

Memorandum

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

To: 125563/0 Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine; (b) (4)

Rana Chattopadhyay Committee Chair, CBER/OVRR/DVRPA/
Kelsy F Hoffman, Reg Project Manager, DVRPA

Cc: Review Committee Members

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From: Nancy Waites, CMC Facility Reviewer, OCBQ/DMPQ

Through: Carolyn Renshaw, Branch Chief, OCBQ/DMPQ/B1

Through: John Eltermann, Division Director, OCBQ/ DMPQ

Subject: Primary Review Memo (Final)

Indication: Active immunization against diphtheria, tetanus, pertussis, poliomyelitis (caused by poliovirus Types 1, 2, and 3), against invasive disease caused by *Haemophilus influenzae* type b and infection caused by all known subtypes of hepatitis B virus in infants at 2, 4, and 6 months of age.

Applicant: MCM Vaccine Company U.S. License # 2007 (Pending)

Facility Sites: Sanofi Pasteur Limited Ontario, Canada (FEI: 3002888623)

Sanofi Pasteur (b) (4)

Merck Sharp & Dohme Corp. (b) (4)

Primary Review Memo Due Date Goal: 04 Apr 2015

Final Action Due Date: 12 Aug 2015

Recommendation: DMPQ is recommending approval as long as the Product Office does not have any issues. Final approval cannot be determined until STN 125581/0 and STN 125580/0 are approved.

Summary

On 12 Aug 2014 the FDA received an original Biologics License Application (BLA) submitted electronically in eCTD. The filing memo was completed on 25 Sep 2014 and concluded the application could be filed per 21 CFR 601.2.

During the filing review, it was determined that this single BLA should have been submitted as three separate BLAs. Thus, the information provided by Merck for their portion of manufacturing was withdrawn from this application and submitted as two “For Further Manufacturing Use” BLAs – STN 125580/0 and STN 125581/0. The Merck information will be reviewed under those STNs while only the Sanofi information will be reviewed in this review memorandum.

I initiated my Primary Review on 12 Sep 2014 and completed my memo on 03 Apr 2015.

Information Request Dates:

None

Telecon Dates:

None

Noteworthy Aspects

As noted below, this vaccine is manufactured using modified and/or existing bulk intermediates from vaccines licensed in the US by Sanofi Pasteur and Merck.

Review Milestones

Milestone	Due Date
Application Received	12 Aug 2014
First Committee Meeting	02 Sep 2014
Filing Meeting	26 Sep 2014
Filing Action	11 Oct 2014
Deficiencies Identified	25 Oct 2014
Internal Mid-Cycle Meeting	26 Jan 2015
Mid-Cycle Communication	11 Feb 2015
Late-Cycle Meeting	27 Apr 2015
Action Due Date	12 Aug 2015

Facilities and Inspections

The facilities involved in the manufacture and testing of PR5I are listed below along with a short description of their manufacturing responsibilities and a proposal for the need for an inspection for each facility.

Name / Address	Responsibilities	FEI	DUNS	Insp. Y/N/W	Enter RMS-BLA?	Compliance Check?
Sanofi Pasteur Limited 1755 Steeles Avenue West Toronto, Ontario M2R 3T4 Canada	1. Drug Substance Manufacturing 2. Final Bulk Product Formulation 3. Filling and Packaging 4. Quality Control and Stability Testing	3002888623	208206623	W	Y	Y
Sanofi Pasteur (b) (4)	1. Drug Substance Manufacturing 2. Final Bulk Product Formulation 3. Quality Control and Stability Testing	(b) (4)	(b) (4)	W	Y	Y

Review Comment: The inspection waiver memos for the facilities listed in the table above were written, approved, and uploaded into the EDR.

Scope of Review

I have performed a review of this application per CBER SOPP 8401.4: Review Responsibilities for the CMC Section of Biologic License Applications and Supplements. I specifically reviewed the contents for the information that falls under DMPQ responsibility for review.

Items Reviewed

The following sections are included in this BLA. I have provided a summary of information provided in the submission that is under DMPQ purview in this review memorandum. The topics of review follow the sections of the eCTD format.

