SOP) Verification, Training Verification, Temperature and
Relative Humidity, Total Airborne Particulate Testing, Viable ---(b)(4)---- Airborne
Testing and Surface Viable Testing.

Temperature and Relative Humidity Testing

Temperature and Relative Humidity were monitored during at rest and in operation
conditions while the environmental monitoring was executed. The protocol requirements
for each room were -----(b)(4)-----

Environmental Monitoring Testing

Testing was performed in accordance with the procedures identified in the PQ protocol.
The results demonstrate that total particulates, air viable, and surface viable levels meet
the acceptance criteria during both at rest and in operation conditions. See the tables
below for the action levels. See Table 3-4 through Table 3-7 within the submission for
the test results.

Action Levels for Total Particulate Counts

[(b)(4)]

Action Levels for Air Viables

[(b)(4)]

Action Levels for Surface Viables (-(b)(4)-)

[(b)(4)]

Deviations

Wyeth recorded the deviations encountered during the validation within the submission. I reviewed the deviations and they were appropriately investigated and closed out.

Routine Environmental Monitoring

Classified areas are monitored on a routine basis for viable and non-viable airborne particulates, and viable microorganisms on surfaces according to the frequencies specified in the tables below. -----(b)(4)---- are used to monitor the clean room surfaces.

Per Wyeth, the frequency of sampling in the tables and the text below are subject to change based on an annual review along with trending of monitoring results obtained in order to continually improve the program.

Environmental Monitoring in BSCs

[(b)(4)]

Environmental Monitoring Grade (b)(4)

[(b)(4)]

Environmental Monitoring Grade (b)(4)

[(b)(4)]

Environmental Monitoring Grade (b)(4)

[(b)(4)]

Clean Steam

The clean steam system for the commercial manufacturing areas were designed and qualified to meet the criteria specified in -----(b)(4)-----.
The clean steam system serving the clean rooms has been validated and the quality (-----
----- (b)(4)-----) of the clean steam is requalified --- (b)(4) --. The quality is monitored by routine sampling of the clean steam --- (b)(4) ---- and tested as per ----- (b)(4) ----- requirements. For additional information, refer to 3.2.A.1 Facilities and Equipment, Pearl River, Building (b)(4), Clean Steam and **476-0085-VS-01 Clean Steam System Qualification**. The Clean Steam System is illustrated within the submission in Section 3.2.A.1, Pearl River, Drug Substance - Building (b)(4), DRW C-079409: (b)(4) Clean Steam Flow Block Diagram.

I reviewed 476-0085-VS-01 Clean Steam System Qualification and DRW C-079409: (b)(4) Clean Steam Flow Block Diagram and found them to be acceptable. The Clean Steam system serving Building (b)(4) at Wyeth, Pearl River is installed as designed and specified, operates within the established design parameters, and produces clean steam meeting current ---- (b)(4) ----- requirements for (b)(4). All deviations associated with the qualification activities have been successfully resolved. The installation, operational, and performance qualifications for the Clean Steam System were satisfactorily completed.

**476-0085-VS-01 Clean Steam System Qualification Summary Report
System Description**

The Clean Steam System utilizes --(b)(4)---- water to produce clean steam that meets the ----(b)(4)----- requirements for -----(b)(4)----- . The Clean Steam System in Building --- (b)(4) --- consists of ----- (b)(4) ----- . Clean Steam from the CSG is distributed at a ----- (b)(4) ----- clean steam distribution header supplies clean steam generated by the CSGs throughout Building --- (b)(4) --- to various points of use for autoclaves, product contact

vessels, equipment and piping for sanitization/sterilization requirements to support manufacturing of Pneumococcal Polysaccharides.

Per Wyeth, an IQ and OQ were performed to provide documented evidence that the clean steam system was installed and operating in accordance with the specifications and the intended use of the system.

Performance Qualification (PQ)

The purpose of the Performance Qualification (PQ) was to document the performance of the Clean Steam system in Building ----(b)(4)---- operated in accordance with the specifications listed below.

Clean Steam ----(b)(4)----- Parameters Qualified

[(b)(4)]

Testing for the Building (b)(4) Clean Steam Distribution System was conducted by sampling each of the sample ports, including the Clean Steam ----(b)(4)--- sampling port. Samples were collected at a frequency as found in each protocol and the ---(b)(4)--- was tested for chemical attributes -----(b)(4)----- and microbiological contents (----- (b)(4)-----).

Testing for -----(b)(4)----- was performed for the Building (b)(4) Clean Steam Distribution System by sampling the -----(b)(4)----- . The protocols that were executed for the qualification of the

Clean Steam System are the following:

- Protocol 476-0005-PQ-03**
- Protocol 476-0005-PQ-04**
- Protocol 476-0005-PQ-05**
- Protocol 476-0085-PQ-01**
- Protocol 476-0085-PQ-02**
- Protocol 476-0121-PQ-01**

Deviations

Deviations that occurred during sampling and testing of clean steam were evaluated and addressed for their potential impact on the validation study. I reviewed the deviations recorded by Wyeth and agree that they were appropriately investigated and closed out.

Routine Clean Steam Monitoring

Clean Steam Quality is monitored by routine --(b)(4)-- sampling of the clean steam --- (b)(4) --- and tested to -----(b)(4)----- requirements. Additionally, the clean steam system is tested for -----(b)(4)-----
-----.

Compressed Air

Compressed Air System Description

----(b)(4)----- air compressors provide compressed air directed into a common air receiver before it is divided into (b)(4) main subsystems: -----

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

Validation of the Processed Compressed Air System

A summary of the qualifications performed is detailed within the submission in Section 3.2.A.1, Pearl River, Drug Substance - Building (b)(4), 476-0012-VS-01: Process Compressed Air Qualification Summary Report and demonstrates that the system operates according to design specifications. The following test functions have been met for the Process Compressed Air system at Building 9b(4), Pearl River:

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

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

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

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

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

I reviewed 3.2.A.1, Pearl River, Drug Substance - Building (b)(4), 476-0012-VS-01: Process Compressed Air Qualification Summary Report and found it to be acceptable. The Process Compressed Air System serving Building ---(b)(4)--- at Wyeth, Pearl River, NY is installed as designed and specified, operates within the established design parameters, and produces compressed air meeting qualification testing requirements. All deviations were successfully resolved. The Installation, Operational, and Performance Qualifications for the Process Compressed Air System have been satisfactorily completed. I do not have any questions or comments

**476-0012-VS-01 Process Compressed Air Qualification Summary Report
Installation Qualification (IQ)**

Installation Qualification (IQ) for the Compressed Air System in ---(b)(4)--- was executed to verify that all piping and equipment were installed according to engineering specifications and Wyeth's requirements. The IQ tests included verification of the following items: equipment calibration, electrical specifications, piping specifications, engineering drawings, technical literature, supporting utilities and all applicable system documentation. The results of the IQ demonstrated that the Compressed Air System was designed and installed as specified. All deviations encountered during IQ execution were investigated and successfully resolved with no impact on the system.

Operational Qualification (OQ)

Operational Qualification (OQ) for the Compressed Air System in ---(b)(4)--- was executed to demonstrate that the Compressed Air System, including the control system and its components, operates according to specification. Verification of alarms / interlocks / controls / indicators, graphic and screen navigation, password functionality, input error verification, start up / shut down sequences and load / unload tests for the air compressors and air dryers were also completed. The results of the OQ demonstrated that the Compressed Air System including the control system and its components operate as specified. All deviations encountered during OQ execution were investigated and successfully resolved with no impact on the system.