1. FDA Regional Information (shared review)

- 1.1 Forms
- 1.2 Cover Letters
- 1.6 Meetings
- 1.12 Other Correspondence (request for categorical exclusion)

2. Common Technical Document Summaries (shared review)

- 2.2 Introduction
- 2.3 Quality Overall Summary (shared review)
- 2.3 Introduction

2.3.S Drug Substance (shared review)

- 2.3.S Diphtheria – Sanofi Pasteur
- 2.3.S Pertussis - Sanofi Pasteur
- 2.3.S Tetanus - Sanofi Pasteur
- 2.3.S vIPV - Sanofi Pasteur

2.3.P Drug Product (shared review)

- 2.3.P PR5I - Suspension for Injection – Sanofi Pasteur
- 2.3.A Appendices (shared review)
- 2.3.R Regional Information (shared review)

3.0 Quality

3.2.S Drug Substance (Applies to all 4 DS)

- 3.2.S Diphtheria – Sanofi Pasteur
- 3.2.S Pertussis - Sanofi Pasteur
- 3.2.S Tetanus - Sanofi Pasteur
- 3.2.S vIPV - Sanofi Pasteur
- 3.2.S.1 General Information
- 3.2.S.1.3 General Properties (shared review)
- 3.2.S.2 Manufacture
- 3.2.S.2.1 Manufacturer(s)
- 3.2.S.2.2 Description of Manufacturing Process and Process Controls (shared review)
- 3.2.S.2.3 Control of Materials (shared review)
- 3.2.S.2.4 Control of Critical Steps and Intermediates (shared review)
- 3.2.S.2.5 Process Validation and/or Evaluation
- 3.2.S.2.6 Manufacturing Process Development
- 3.2.S.3 Characterization (shared review)
- 3.2.S.3.2 Impurities

- 3.2.S.4 Control of Drug Substance
 - 3.2.S.4.1 Specification (shared review)
 - 3.2.S.4.2 Analytical Procedures (shared review)
 - 3.2.S.4.3 Validation of Analytical Procedures (shared review)
 - 3.2.S.4.4 Batch Analysis (shared review)
 - 3.2.S.4.5 Justification of Specification (shared review)
- 3.2.S.6 Container Closure System
- 3.2.S.7 Stability
 - 3.2.S.7.1 Stability Summary and Conclusion (shared review)
- Note to Reviewers – Diphtheria Toxoid Adsorbed (shared review)
- Note to Reviewers – 5-Component Acellular Pertussis Adsorbed (shared review)
- Note to Reviewers – Tetanus Toxoid Adsorbed (shared review)
- Note to Reviewers – Inactivated Vero Trivalent Poliovaccine Bulk (shared review)

3.2.P Drug Product

- 3.2.P PR5I Suspension for Injection – Sanofi Pasteur
 - 3.2.P.1 Description and Composition of the Drug Product (shared review)
 - 3.2.P.2 Pharmaceutical Development (shared review)
 - 3.2.P.3 Manufacture
 - 3.2.P.3.1 Manufacturer(s) (shared review)
 - 3.2.P.3.2 Batch Formula (shared review)
 - 3.2.P.3.3 Description of Manufacturing Process and Process Controls (shared review)
 - 3.2.P.3.4 Controls of Critical Steps and Intermediates (shared review)
 - 3.2.P.3.5 Process Validation and / or Evaluation (shared review)
 - 3.2.P.5 Control of Drug Product (shared review)
 - 3.2.P.5.1 Specifications (shared review)
 - 3.2.P.5.2 Analytical Procedures (shared review)
 - 3.2.P.5.3 Validation of Analytical Procedures (shared review)
 - 3.2.P.5.4 Batch Analysis (shared review)
 - 3.2.P.5.6 Justification of Specifications (shared review)
 - 3.2.P.7 Container Closure System (shared review)
 - 3.2.P.8 Stability (shared review)
 - 3.2.P.8.1 Stability Summary and Conclusion (shared review)
- Note to Reviewer – Summary of Differences between PR5I and Pentacel Vaccines Drug Product (shared review)

3.2.A Appendices

- 3.2.A.1 Facilities and Equipment
 - 3.2.A.1 Merck - HBsAg - Suspension for Injection - PR5I
 - 3.2.A.1 Merck - PRP-OMPC - Suspension for Injection - PR5I
 - 3.2.A.1 sanofi pasteur - Diphtheria - Suspension for Injection - PR5I
 - 3.2.A.1 sanofi pasteur - NA - Suspension for Injection - PR5I
 - 3.2.A.1 sanofi pasteur - Pertussis - Suspension for Injection - PR5I
 - 3.2.A.1 sanofi pasteur - Tetanus - Suspension for Injection - PR5I
 - 3.2.A.1 sanofi pasteur - vIPV - Suspension for Injection - PR5I

3.2.R Regional Information (shared review)

Amendments Reviewed

None

DMF Reviewed

None.

Topics Deferred to Other Review Divisions

I have deferred review responsibilities to the Product Office or other appropriate office as outlined in SOPP 8401.4.

Review Issues and Resolution

Amendments from the Review

None

Review Issues

None

Review and Comment

Module 1.0

1. FDA Regional Information (shared review)

1.1 Forms

I reviewed the 356h and it appeared to be completely filled out and acceptable.

1.2 Cover Letters

I reviewed the cover letter and do not have any comments. No notable requests were made in the cover letter.

1.6 Meetings

1.6.3 Correspondence Regarding Meetings – CBER Meeting Minutes of 25 April 2014

I reviewed only Section 1.6.3 to determine if there were any agreements reached prior to the submission of the BLA. A DMPQ representative was not listed in the meeting minutes as having been in attendance at the Type B, Pre-BLA meeting. None of the questions submitted for the Pre-BLA meeting fell under the purview of DMPQ.

1.12 Other Correspondence (request for categorical exclusion)

1.12.14 Environmental Analysis

PR5I

Sanofi Pasteur Limited claims that the action on the Biologics License Application (BLA) for Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate (Meningococcal Outer Membrane Protein Complex), and Hepatitis B (Recombinant) Vaccine qualifies for categorical exclusion from filing an Environmental Assessment under 21 CFR §25.31(c). To the knowledge of Sanofi Pasteur Limited no extraordinary circumstances exist (21 §CFR 25.15(d)).

Note: A categorical exclusion for the Merck portion of the vaccine is included in the review memos for STN 125580/0 and STN 125581/0.

Review Comment: I reviewed the request for a categorical exclusion and found it to be acceptable.

Module 2 and Module 3

Organization of Review Memo: This review memorandum is divided into five sections with each section divided into Part I and Part II. Part I contains the new information for the BLA that DMPQ reviewed. Part II contains information that is currently approved in other US licensed products, thus it is provided for information only so that all of the information is contained in one review memo instead of having to find information in the various other licensed applications.

The major sections of this review memo consists of the following:

Drug Substance

- Diphtheria – Sanofi Pasteur
- Pertussis - Sanofi Pasteur
- Tetanus - Sanofi Pasteur
- vIPV - Sanofi Pasteur

Drug Product

- PR5I Suspension for Injection – Sanofi Pasteur

Section 2.2 – CTD Introduction

Introduction

A partnership arrangement has been established since 1992 between Sanofi Pasteur Inc. and Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (hereafter designated “Merck”) to support the co-development and commercial manufacturing of the Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] (PR5I) Vaccine.

The name of the partnership is MCM Vaccine Company (MCM Vaccine Co.). Under this agreement, Merck is responsible for matters pertaining to clinical items. Sanofi Pasteur is the Applicant for the United States (US) Biological License Application, on behalf of MCM Vaccine Co. as the US Marketing Authorization License holder. The principal office of MCM Vaccine Co. is maintained at the Sanofi Pasteur US office located in Swiftwater, Pennsylvania.

PR5I is a hexavalent vaccine being developed to provide protection against 6 childhood diseases with the convenience of 1 injection. The vaccine under evaluation is a combination vaccine containing components of vaccines currently licensed in the US and/or European Union (EU).

Pharmacological Class

The Anatomical Therapeutic Chemical Classification System (ATC) code for PR5I is J07CA09.