Performance Qualification (PQ)

Performance Qualification (PQ) for the Compressed Air System in ---(b)(4)--- was executed to demonstrate that the Compressed Air System performs according to specification.

The table below summarizes the acceptance criteria for each executed PQ protocol. Each sample was tested for (b)(4) days with the results for each sample meeting acceptance criteria.

Performance Qualification Acceptance Criteria

[(b)(4)]

Deviations

Wyeth recorded 9 deviations during the execution of the PQ. All were appropriately investigated and closed out. I agree with Wyeth's assessment that the deviations did not effect the qualification.

Report No.: 476-0084-VS-01: Water for Injection Qualification Summary Report

Installation Qualification (IQ)

Installation Qualification (IQ) was executed to verify that the system is purchased and installed as designed and specified. The IQ tests included verification that the WFI system and components were delivered as specified, adequately marked/tagged, accompanied by adequate documentation, and installed correctly according to drawings and specifications. In addition, all critical instruments were confirmed as calibrated and preventive maintenance checklists were confirmed to be in place and maintained.

Operational Qualification (OQ)

Operational Qualification (OQ) for the WFI system was executed to demonstrate that the WFI system, including the control system and its components, operates according to specification. The OQ tests included verification of proper operation of the system components, alarms, control loops, safety and mechanical functions, verification of capacity, and verification of the sterilization temperature ----(b)(4)-----.

The results of the OQ demonstrate that the WFI system operates as specified. All deviations associated with the OQ were successfully resolved.

Performance Qualification (PQ)

Performance Qualification (PQ) for the WFI System was executed to demonstrate that the WFI system performs according to specification. The parameters qualified are detailed in the table below.

Water for Injection Parameters Qualified

[(b)(4)]

Monitoring charts of the WFI system

The results of the in-line instruments that monitor the chemical and physical parameters of the WFI quality and distribution loops were evaluated. The results from each of the

7 pages determined not to be releasable; (b)(4)

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

Equipment Cleaning Procedures and Cleaning Validation

Product contact equipment / systems used in the production of the pneumococcal polysaccharide serotypes in Pearl River are dedicated to polysaccharide manufacturing. The product contact surfaces are cleaned using validated procedures.

Cleaning Procedures

The production contact equipment / systems are cleaned to prepare the equipment/ systems for the subsequent batch. Larger fixed equipment, such, as tanks, and (b)(4)-, are -----(b)(4)----- . Small, easily removed/easy to breakdown equipment, such as drums, gaskets or valves may be -----(b)(4)----- .

These cleaning procedures generally consist of the following steps:

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

All of the steps mentioned utilize -----(b)(4)----- . and the cleaning steps in some cases use cleaning agents for equipment and parts and, -----(b)(4)----- . as a ---(b)(4)--- agent for the ---(b)(4)--- and the (b)(4) column.

Routine monitoring is performed for -----(b)(4)----- in addition to visual inspection of the equipment in order to monitor the cleaning process. The results are held to the same requirements as the Cleaning Validation for each applicable cleaning process.

Cleaning Validation

Prior to cleaning validation, commissioning, qualification and cleanability / development studies were performed to demonstrate, through testing, that the equipment / systems perform as designed and are able to reduce challenge material to within the predefined acceptance criteria.

Cleaning validation was performed to demonstrate that the intended cleaning procedures to be used to clean polysaccharide product contact surfaces are effective, robust and consistently meet the requirements for residual product, -----(b)(4)----- .

Cleaning validation studies consisted of three cleaning validation runs using a representative or challenge material held for a defined extended ----(b)(4)----- . When grouping strategies apply, three runs would be validated on the most challenging

I reviewed 476-0128-VS-04: Cleaning Validation Summary Report and found it to be acceptable. The cleaning procedures/processes associated with cleaning the equipment/systems used in the production of Pneumococcal Polysaccharides were challenged. Results demonstrate that the procedures are robust and reproducible. The Cleaning Validation protocols were completed and the results documented. All cleaning procedures/processes were validated successfully and are suitable for their intended purposes. All deviations recorded by Wyeth have been appropriately investigated and closed out. I do not have any questions or comments.

Document # 476-0128-VS-04D Cleaning Validation Summary Report

Cleaning Validation Test Method and Acceptance Criteria

[(b)(4)]

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

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

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

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

11 pages determined not to be releasable; (b)(4)

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

-----~~(b)(4)~~-----
 -----~~(b)(4)~~-----
 • -----~~(b)(4)~~-----
 • -----~~(b)(4)~~-----
 • -----~~(b)(4)~~-----

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

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

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

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

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

Routine Cleaning Monitoring

Routine monitoring is performed for -----~~(b)(4)~~-----
 ----- in addition to visual inspection of the equipment in order to monitor the
 cleaning process. The results are held to the same requirements as the cleaning validation
 for each applicable cleaning process.

Differential Pressure

Differential pressure of ---(b)(4)--- inches of water are maintained across closed doors between areas of different classifications. The pressure in the ----(b)(4)---- down area with the more stringent classification --(b)(4)-- maintains the highest pressure.

Temperature throughout the Component Preparation area is maintained at -----(b)(4)---- for manufacturing operations. Relative humidity is maintained between a range of --(b)(4)--- RH.

Differential pressure, temperature and humidity measurements are ----(b)(4)---- monitored and recorded. Alarms for each of these parameters are also monitored and recorded.

I reviewed the drawings listed above for the Component Preparation Area along with 3.2.A.1, Pearl River, Drug Product – Building (b)(4), Environmental Qualification and Monitoring and 3.2.A.1, Pearl River, Drug Product – Building (b)(4), 415-0021-VS-01: Environmental Qualifications and Monitoring Summary Report and found them to be acceptable. My review for 3.2.A.1, Pearl River, Drug Product – Building (b)(4), Environmental Qualification and Monitoring and 3.2.A.1, Pearl River, Drug Product – Building (b)(4), 415-0021-VS-01: Environmental Qualifications and Monitoring Summary Report is located within this review report.

Building ---(b)(4)--- Floor Aluminum Phosphate and 13vPnC Bulk Formulation

The manufacturing areas for aluminum phosphate and 13vPnC bulk vaccine formulation are located on the (b)(4) floor and -(b)(4)- from the rest of the building with a -----(b)(4)----- . These areas are classified in accordance with the activities that occur within each area. The areas are illustrated within the submission in Section 3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW E-080078: 13V HVAC Building ---(b)(4)--- Floor Area Classification / Air Pressurization.

Area Classifications

The area and the environmental classifications are mostly --(b)(4)- with a few less critical areas classified as --(b)(4)- . The laminar flow unit is classified as --(b)(4)- .

The area classifications are illustrated on 3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW E-080078: 13V HVAC Building --(b)(4)--- Floor Area Classification / Air Pressurization. Environmental monitoring procedures and specifications supporting these area classifications are detailed in 3.2.A.1, Pearl River, Drug Product – Building (b)(4), Environmental Qualification and Monitoring.

Differential Pressure

Differential pressure of --(b)(4)-- inches of water are maintained across closed doors between areas of different classifications. The pressure in the ----(b)(4)---- down area with the more stringent classification --(b)(4)- maintains the highest pressure. Temperature throughout the Component Preparation area is maintained at -----(b)(4)---- for manufacturing operations. Relative humidity is maintained between a range of --- (b)(4)----- RH.

Differential pressure, temperature and humidity measurements are ----(b)(4)---- monitored and recorded. Alarms for each of these parameters are also monitored and recorded.