Mode of Action

The ATC group for PR5I is General Anti-Infectives for Systemic Use – Vaccines – Bacterial and Viral Vaccines, Combined - Diphtheria-haemophilus influenzae B-pertussis-poliomyelitis-tetanus-hepatitis B. It is formulated to stimulate the human antibodies responses to diphtheria, tetanus, pertussis (PT, FHA, PRN, and FIM types 2 and 3), poliomyelitis, hepatitis B, and *Haemophilus influenzae* type b (Hib).

Proposed Clinical Use

PR5I is indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to *H. influenzae* type b. PR5I is proposed for use as a 3 dose series in children from 6 weeks through 4 years of age (up to the 5th birthday).

Section 2.3 - Introduction

Name

Proposed Proprietary Name of the Drug Product

(b) (4) [®]

Common Name of the Drug Product

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine (PR5I)

Common Name of the Drug Substance

PR5I is a hexavalent combination vaccine formulated with the following drug substances:

1. Diphtheria Toxoid Adsorbed
2. Tetanus Toxoid Adsorbed
3. 5-Component Acellular Pertussis Adsorbed which is comprised of the following five antigens:
 - a. Pertussis Toxoid (PT) Adsorbed
 - b. Filamentous Haemagglutinin (FHA) Adsorbed
 - c. Pertactin (PRN) Adsorbed
 - d. Fimbriae Types 2 and 3 (FIM) Adsorbed
4. Inactivated Vero Trivalent Poliovaccine bulk (vIPV)

5. Haemophilus b conjugate (PRP-OMPC)
6. Hepatitis B Surface Antigen Surface Antigen (HBsAg)

Company Name

Drug Product manufactured by:
Sanofi Pasteur Limited
Toronto Ontario Canada

Distributed by:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Whitehouse Station NJ USA
and
Sanofi Pasteur Inc.
Swiftwater PA USA

Dosage Form(s)

Suspension for intramuscular injection in a single-dose vial

Strength(s)

Each 0.5 mL dose contains 15 Lf Diphtheria Toxoid Adsorbed, 5 Lf Tetanus Toxoid Adsorbed, 5-Component Acellular Pertussis Adsorbed [20 µg Pertussis Toxoid (PT), 20 µg Filamentous Hemagglutinin (FHA), 3 µg Pertactin (PRN), 5 µg Fimbriae Types 2 and 3 (FIM)], Inactivated Vero Trivalent Poliomyelitis [29 D antigen units (DU) Type 1 (Mahoney), 7 DU Type 2 (MEF-1), 26 DU Type 3 (Saukett)], 3 µg PRP- polyribosylribitol phosphate of *Haemophilus influenza* type b covalently bound to 50 µg of OMPC-outer membrane protein complex of *Neisseria meningitidis* serogroup B, and 10 µg Hepatitis B surface antigen (HBsAg).

Route of Administration

Intramuscular injection

Proposed Indication

PR5I is a vaccine for active immunization against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to *Haemophilus influenzae* type b (Hib), for use as a three-dose series in children from 6 weeks through 4 years of age (up to the 5th birthday).

PART I – NEW INFORMATION**DRUG SUBSTANCE - Diphtheria – Sanofi Pasteur****Part I – New Information**

Per Sanofi, the following is a list of differences in the CMC documentation of the Diphtheria Toxoid Adsorbed drug substance of PR5I Vaccine compared to this component of Pentacel

(STN: BL 125145)

Review Note: I have reviewed the new information that is different from what is currently on file for the licensed Diphtheria Toxoid Adsorbed drug substance of Pentacel (STN: BL 125145) in the first part of the review memorandum. In the second part (Part II) of this review memorandum I have included information on the manufacturing process, facility, and equipment for information only since it has not changed from what is currently approved.

3.2.S Drug Substance - Diphtheria Toxoid Adsorbed

This document provides details on differences in the CMC documentation of the Diphtheria Toxoid Adsorbed drug substance of PR5I Vaccine compared to this component of Pentacel® (STN: BL 125145).






3.2.S.1 General Information

The CMC documentation provided in 3.2.S.1.1 Nomenclature, 3.2.S.1.2 Structure and 3.2.S.1.3 General Properties is the same as that on file for Pentacel®.

Review Comment: This additional information does not fall under the purview of DMPQ. A subset of this information has been included in later sections of this review memorandum for information only.

3.2.S.2 Manufacture

(b) (4)



(b) (4)

(b) (4)

DRUG SUBSTANCE - 5-Component Acellular Pertussis Adsorbed - Sanofi Pasteur

Part I – New Information

Per Sanofi, the following is a list of differences between the information submitted for the subject BLA and the currently licensed 5-Component Acellular Pertussis Adsorbed.

Review Note: I have reviewed the new information that is different from what is currently on file for the licensed 5-Component Acellular Pertussis Adsorbed in the first part of this review memorandum. In the second part of this review memorandum I have included information on the manufacturing process, facility, and equipment for information only since it has not changed from what is currently approved.

3.2.S. Drug Substance – 5-Component Acellular Pertussis Adsorbed

This document provides details on differences in the CMC documentation of the 5-Component Acellular Pertussis Adsorbed drug substance of PR5I Vaccine compared to this component of Pentacel® (STN: BL 124145).

3.2.S.1 General Information


The CMC documentation provided in 3.2.S.1.1 Nomenclature, 3.2.S.1.2 Structure and 3.2.S.1.3

General Properties is the same as that on file for Pentacel, with the exception that some additional information regarding biological activity has been provided in 3.2.S.1.3 General Properties.

Review Comment: This additional information does not fall under the purview of DMPQ. A subset of this information has been included in later sections of this review memorandum for information only.

3.2.S.2 Manufacture

(b) (4)



(b) (4)

DRUG SUBSTANCE- Tetanus Toxoid- Sanofi Pasteur

Part I – New Information

Per Sanofi, the following is a list of differences in the CMC documentation of the Tetanus Toxoid Adsorbed drug substance of PR5I Vaccine compared to this component of Pentacel (STN: BL 125145)

Review Note: I have reviewed the new information that is different from what is currently on file for the licensed Tetanus Toxoid Adsorbed drug substance of Pentacel (STN: BL 125145) in the first part of this review memorandum. In the second part (Part II) of this review memorandum I have included information on the manufacturing process, facility, and equipment for information only since it has not changed from what is currently approved.

3.2.S Drug Substance - Tetanus Toxoid Adsorbed

This document provides details on differences in the CMC documentation of the Tetanus Toxoid Adsorbed drug substance of PR5I Vaccine compared to this component of Pentacel® (STN: BL 125145).


3.2.S.1 General Information

The CMC documentation provided in 3.2.S.1.1 Nomenclature, 3.2.S.1.2 Structure and 3.2.S.1.3 General Properties is the same as that on file for Pentacel®.

Review Comment: This additional information does not fall under the purview of DMPQ. A subset of this information has been included in later sections of this review memorandum for information only.

3.2.S.2 Manufacture

(b) (4)



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DRUG SUBSTANCE – vIPV - **Inactivated Vero Trivalent Poliovaccine Bulk - Sanofi Pasteur**

Part I – New Information

Per Sanofi, the following is a list of differences in the CMC documentation of the Inactivated Vero Trivalent Poliovaccine Bulk drug substance (also called Poliomyelitis Concentrated Trivalent) of PR5I Vaccine compared to this component of IPOL® (BL 103930).

Review Note: I have reviewed the new information that is different from what is currently on file for the licensed Inactivated Vero Trivalent Poliovaccine Bulk drug substance of IPOL® (BL 103930) in the first part of this review memorandum. In the second part (Part II) of this review memorandum I have included information on the manufacturing process, facility, and equipment for information only since it has not changed from what is currently approved.




3.2.S.1 General Information

The CTD sections 3.2.S.1.1 Nomenclature, 3.2.S.1.2 Structure and 3.2.S.1.3 General Properties are not on file for IPOL® and have been created for Inactivated Vero Trivalent Poliovaccine Bulk drug substance of PR5I Vaccine.