I reviewed the drawings listed above for the manufacturing areas for aluminum phosphate and formulated bulk vaccine along with 3.2.A.1, Pearl River, Drug Product – Building (b)(4), Environmental Qualification and Monitoring and 3.2.A.1, Pearl River, Drug Product – Building (b)(4), 415-0021-VS-01: Environmental Qualifications and Monitoring Summary Report and found them to be acceptable. My review for 3.2.A.1, Pearl River, Drug Product – Building (b)(4), Environmental Qualification and Monitoring and 3.2.A.1, Pearl River, Drug Product – Building 215, 415-0021-VS-01: Environmental Qualifications and Monitoring Summary Report is located within this review report.

Environmental Qualification and Monitoring

Environmental Qualifications

All areas within Building (b)(4) used for the manufacturing 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 -----(b)(4)----- . Classified areas are monitored on a routine basis for viable and non-viable airborne particulates, and viable microorganisms on surfaces. --- (b)(4)---- are used to monitor the clean room surfaces. Personnel monitoring is performed in the --(b)(4)-- area for Building (b)(4); there are no --- (b)(4)--- operations.

The environmental qualifications involved sampling for -----(b)(4)----- days at rest and in operation in the -----(b)(4)----- areas. There are no --(b)(4)-- areas in Building (b)(4). A summary of the qualifications performed is provided in 3.2.A.1, Pearl River, Drug Product – Building (b)(4), 415-0021-VS-01: Environmental Qualifications and Monitoring Summary Report. The testing evaluated multiple sample sites in the various environments for viable microorganisms, using air sampling, settle plates and contact plates, and for non-viable particulates -----(b)(4)----- using particle counters. The number of sample sites in each classification was based on --- (b)(4)----. The results of the qualifications demonstrated that the classified areas in Building (b)(4) met the environmental quality requirements defined in the protocol. During qualification, all media used was certified for growth promotion prior to use.

Specific sites for each area were selected for the routine monitoring program based on worst case or the data collected during qualification.

Routine Environmental Monitoring

Classified areas are monitored for viable and non-viable airborne particulates and viable microorganisms on surfaces (contact plates). Air monitoring for viable microorganisms is performed -----(b)(4)----- . ---(b)(4)----- are exposed for a maximum of (b)(4). Air monitoring for non-viable particulates is performed using -----(b)(4)----- . Personnel monitoring is performed in the ---(b)(4)--- area for Building (b)(4); there are no ---(b)(4)--- operations.

Summaries of the tests performed, frequency, and action levels for -----(b)(4)----- areas in operation are detailed in the tables below.

Environmental Monitoring – (b)(4)

[(b)(4)]

Environmental Monitoring – (b)(4)

[(b)(4)]

Environmental Monitoring – (b)(4)

[(b)(4)]

I reviewed 3.2.A.1, Pearl River, Drug Product – Building (b)(4), 415-0021-VS-01: Environmental Qualifications and Monitoring Summary Report and found it to be acceptable. The Building (b)(4) heating, ventilation, and air conditioning (HVAC) environmental qualifications were executed to ensure the graded environments met air quality requirements as detailed in the qualification protocols. All samples met specifications. All deviations associated with the qualification activities have been successfully resolved. The results obtained demonstrate that the Building (b)(4) environments were successfully qualified. I agree with Wyeth’s assessment of the

deviations as being minor with no impact on the validation. I do not have any questions or comments.

Flows

I reviewed the following flow diagrams and verbal descriptions of the flows for Building (b)(4) and found them to be acceptable. I do not have any questions or comments.

Flows for Component Preparation Area

Personnel Flow

3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW E-080080: 13V Personnel Flow Diagram Building ---(b)(4)--- Floor.

Equipment and Material Flow

3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW E-080081: 13V Material Flow Diagram Building ---(b)(4)--- Floor.

Soiled Equipment/Waste Material Flow

3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW E-080082: 13V Solid Waste Flow Building ---(b)(4)--- Floor.

Flows for Aluminum Phosphate and Formulated Bulk Vaccine Manufacturing Areas

Personnel Flow

3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW E-080084: 13V Personnel Flow Diagram Building ---(b)(4)--- Floor.

Component and Material Flow

3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW E-080085: 13V Material Flow Diagram Building ---(b)(4)--- Floor.

Product Flow

3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW E-080085: 13V Material Flow Diagram Building ---(b)(4)--- Floor.

Soiled Equipment/Waste Material Flow

3.2.A.1, Pearl River, Drug Product - Building (b)(4), DRW E-080086: 13V Solid Waste Flow Building 215 – (b)(4) Floor

3.2.A.1, Pearl River, Drug Product - Building (b)(4), DRW E-080083: 13V Material Flow Diagram – Building ---(b)(4)--- Floor.

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

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

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

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

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

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

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

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

Building (b)(4) Utilities
Clean Steam

The Clean Steam system for the commercial manufacturing areas were designed and qualified to meet the criteria specified in -----(b)(4)-----.

The clean steam system serving Building (b)(4) has been validated and is requalified ---(b)(4)----- Quality is monitored by (b)(4)--- routine sampling and testing of the clean steam -----(b)(4)----- requirements.

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

Deviation Summary

Deviations encountered during the execution of the qualification studies were investigated by Wyeth. The investigations assessed the potential impact on the qualification studies. The deviation descriptions, resolution and qualification impact are summarized within the submission in Table 5-1. I reviewed the deviations and agree with the investigations and closeout of the deviations.

Routine Clean Steam Monitoring

Clean Steam quality is monitored by (b)(4) routine sampling and testing of the clean steam -----(b)(4)----- requirements. Additionally, the clean steam system is tested (b)(4) for -----(b)(4)-----.

Process Compressed Air

The Building (b)(4) Compressed Air System provides compressed air to various process and instrument use points in Building (b)(4).

Compressed air is produced by compressing ambient air to a design pressure of approximately -----(b)(4)----- . The compression is accomplished by (b)(4) air compressor systems that feed a common air receiver. The compressed air is directed to -----(b)(4)-----

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

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

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

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

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

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

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

Performance Qualification Acceptance Criteria

[(b)(4)]

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

Deviations

Deviations encountered during the execution of the qualification studies were investigated by Wyeth. The investigations assessed the potential impact on the qualification studies and on product quality. The deviation descriptions, resolution and qualification impact are summarized within the submission in Table 4-1. I reviewed the deviations and agree with Wyeth’s assessment, investigation, and closeout of the deviations.

Routine Monitoring of the Processed Compressed Air System

----- (b)(4) ----- critical use points are sampled and tested at least ----- (b)(4) ----- for ----- (b)(4) ----- Viable Particulates and Non-Viable Particulates ----- (b)(4) ----- . The presence of ----- (b)(4) ----- and Pressure are ----- (b)(4) ----- measured at the compressed air source.

Heating, Ventilation and Air Conditioning

The Heating, Ventilation, and Air Conditioning (HVAC) systems serving the ----- (b)(4) ----- floors in Building (b)(4) consist of (b)(4) Air Handling Units (AHU). The areas served by each AHU are illustrated within the submission in Section 3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW E-080079A: (b)(4) Floor Area Classification/Air Pressurization and DRW E-080078A: (b)(4) Floor Area Classification/Air Pressurization.

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

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

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

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

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

HVAC Qualification

The HVAC systems servicing the production areas have been qualified. A summary of the qualifications performed is detailed within the submission in Section 3.2.A.1, Pearl River, Drug Product – Building (b)(4), 415-0020-VS-01: HVAC Qualification Summary Report. The qualifications demonstrated that the HVAC systems for the commercial manufacturing areas maintained the classified environments at temperatures of -----
(b)(4)---- relative humidity at ---(b)(4)-----adequate differential pressures between rooms, and minimum air change rate.

Environmental Qualifications were also performed as detailed within the submission in Section 3.2.A.1, Pearl River, Drug Product – Building (b)(4), 415-0021-VS-01: Environment Qualification Summary Report. This document was reviewed and discussed earlier in this report. As part of the qualification, all classified production areas were tested under at rest and in operation conditions. Rooms were monitored for -----
-----~~(b)(4)~~-----
----- The HVAC qualifications also included the controllers and the Building Management System. In addition, the HEPA filters are regularly certified.

I reviewed 3.2.A.1, Pearl River, Drug Product – Building (b)(4), 415-0020-VS-01: HVAC Qualification Summary Report and 3.2.A.1, Pearl River, Drug Product – Building 215, 415-0021-VS-01: Environment Qualification Summary Report and found them to be acceptable. The Installation and Operational Qualification of the Heating, Ventilation, and Air Conditioning (HVAC) system serving Building --- (b)(4)----- floors demonstrated that the system is installed as designed and specified, and operates within the established design parameters. Environmental monitoring was performed as a Performance Qualification of the HVAC system, as detailed in 3.2.A.1, Pearl River, Drug Product – Building (b)(4), Environmental Qualifications and Monitoring. All deviations were addressed by Wyeth and closed out. None of the deviations had a negative impact on the qualification. I do not have any questions or comments.

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

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

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

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

Water for Injection System

The WFI System is illustrated in 3.2.A.1, Pearl River, Drug Product - Building (b)(4), DRW C-079405: Building (b)(4) WFI Loop No. (b)(4) Block Flow Diagram and DRW C-079406: Building (b)(4) WFI Loop No. (b)(4) Block Flow Diagram.

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

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

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

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

- 2. -----(b)(4)-----
- 3. -----(b)(4)-----
- 4. -----(b)(4)-----

I have reviewed 3.2.A.1, Pearl River, Drug Product – Building (b)(4), 415-0265-VS-01: Water for Injection Validation Summary Report and found it to be acceptable. The Water for Injection (WFI) system serving Building (b)(4) is installed as designed and specified, operates within the established design parameters, and produces WFI meeting current -----(b)(4)----- Requirements. The installation, operational, and performance qualifications for the WFI system have been satisfactorily completed. All deviations recorded by Wyeth have been appropriately investigated and closed out. I agree with Wyeth’s assessment that the deviations did not have a negative impact on the qualification. I do not have any questions or comments.

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

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

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

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

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

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

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

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

1. ----- (b)(4) -----.
2. ----- (b)(4) -----
3. ----- (b)(4) -----

I reviewed 401-0100-VS-02: Process Validation Summary Report for 13vPnC Formulation, Filling and Inspection of 13vPnC Syringes at Pearl River and found it to be acceptable. All completed formulation process validation and GMP runs were performed within the established processing parameters for the formulation process, and met all in-process controls and release acceptance criteria. These results validate the formulation process, and establish a -----(b)(4)----- hold time of -(b)(4)- at -----(b)(4)----- and a -----(b)(4)----- vaccine hold time of--- (b)(4)-- at -----(b)(4)----- formulation vessel and -----(b)(4)----- in the ---(b)(4)--- including up to ---(b)(4)-- at -----(b)(4)----- I do not have any questions or comments.

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

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

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

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

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

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

Process Validation

The results of the process validation are detailed in 3.2.A.3, Pearl River, Drug Product – Building (b)(4), 415-0208-VS-01: Process Validation Summary Report for Aluminum Phosphate Manufacture in Building (b)(4).

Three full-scale manufacturing lots of AlPO4 were manufactured in Building (b)(4) using Media Preparation -(b)(4)-. All three process validation lots met the release specifications for aluminum phosphate.

Additionally, the three process validation batches were evaluated for ---(b)(4)--- levels prior to -----(b)(4)----- The results obtained met pre-determined acceptance criteria for these parameters.

There were three deviations during the process validation. The deviations were investigated and determined not to impact the validation performed. The results obtained met the acceptance criteria of the study, demonstrating that the manufacturing process consistently produces product that achieves its final quality attributes.

I reviewed 3.2.A.3, Pearl River, Drug Product – Building (b)(4) 415-0208-VS-03: Media Fill Summary Report and 3.2.A.3, Pearl River, Drug Product – Building (b)(4) 415-0208-VS-01: Process Validation Summary Report for Aluminum Phosphate Manufacture in Building (b)(4) and found them to be acceptable. The three process validation runs performed to validate the manufacture of AlPO4 ----(b)(4)----- using ----(b)(4)----- in Building (b)(4) at Wyeth, Pearl River were completed successfully. The results obtained met the acceptance criteria of the study, demonstrating that the manufacturing process consistently produces product that achieves its final quality attributes. Therefore, the production process for manufacture of AlPO4

Deviations

Deviations encountered during the execution of the validation study were investigated. The investigations assessed the potential impact on the validation study and on product quality. The deviation description, resolution, and validation impact are summarized in Table 3-1 of the report. I reviewed the deviations and agree with Wyeth's assessment, investigation, and closeout of the deviations.

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

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

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

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

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

Deviations

Deviations encountered during the execution of the validation study were investigated. The investigations assessed the potential impact on the validation study and on product quality. The deviation description, resolution, and validation impact are summarized in Table 3-1 within the submission. I reviewed the deviations and agree with Wyeth's assessment, investigation and closeout of the deviations.

Support Equipment

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

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

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

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

Equipment Cleaning Validation

Cleaning validation has been performed for the equipment and parts used in the manufacture of Aluminum Phosphate (AlPO₄) ---(b)(4)-- and 13vPnC formulated bulk vaccine. The equipment used for AlPO₄ may also be used for other -----(b)(4)-----
Product contact equipment and parts used in 13vPnC production are restricted to the use of Prevnar® and 13vPnC. All the equipment and parts are cleaned using validated procedures. The production equipment and systems are cleaned and sterilized to prepare the equipment and systems for each subsequent batch. Large fixed equipment, such as tanks, is -----(b)(4)-----

Small, easily removed, easy to breakdown equipment, such as valves, may be -----(b)(4)----- procedures generally consist of -----(b)(4)-----

Routine monitoring is performed for -----(b)(4)----- in addition to visual inspection to verify cleanliness. The results are held to the same requirements as the Cleaning Validation for each applicable cleaning process.

Cleaning Validation

The results of cleaning validation are detailed in 3.2.A.1, Pearl River, Drug Product – Building (b)(4), 415-0208-VS-02: Cleaning Validation – Manufacture of Aluminum Phosphate in Building (b)(4), and 415-0210-VS-01: Cleaning Validation – Media Preparation ---(b)(4)--, Cleaning Cycle for 13vPnC Process.

Prior to cleaning validation, commissioning, qualification and cleanability / development studies were performed to demonstrate, through testing, that the equipment / systems perform as designed and are able to reduce challenge material to within the predefined acceptance criteria.

For the cleaning validation for AlPO₄ equipment, studies were performed following a ---(b)(4)----- Media Simulation and each of three (b)(4) Process Validation runs, with the equipment held for a defined -----(b)(4)----- . For the 13vPnC formulation process, cleaning validation studies were performed following three 13vPnC development studies and (b)(4) runs.