Review Comment: This additional information does not fall under the purview of DMPQ. A subset of this information has been included in later sections of this review memorandum for information only.

3.2.S.2 Manufacture

(b) (4)



(b) (4)

DRUG PRODUCT - PR5I Suspension for Injection – Sanofi Pasteur

Part I – New Information

Summary of Differences Between PR5I and Pentacel® Vaccines Drug Product

Table 1 summarizes the differences between PR5I Drug Product and Pentacel® Drug Product (STN: BL124145).

Review Note: I have reviewed the new information that is different from what is currently on file for the licensed Pentacel Drug Product (STN: BL124145) in the first part of this review memorandum. In the second part (Part II) of this review memorandum I have included information on the manufacturing process, facility, and equipment for information only since it has not changed from what is currently approved.

Table 1: Summary of Differences Between PR5I and Pentacel® Drug Products

(b) (4)

(b) (4)

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

Review Comment: The differences noted in the table above do not incorporate anything that falls under DMPQ review responsibilities. The information provided in this section is included below for information only.

Description of the Drug Product

PR5I Vaccine is a sterile, preservative-free, uniform, cloudy, white to off-white suspension for intramuscular injection. PR5I Vaccine is presented as a 0.5-mL single-dose vial.

PR5I is a hexavalent combination vaccine formulated with the following preservative-free bulk concentrates:

- P - PRP-OMP_{Ca} (Haemophilus b conjugate) Bulk Intermediate
- R - Hepatitis B surface Antigen (HBsAg) Bulk Intermediate
- 5 - Five Component Acellular Pertussis Adsorbed Antigens (Pertussis Toxoid, Filamentous Haemagglutinin, Pertactin, and Fimbriae Types 2 and 3), Diphtheria Toxoid Adsorbed and Tetanus Toxoid Adsorbed Concentrates
- I - Inactivated Vero Trivalent Poliomyelitis Vaccine (vIPV) Bulk

Composition

The composition of PR5I Vaccine, each 0.5-mL single-dose, is described in Table 1.

Table 1: Composition of PR5I Drug Product

Component*	Amount on a per unit basis (0.5 mL)	Function	Reference
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Haemophilus b conjugate (PRP-OMPC)	3 µg PRP covalently bound to 50 µg of OMPC†	Active substance (Haemophilus type b immunization)	In-house
Hepatitis B surface Antigen (HBsAg)	10 µg	Active substance (Hepatitis B immunization)	In-house
5-Component Acellular Pertussis Adsorbed Antigens: -Pertussis Toxoid (PT) -Filamentous Hemagglutinin (FHA) -Pertactin (PRN) -Fimbriae types 2 and 3 (FIM)	20 µg 20 µg 3 µg 5 µg	Active substance (Pertussis immunization)	In-house
Diphtheria Toxoid Adsorbed	15 Lf	Active substance (Diphtheria immunization)	In-house
Tetanus Toxoid Adsorbed	5 Lf	Active substance (Tetanus immunization)	In-house
Inactivated Vero Trivalent Poliomyelitis Vaccine (vIPV): - Type 1 (Mahoney) - Type 2 (MEF-1) - Type 3 (Saukett)	29 D-antigen Units‡ 7 D-antigen Units 26 D-antigen Units	Active substance (Poliomyelitis immunization)	(b) (4)
Aluminum§	319 µg	Adjuvant	In-house
Water for injection	q.s. 0.5 mL	Diluent	(b) (4)

* (b) (4)

Product. Refer to 3.2.P.3.2 Batch Formula and 3.2.P.3.3 Description of Manufacturing Process for details.

† In each dose of PR5I, Haemophilus b conjugate is comprised of 3 µg of PRP- polyribosylribitol phosphate of *Haemophilus influenzae* type b covalently bound to 50 µg of OMPC-outer membrane protein complex of *Neisseria meningitidis* serogroup B.

‡ vIPV D-antigens Units are calculated using the (b) (4) test method.

§ Aluminum content in each dose is estimated at 319 µg (b) (4)

The final product may contain trace amounts of following materials used in the manufacturing process as listed in Table 2.