Sampling and testing was performed to demonstrate that the intended cleaning were effective, robust and consistently met the requirements for -----(b)(4)----- . Sample plans and sample locations were clearly defined in the cleaning validation protocols and were dependent on the equipment being cleaned. Sample locations were selected based on most difficult to clean and representative product-contact locations.

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

All of the results met the acceptance criteria detailed in the applicable cleaning validation protocols, establishing validation of the cleaning procedures.

I reviewed 3.2.A.1, Pearl River, Drug Product – Building (b)(4), 415-0208-VS-02: Cleaning Validation – Manufacture of Aluminum Phosphate in Building (b)(4), and 415-0210-VS-01: Cleaning Validation – Media Preparation –(b)(4)-- Cleaning Cycle for 13vPnC Process and found them to be acceptable. Cleaning validation runs were performed to validate the cleaning procedures used to clean the Aluminum Phosphate ---(b)(4)--- manufacturing equipment and the 13vPnC manufacturing equipment used in Building (b)(4) at Wyeth, Pearl River. All results met the pre-determined acceptance criteria for cleanliness including visual inspection, and test results for -----(b)(4)----- . These results provided documented evidence that the cleaning procedures are suitable for their intended purpose.

3 pages determined not to be releasable; (b)(4)

Overview of Pearl River Facilities – Building (b)(4)

13-Valent Pneumococcal Conjugate Vaccine (13vPnC) is filled, inspected, labeled and packaged, into syringes in the Building (b)(4) complex. The site plan for the Pearl River manufacturing facilities is depicted in 3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW E-079421: Wyeth Pearl River Site Plan.

Building (b)(4) Complex

The Building (b)(4) Complex is one building comprised of ----(b)(4)-----, identified as Buildings -----(b)(4)----- . The Syringe Filling/Inspection and the Component Preparation areas are located in Building (b)(4) and the Syringe Packaging Line (b)(4) is located in Building (b)(4). The Building (b)(4) Complex is a multi-product facility and includes separate areas for Vaccine Development use. All production areas and systems are built in conformance with current Good Manufacturing Practices.

Building ---(b)(4)--- Floor Component Preparation Area

The Building ---(b)(4)--- Floor Component Preparation Area (comprised of Rooms -----(b)(4)----- is serviced by AHU(b)(4), which is a dedicated air handler with ----(b)(4)-----ability.

The Building ---(b)(4)---Floor Component Preparation Area is used for the cleaning and sterilizing of filling/stoppering equipment parts.

Area Classification

Areas within the Component Preparation Area are classified in accordance with the activities that occur within each area. The areas are illustrated on the Area Classification 3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW G-080068: Component Preparation Area Classification --(b)(4)-- Floor located within the submission.

Differential Pressures

Differential pressure of -----(b)(4)----- are maintained across closed doors between areas of different classifications. The pressure in the room with the more stringent classification ---(b)(4)-- maintains the highest pressure. Temperature throughout the Component Preparation area is maintained at ----(b)(4)----- for manufacturing operations. Relative humidity is maintained between a range of -(b)(4)-RH. Differential pressure, temperature and humidity measurements are continuously monitored and recorded. Alarms for each of these parameters are also monitored and recorded.

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

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

Area Classifications

All areas within the Syringe Filling Suite are classified in accordance with the activities that occur within each area and the level of containment, as required. The area classifications are illustrated in 3.2.A.1, Pearl River, Drug Product – Building (b)(4) DRW G-080069: Area Classification Syringe Filling Facility –(b)(4)-- Floor located within the submission.

Differential Pressures

Differential pressure of ----(b)(4)----- of water are maintained across closed doors between areas of different classifications. The pressure in the room with the more stringent classification --(b)(4)-- maintains the highest pressure.

Temperature in Room (b)(4) and all supporting classified areas is maintained at ---(b)(4)- ----- for manufacturing operations. Relative humidity is maintained in a range of -(b)(4)- RH in room (b)(4) and in the supporting classified areas. Differential pressure, temperature and humidity measurements are continuously monitored and recorded. Alarms for each of these parameters are also monitored and recorded.

Flows

I reviewed the following flow diagrams and descriptions and found them to be acceptable. I do not have any questions or comments.

Building –(b)(4)-- Floor Component Preparation Area

Personnel Flow

3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW G-080104: Personnel Flow Component Preparation Building ---(b)(4)-- Floor.

Equipment and Material Flow

3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW G-080105: Material Flow Component Preparation Building ---(b)(4)-- Floor.

Soiled Equipment/Waste Material Flow

3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW G-080106: Solid Waste Flow Component Preparation Building ---(b)(4)-- Floor.

Building ---(b)(4)--- Floor Syringe Filling Suite

Personnel Flow

3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW G-080100: Personnel Flow Syringe Filling Facility Building ---(b)(4)-- Floor.

Component/Material Flow

3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW G-080101: Material Flow Syringe Filling Facility Building ---(b)(4)-- Floor.

Product Flow

3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW G-080101: Material Flow Syringe Filling Facility Building ---(b)(4)-- Floor.

Soiled Equipment/Waste Material Flow

3.2.A.1, Pearl River, Drug Product – Building (b)(4), DRW G-080102: Solid Waste Flow Syringe Filling Facility Building ---(b)(4)-- Floor.

Contamination and Cross-Contamination Controls

Contamination Controls

The Building ---(b)(4)-- Floor Syringe Filling and Inspection Suite has been designed to minimize the potential of product contamination and personnel exposure using a combination of controls including: dedicated air handling units, pressure differential zones, air locks, gowning rooms and defined pathways for the flow of personnel, equipment, materials, and waste. Manufacturing areas are controlled environments appropriate to the operations that take place within the particular area with pressurization maintained and monitored in the area. -----(b)(4)-----

Site SOPs describe the flow of materials through the facility during the manufacturing process to prevent contamination and mix-ups. Procedures also ensure that appropriate storage conditions are met throughout the manufacturing process. All classified areas are routinely monitored, including viable and non-viable air particulate monitoring, viable surface monitoring, and personnel monitoring.

Cross-contamination Controls

The Fill/Finish area is used for aseptically filling 13vPnC and Prevnar into syringes. There is no manufacture of products containing penicillin, cephalosporin, live viruses, spore-forming organisms or cytotoxic drugs in this facility. The Fill/Finish area and site procedures are designed to keep each type of Bulk Formulation segregated. To avoid any potential mix-up or cross-contamination between 13vPnC and Prevnar Bulk Formulations, -----(b)(4)-----

Filling equipment and components being prepared for entry into the filling suite and filled syringes being inspected, including supporting documentation for both activities, are physically segregated within the Fill/Finish area.

A product group changeover procedure is in place for switching from filling and inspection activities between different drug products. Product-contact equipment is dedicated and labeled.

All portable equipment is cleaned and disinfected in accordance with validated written procedures between batches. Stationary equipment is ---(b)(4)--- disinfected as per site procedures. Rooms are cleaned and disinfected using validated disinfectants according to written procedures. Room clearance of components and equipment together with area inspection provides assurance that no specific materials or documents remain from a previous manufacture of a different product. A more intensive cleaning and disinfection procedure is used any time there is a disruption to any controlled environment, as per site procedures.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Environmental Qualification and Monitoring – Building (b)(4)

Environmental Qualifications

The environmental qualifications involved sampling for ---(b)(4)---- days at rest and in operation. A summary of the qualifications performed is provided in 3.2.A.1, Pearl River, Drug Product - Building (b)(4), 422-0103-VS-02: Environmental Qualifications and Monitoring Summary Report. The testing evaluated multiple sample sites in the various environments for viable microorganisms (using ---(b)(4)-----
-----) and for non-viable particulates----- (b)(4)----- using particle counters. The results of the qualifications demonstrated that the classified areas in Building (b)(4) met the environmental quality requirements defined in the protocol. During qualification, all media used was certified for growth promotion prior to use.

I reviewed 3.2.A.1, Pearl River, Drug Product - Building (b)(4), 422-0103-VS-02: Environmental Qualifications and Monitoring Summary Report and found it to be acceptable. The ---(b)(4)--- Floor Syringe Filling Suite environmental qualifications were executed to ensure the graded environments met air quality requirements as detailed in the qualification protocols. All deviations associated with the qualification activities have been successfully resolved. The results obtained demonstrate that the Syringe Filling Suite environments were successfully qualified. I do not have any questions or comments.

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

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

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

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

Environmental Monitoring – (b)(4)

[(b)(4)]

**Building (b)(4) – Utilities
Water for Injection (WFI) System**

The WFI system is illustrated within the submission in Section 3.2.A.1, Pearl River, Drug Product - Building ---(b)(4)-- Floor, DRW C-079403: Component Preparation WFI/Clean Steam Flow Block Diagram. Included in the WFI system are a -----

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

----- Distribution pumps in Building (b)(4) continuously circulate and supply WFI to the points of use. The WFI distribution loop (----- (b)(4) -----) and the associated equipment in Building (b)(4) are --- (b)(4) --- sanitized. The WFI is maintained at ----- (b)(4) -----
----- All parts wetted by feed water and WFI are manufactured with -----
----- (b)(4) -----

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

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

- 2. ----- (b)(4) -----
- 3. ----- (b)(4) -----
- 4. ----- (b)(4) -----

**I have reviewed 3.2.A.1, Pearl River, Drug Product - Building –(b)(4) Floor, DRW C-079403: Component Preparation WFI/Clean Steam Flow Block Diagram and 3.2.A.1, Pearl River, Drug Product – Building (b)(4), 422-0110-VS-01: Water for Injection Qualification Summary Report and found it to be acceptable. The Water for Injection (WFI) system serving the (b)(4) Floor Component Preparation Area in Building (b)(4), Wyeth, Pearl River, NY is installed as designed and specified, operates within the established design parameters, and produces WFI meeting current -----
---(b)(4)----- requirements. All deviations were successfully resolved. The installation, operational, and performance qualifications for the WFI system have been satisfactorily completed. I do not have any questions or comments.**

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

I reviewed 3.2.A.1, Pearl River, Drug Product - Building (b)(4) Floor, DRW C-079403: Component Preparation WFI/Clean Steam Flow Block Diagram and 3.2.A.1, Pearl River, Drug Product - Building (b)(4), 422-0111-VS-01: Clean Steam Validation Summary Report and found them to be acceptable. The Clean Steam System serving the (b)(4) Floor Component Preparation Area in Building (b)(4) at Wyeth, Pearl River is installed as designed and specified, operates within the established design parameters, and produces clean steam meeting current (b)(4) requirements for WFI. All deviations associated with the qualification activities have been successfully resolved. The installation, operational, and performance qualifications for the Clean Steam System were satisfactorily completed. I do not have any questions or comments.

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

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

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

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

[(b)(4)]

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

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

Deviations

Wyeth recorded the deviations encountered during the execution of this protocol within the submission in Table 5-1. I reviewed the deviations and all deviations were investigated and satisfactorily resolved.

Routine Clean Steam Monitoring

Clean Steam quality is monitored by routine (b)(4) sampling and testing of the clean steam -----(b)(4)----- requirements. Additionally, the clean steam system is tested --(b)(4)-- for -----(b)(4)-----.

Heating, Ventilation and Air Conditioning

The Heating, Ventilation, and Air Conditioning (HVAC) systems serving the Fill Finish Production Area are composed of -----(b)(4)----- serving Building --(b)(4)-----
----- Syringe Filling Suite and the other serving Building ---(b)(4)----- Floor Component Preparation Area. The HVAC system for the (b)(4) floor Syringe Suite is illustrated within the submission in Section 3.2.A.1, Pearl River, Drug Product - Building

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

The HVAC system qualifications also included the controllers and the Building Management system. Additionally, the HEPA filters are re-certified every (b)(4).

I reviewed 3.2.A.1, Pearl River, Drug Product - Building (b)(4), 422-0103-VS-01: HVAC Qualification Summary Report and 3.2.A.1, Pearl River, Drug Product - Building (b)(4), 422-0103-VS-02: Building (b)(4) Classified Environment Qualification Summary Report and found them to be acceptable. My review of 422-0103-VS-02 is contained in a previous section of this report. My review of 422-0103-VS-01 is below. Installation and Operational Qualification of the Heating, Ventilation, and Air Conditioning (HVAC) system and associated Down Flow Laminar Air Flow Units serving Fill/ Finish Production Areas (b)(4) Floor Syringe Filling Suite and (b)(4) Floor Component Preparation Area) in Building (b)(4) demonstrated that the system is installed as designed and specified, and operates within the established design parameters. Environmental monitoring was performed as a Performance Qualification of the HVAC system. I do not have any questions or comments.

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

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

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

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

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

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

Routine HVAC Monitoring

The Building Management system controls and monitors both the HVAC systems and the production areas served. The system collects data such as equipment status, room pressurization, temperature, and relative humidity, and provides a graphical user interface to view the data in the form of trends or tables.

Process Compressed Air

The Building (b)(4) Complex PCA System provides (b)(4) compressed air to various equipment and instruments located throughout the Building (b)(4) complex, including the -----(b)(4)----- on the (b)(4) floor of Building (b)(4). This system is supplied by central compressed air equipment located in the Building -----(b)(4)-----.

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

In addition to process compressed air,---(b)(4)--- compressed air, regulated to the applicable pressure requirements, is provided to -----(b)(4)-----

Validation of the Processed Compressed Air System

A summary of the qualifications performed is detailed within the submission in Section 3.2.A.1, Pearl River, Drug Product - Building (b)(4), 422-0072-VS-03: Plant Compressed Air System Validation Summary Report and demonstrates that the system operates according to design specifications.

The following functions have been verified by testing for the Process Compressed Air system at Building (b)(4), Pearl River:

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

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

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

I reviewed 3.2.A.1, Pearl River, Drug Product - Building (b)(4), 422-0072-VS-03: Plant Compressed Air System Validation Summary Report and found it to be acceptable. The Building (b)(4) Complex, (b)(4) Process Compressed Air (PCA) system serving the (b)(4) floor of Building (b)(4) at Wyeth, Pearl River is installed as designed and specified, operates within the established design parameters, and produces

compressed air meeting qualification testing requirements. All deviations were successfully resolved. The installation, operational, and performance qualifications for the PCA system have been satisfactorily completed. I do not have any questions or comments.

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

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

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

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

Process Compressed Air Performance Qualification Acceptance Criteria

[(b)(4)]

9 pages determined not to be releasable; (b)(4)

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

Final Product Testing

Final product test results are summarized within the submission in Table 3-12. All final product test results met the pre-determined acceptance criteria. This testing includes sterility testing. Sterility testing is also included during stability studies at Initial, 12, 24, (b)(4) and (b)(4) months. The specification is “Meets the requirement of the test; no growth observed”.

Deviations

Deviations to the process validation protocols were investigated and assessed for their potential impact on the validation study. The deviations were reviewed and approved by Quality Assurance. The deviation description, resolution and validation impact associated with the data in this validation summary are summarized within the submission in Table 4-1 and Table 4-2. I reviewed the deviations and agree with Wyeth’s assessment, investigation and closeout of the deviations.