Table 2: Residual components of PR5I Drug Product

Residual Components	Amount per unit dose (0.5 mL)
Yeast Protein	≤ 0.1 µg (Maximum 1.0% relative to HBsAg protein)
Bovine Serum Albumin	≤ 50 ng
Thiocyanate	≤ 0.125 µg as ammonium thiocyanate
Formaldehyde	(b) (4)
Glutaraldehyde	≤ 50 ng
Neomycin	< 5 ng
Polymyxin B	< 25 ng
Streptomycin	< 200 ng

3.2.P.2 Pharmaceutical Development

Review Comment: The majority of the information noted in the table above does not incorporate anything that falls under DMPQ review responsibilities. The information is included below for information only.

3.2.P.2.1 – Components of the Drug Product


PR5I Vaccine is a sterile, preservative-free, uniform, cloudy, white to off-white suspension for intramuscular injection. PR5I is presented as a 0.5-mL single-dose, in a 2.0-mL glass vial with a stopper (not made with natural rubber latex) and aluminum seal.

PR5I is formulated with Drug Substances and Excipients listed under 3.2.P.1 Description and Composition and 3.2.P.3.2 Batch Formula section of the Drug Product dossier.

The primary focus of the development program was to develop a safe and well-tolerated formulation capable of maintaining its quality throughout the shelf-life.

Drug Substance

(b) (4)



(b) (4)

3.2.P.2.4 - Container Closure System

Introduction

The choice and rationale for the selection of the container closure systems used for PR5I Final Bulk Product and Filled Product is provided below.

The two main materials used for the container closure systems (b) (4) -Final Bulk Product, glass-Filled Product) have been selected as they are inert materials that do not interact with aqueous suspensions (such as PR5I), can be cleaned and sterilized and offer suitable protection to the product during transportation and storage. Furthermore, equivalent container closure systems (b) (4), glass, bromobutyl stopper), as described for PR5I, are used for other licensed Sanofi Pasteur Limited combination vaccines and were proven to be suitable for the purpose of formulation of Final Bulk Product and storage of the Final Bulk Product and Filled Product. To support the use of these container closure systems, stability studies have been performed for PR5I Final Bulk Product and Filled Product stored for the duration of its shelf-life at (b) (4) (3.2.P.8.3 Stability Data). No adverse effect on the identity, strength, quality, purity or potency of the PR5I was observed in these studies. Additional information is included in 3.2.P.2.5 Microbiological Attributes, 3.2.P.7 Container Closure System and 3.2.P.8.3 Stability Data for more information regarding the suitability of the container closure systems. Certificates of Compliance and Certificates of Analysis that demonstrate the quality attributes of the primary packaging materials that make up the container closure systems are provided in 3.2.P.7 Container Closure System.

3.2.P.2.5 – Microbiological Attributes

Introduction




PR5I Vaccine was formulated to be preservative-free and was filled in a unit dose vial. The container closure system is suitable for maintaining the sterility of the product over the shelf life.

This was confirmed by the routine sterility testing for release and stability monitoring of the PR5I Vaccine (b) (4) Filled Product, (b) (4) hold studies in the (b) (4), a Container Closure (b) (4) Test using the (b) (4) method and a Container Closure Integrity Test (CCIT) at the Filled Product stage using the (b) (4) method. The sterility test

results for the clinical lots have met the acceptance criteria and are provided in 3.2.P.8.3 Stability Data.

PR5I Final Bulk Product

(b) (4)



PR5I Vaccine, Unit Dose Vials – (b) (4) Study Using the (b) (4) Method

PR5I Vaccine is filled in the 2.0-mL single-dose (b) (4) glass vial, bromobutyl rubber stopper and 13 mm aluminum seal with plastic flip-off cap. The container closure system is described in 3.2.P.7 Container Closure System. Sterility and Container Closure Integrity Tests data from the stability studies for four PR5I Vaccine lots, (b) (4) demonstrate that the proposed shelf-life for PR5I does not impact the stability of the Finished Product. Refer to 3.2.P.8.1 Stability Study and Conclusion and 3.2.P.8.3 Stability Data for additional information.