Autoclaves

The (b)(4) sterilization autoclaves are located between Rooms ---(b)(4)----- in Building (b)(4) and are used for sterilization of equipment used for the filling of syringes.

Both autoclaves have been qualified by performing Installation, Operation, and Performance Qualification. The autoclaves are re-qualified every (b)(4). The validation of the autoclaves is detailed in 3.2.A.1, Pearl River, Drug Product – Building (b)(4), Report 422-0106-VS-01: Autoclave PQ Summary Report and demonstrates that the equipment operates according to design specifications and is maintained within the design parameters.

I reviewed 422-0106-VS-01: Autoclave PQ Summary Report and found it to be acceptable. Installation (IQ), Operational (OQ) and Performance Qualification (PQ) runs were performed to validate the -----(b)(4)----- located on the (b)(4) floor of Building (b)(4) at Wyeth, Pearl River. The PQ runs consisted of worst-case minimum and maximum load configurations. The data obtained from each of three consecutive runs met the acceptance criteria for heat

distribution and heat penetration, including inactivation of Biological Indicators, and minimum F₀ values of (b)(4). I do not have any questions or comments.

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

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

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

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

Autoclave Performance Qualification Testing Parameters

[(b)(4)]

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

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

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

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

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

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

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

I reviewed 422-0112-VS-01: Cleaning Validation Summary Report and found it to be acceptable. Three cleaning validation runs were performed to validate the cleaning procedures used to clean the 13vPnC vaccine filling equipment used in Building (b)(4). All results obtained met the pre-determined acceptance criteria for cleanliness, including visual inspection, and test results for ----- (b)(4) ----- levels. These results provide documented evidence that the cleaning procedures are suitable for their intended purposes. I do not have any questions or comments.

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

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

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

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

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

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

Overview of (b)(4) Facilities (written by NW)

------(b)(4)-----
----- The facility is situated on an approximately (b)(4)-acre lot inside an industrial zone on the city’s west side, as illustrated in 3.2.A.1, (b)(4), Drug Product – --- (b)(4)---, Drawing CIVA- 002: Site Plan. -----(b)(4)-----
----- 13-Valent Pneumococcal Conjugate Vaccine (13vPnC) is formulated and filled in --- (b)(4) ---.

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

---(b)(4)--- is a multi-product facility and includes separate areas for component preparation, 13vPnC bulk vaccine formulation, and 13vPnC syringe filling. All production areas and systems comply with current Good Manufacturing Practices.

Area Classifications

The controlled areas in ---(b)(4)--- are classified in accordance with the activities that occur within each area. The area classifications are illustrated on 3.2.A.1, -(b)(4)---, Drug Product – ---(b)(4)--- , Drawing ROM-D-PRD5, Classified Environments, Production Block, (b)(4) Floor - ---(b)(4)---, and 3.2.A.1, (b)(4)---, Drug Product – ---(b)(4)---, Drawing ROM-D-PRD6, Classified Environments, Production Block, --(b)(4)-- Floor - --(b)(4)---. Environmental monitoring procedures and specifications supporting these area classifications are detailed in 3.2.A.1, (b)(4)---, Drug Product – ---(b)(4)---, Environmental Qualification and Monitoring.

Differential Pressure

Differential pressure ranges of -----(b)(4)----- are maintained in positive-pressure rooms. All critical areas are maintained at---(b)(4)--- inches of positive pressure relative to lower classified rooms. Temperature in all clean rooms is maintained at --- (b)(4)---- during manufacturing operations. Differential pressure between rooms, temperature, and humidity are measured in some critical rooms on a continuous basis using the -----(b)(4)-----.

Component Preparation Area

The Component Preparation Area is designed to support cleaning, preparation and sterilization of -----(b)(4)----- and other miscellaneous parts used for manufacturing operations. The Component Preparation Area is located on the (b)(4) floor and is --(b)(4)----- (b)(4)-----
----- The areas and their environmental classifications are ---(b)(4)----.

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

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

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

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

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

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

Environmental Qualifications and Monitoring

All areas within the Production Block are classified in accordance with the activities that can occur within that area and the level of containment required. Areas are classified as per -----~~(b)(4)~~-----

Environmental Qualifications

The environmental qualifications performed by (b)(4) involved (b)(4) days of static (Inactive) monitoring and (b)(4) days of dynamic (Active) monitoring in the ---~~(b)(4)~~----- areas. A summary of the qualifications is provided within the submission in Section 3.2.A.1, (b)(4), Drug Product – ---~~(b)(4)~~---, SR REC 31551, Environmental Monitoring Performance Qualification Summary Report: (b)(4) – ---~~(b)(4)~~---. The testing evaluated multiple sample sites in the various environments for viable microorganisms (-----~~(b)(4)~~-----) and non-viable particulates -----~~(b)(4)~~-----. The results of the qualifications demonstrated that the classified areas in ---~~(b)(4)~~--- met the environmental quality requirements defined in the protocol. Based on the data collected, specific sites for each area were selected for the routine monitoring program.

I reviewed 3.2.A.1, (b)(4), Drug Product – ---~~(b)(4)~~---, SR REC 31551, Environmental Monitoring Performance Qualification Summary Report: -----~~(b)(4)~~----- and found it to be acceptable. I do not have any questions or comments.

Environmental Monitoring

Summaries of the tests performed, frequency, and action levels for Personnel, -----~~(b)(4)~~----- and gowning areas are detailed in the tables below. The frequency and action levels in the tables and the text below are subject to change based on (b)(4)-- review and trending of monitoring results obtained, in order to continually improve the program.

2 pages determined not to be releasable; (b)(4)

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

-----~~(b)(4)~~----- **Flows**

I reviewed the following diagrams and descriptions and found them to be acceptable. I do not have any questions or comments.

Personnel Flow

- 3.2.A.1 ~~(b)(4)~~- Drug Product -----~~(b)(4)~~---, DMF-D-1 Personnel Flow ---~~(b)(4)~~-- Floor
- 3.2.A.1 ~~(b)(4)~~- Drug Product -----~~(b)(4)~~---, DMF-D-2 Personnel Flow ---~~(b)(4)~~-- Floor

Material and Component Flow

- 3.2.A.1 ~~(b)(4)~~- Drug Product -----~~(b)(4)~~---, DMF-D-5 Material and Component Flow ---~~(b)(4)~~-- Floor
- 3.2.A.1 ~~(b)(4)~~- Drug Product -----~~(b)(4)~~---, DMF-D-6 Material and Component Flow --~~(b)(4)~~-- Floor

Product Flow

- 3.2.A.1 ~~(b)(4)~~- Drug Product -----~~(b)(4)~~---, DMF-D-3 Product Flow First Floor
- 3.2.A.1 ~~(b)(4)~~- Drug Product -----~~(b)(4)~~---, DMF-D-4 Product Flow ---~~(b)(4)~~-- Floor

Waste Flow

- 3.2.A.1 ~~(b)(4)~~- Drug Product -----~~(b)(4)~~---, DMF-D-7 Waste Flow ---~~(b)(4)~~-- Floor
- 3.2.A.1 ~~(b)(4)~~- Drug Product -----~~(b)(4)~~---, DMF-D-8 Waste Flow ---~~(b)(4)~~-- Floor

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

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

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

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

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

9 pages determined not to be releasable; (b)(4)

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

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

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

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

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

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

Inspection of Filled Syringes

Inspection of the 13vPnC filled syringes was performed in (b)(4) stages. In the (b)(4) stage, an in-process inspection was performed for ----- (b)(4) -----

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

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

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

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

All results met the acceptance criteria set forth in the cleaning validation protocol, establishing validation of the cleaning procedures.

I reviewed SR CV0804002: Summary Report for Cleaning Validation of the Process Equipment Associated with the Formulation and Filling of 13-Valent Pneumococcal Conjugate (13vPnC) Vaccine on -----(b)(4)----- and found it to be acceptable. Three cleaning validation runs were performed to validate the cleaning procedures used to clean the 13vPnC vaccine formulation and filling equipment used in -----(b)(4)----- . All results obtained met the pre-determined acceptance criteria for cleanliness, including visual inspection, and test results for -----(b)(4)----- . These results provide documented evidence that the cleaning procedures are suitable for their intended purpose. I do not have any questions or comments.

SR CV0804002 Validation Summary Report for Cleaning the Process Equipment Associated with the Formulation and Filling of 13-Valent Pneumococcal Conjugate (13vPnC) Vaccine on -----(b)(4)-----

Cleaning validation was performed using the dedicated -----(b)(4)----- and associated parts designated for use with 13vPnC vaccine. Following soiling, the process equipment was held for at least --(b)(4)--- prior to cleaning. The table below includes the -----(b)(4)----- for the three validation runs.

[(b)(4)]

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

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

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

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

-----**(b)(4)**----- – **Utilities**

Heating Ventilation and Air Conditioning

The Heating Ventilation and Air Conditioning (HVAC) system serving the ---(b)(4)----- classified areas at --(b)(4)-- is composed of a (b)(4) system, (b)(4), serving ---(b)(4)----- floor classified areas. The areas served by (b)(4) are illustrated within the submission in Section 3.2.A.1, (b)(4), Drug Product – ----(b)(4)-----, HVC-D-001 HEPA Filter Locations – ---(b)(4)----- Section 3.2.A.1, (b)(4), Drug Product – ---(b)(4)--, HVC-D-002 HEPA Filter Locations – (b)(4) Floor.

All classified areas are equipped with HEPA filters or -----(b)(4)----- filters. The zone air handlers are designed to provide a minimum air change rate of (b)(4) air volume exchanges per hour for each production area, with greater exchanges where required to maintain the various design conditions. During manufacturing operations, temperature is maintained at --(b)(4)-- inside the filling room and at ----(b)(4)----- in

the aseptic formulation rooms, and relative humidity is maintained at ----(b)(4)----- in these areas. All critical areas are maintained at ---(b)(4)----- of positive pressure relative to lower classified rooms. The temperature and pressurization of each room is monitored and controlled by the HVAC control system.

HVAC Qualification

The HVAC systems servicing the production areas have been qualified. A summary of the qualifications performed is detailed within the submission in Section 3.2.A.1 (b)(4), Drug Product – ---(b)(4)----, SR US1082-Q-OQP-0001: Summary Report for the Installation and Operational Qualification of HVAC System (b)(4), Serving ---(b)(4)---- at (b)(4). Environmental Qualifications were also performed as detailed in the submission in Section 3.2.A.1 (b)(4), Drug Product -----(b)(4)-----, SR REC 31551: Environmental Monitoring Performance Qualification Summary Report: -----(b)(4)----- -----(b)(4)----- . As part of the qualification, all classified production areas were tested under static and dynamic conditions. Rooms were monitored for total particulate levels, airborne viable particulates, and surface viable levels.

HVAC Monitoring

The air handling system is monitored by a validated computer-based system. This system is networked to gather and record data for temperature and pressure of critical areas and equipment. The system is equipped with visual and telecommunications alarms for filling and support areas, incubators, refrigerators, and freezers.

I reviewed SR US1082-Q-OQP-0001: Summary Report for the Installation and Operational Qualification of HVAC System (b)(4), Serving ----(b)(4)----- and SR REC 31551: Environmental Monitoring Performance Qualification Summary Report: -----(b)(4)----- and found them to be acceptable. Installation and Operational Qualification of the Heating Ventilation and Air Conditioning (HVAC) system serving the -----(b)(4)----- Classified Areas of ----(b)(4)----- at -----(b)(4)----- demonstrated that the system is installed as designed and specified, and operates within the established design parameters. The qualifications demonstrated that the HVAC systems for the commercial manufacturing areas maintained the classified environments at temperatures of -----(b)(4)-----, relative humidity at ----(b)(4)----, a differential pressure of ----(b)(4)----- of positive pressure relative to lower classified rooms, and provided air exchange rates of at least (b)(4) air exchanges per hour. Environmental monitoring was performed as a Performance Qualification of the HVAC system, as detailed within the submission in Section 3.2.A.1, (b)(4), Drug Product – --(b)(4)----, Environmental Qualifications and Monitoring. The EMPQ performed for -----(b)(4)----- demonstrated that all the classified rooms were capable of maintaining dynamic and static operating conditions within the proposed limits for quantitative viable air, qualitative viable air and non-viable particulate levels ----(b)(4)----- --. Additionally, the viable surface results demonstrated that adequate sanitization and maintenance programs are in place. I do not have any questions or comments.

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

EMPQ Action Limits: Air Viable Samples

[(b)(4)]

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

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

Deviations and Exceptions

There were 4 classified areas that generated 15 excursions or deviations during the execution of the EMPQ. These excursions were investigated via the Microbiological Investigation Report (MIR) system. Details of the excursions and investigations are summarized in Table 4-1 of the submission. I reviewed the deviations and found the investigation and closeout of the deviations to be acceptable.

I reviewed Report SR US1082-Q-OQP-0003, WFI Validation Summary Report and found it to be acceptable. The Water for Injection (WFI) system serving ----(b)(4)----- is installed as designed and specified, operates within the established design parameters, and produces WFI meeting current -----(b)(4)----- requirements. All deviations have been successfully resolved. The installation, operation, and performance qualifications for the WFI system have been satisfactorily completed. I do not have any questions or comments.

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

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

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

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

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

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

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

WFI Parameters Qualified

[(b)(4)]

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

Clean Steam Validation

The Clean Steam System serving -----(b)(4)----- has been validated and is re-qualified ----(b)(4), as detailed below. The validation is summarized within the submission in Section 3.2.A.1, (b)(4), Drug Product – ---(b)(4)-----, US1082-Q-OQP-0024: Summary Report for the Installation, Operational and Performance Qualification of the Clean Steam System. The Clean Steam System was designed and qualified to meet current ---(b)(4)----- requirements for WFI, specifically:

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

Routine Clean Steam Monitoring

Clean Steam quality is monitored by routine sampling and testing of the clean steam --(b)(4)--- to -----(b)(4)----- . WFI requirements for -----(b)(4)----- ----- . Each formulation port is sampled and tested every ----(b)(4)----- and during ---(b)(4)----- if there are manufacturing activities. Additionally, the clean steam system is tested -----(b)(4)----- .

Final Product Testing

Filled syringes were sampled for testing across each of the three process validation lots. Samples for testing were obtained according to the Production Batch Records and the validation protocol. The testing of the three process validation lots was expanded from the routine release testing for commercial manufacture. -----(b)(4)----- and ---(b)(4)--- testing were performed at----- (b)(4)----- of each lot in addition to standard release testing. ---(b)(4)----- testing was performed for process validation only and will not be a release test. Final product test results are summarized within the submission in Table 1-4. I reviewed the results and found them to be acceptable.