(b) (4) study was performed as per report Q 0259586 version 1.0 to evaluate container closure integrity, (b) (4)



(b) (4)

Container Closure Integrity Testing of PR5I Vaccine, Unit Dose Vials Using the

(b) (4) **Method**

A container closure integrity test study was performed using the (b) (4) method as per report Q_0526353 version 1.0 to evaluate the container closure integrity in PR5I Vaccine Filled Product.

(b) (4)

[REDACTED]

(b) (4)

Conclusion

Considering the satisfactory results for the sterility testing (both for release and stability monitoring) of the PR5I Vaccine (b) (4) Filled Product, the (b) (4) studies in the (b) (4), the Container Closure (b) (4) Test at the Filled Product stage using the (b) (4) method and the Container Closure Integrity Test study in PR5I Vaccine using the (b) (4) method, the container closure system is suitable for maintaining the sterility of the product over the shelf life.

3.2.P.2.6 - Compatibility

The PR5I Vaccine is a ready-to use formulation and as such, there is no reconstitution, dilution of the PR5I Vaccine or administration with other dosage devices. Suitability of the vial container closure system is demonstrated by compendial testing of the components and Finished Product stability studies. The compendial testing of the vials is documented in 3.2.P.7 Container Closure System. Results of the stability studies are summarized in 3.2.P.8.3 Stability Data.

3.2.P.3 Manufacture

Review Comment: I have reviewed the hold studies and found them to be acceptable. The information is reviewed in 3.2.P.8 – Stability.

I have included the following information below for information only:

- Batch Formula
- Description of Manufacturing Process and Process Controls
- Controls of Critical Steps and Intermediates

I have included the following subset of the information below since this could be considered new information due to the two bulk intermediates manufactured by Merck that are included in the final product:

- (b) (4) Studies – Bulk Intermediates
- (b) (4) Studies – Formulation of PR5I Final Bulk
- Process Validation of Final Bulk Formulation

I reviewed the studies and found them to be acceptable. Details of the studies are provided below. I do not have any comments.

I have included the following information from this section in Part II of this review memorandum for information only since Sanofi is using the same equipment and processes that they currently used for other licensed products:

- Aseptic Process Simulation
- (b) (4) – WFI

- (b) (4) - vIPV Bulk
- Filling Process Validation

The studies were acceptable and I do not have any comments.

3.2.P.3.2 Batch Formula

Batch Formula

The preparation of the PR5I Final Bulk Product begins with (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

Batch Size

Final Bulk Product

The target batch size of PR5I Final Bulk Product may range from (b) (4) .

Filled Product

A Final Bulk Product (b) (4) batch may be filled to provide theoretically a total of approximately (b) (4) vials, which may correspond to one or several Filled Product batches of variable size.

3.2.P.3.3 - Description of Manufacturing Process and Process Controls

Final Bulk Product

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4)

The filling process is conducted aseptically until stoppering of the vials is complete. The Final Bulk Product is transferred to the filling area and (b) (4)

(b) (4)

Refer to 3.2.P.2.3 Manufacturing Process Development for the summary on the PR5I final bulk (b) (4) study.

The Final Bulk Product is filled into 2-mL glass vials and stoppered using an automated vial tunnel filling line. The seals are 13 mm one-piece aluminum seals with plastic flip-off caps and are applied to the vials using a capping machine. The sealed vials are inspected by the automatic vial inspection system and samples are taken for testing (see 3.2.P.5.1 Specifications). The inspected unlabeled vials are stored at (b) (4) until released for labeling and secondary packaging. Refer to 3.2.A.1 Facilities and Equipment- Equipment (Building (b) (4) for more details.

The filled vials are labeled and packed with or without a pre-formed blister tray into a cardboard carton containing a leaflet. The Finished Product is stored at 2°C to 8°C until released to market.

In-Process Controls during the Filled Product Manufacture Overview of In-Process Controls

The following in-process controls are performed:

- (b) (4)

Storage and Transportation

The Final Bulk Product, Filled and Labeled Product are stored (b) (4) The product is packaged in a corrugated cardboard shipper box identified with the product name, material number, lot number, and expiry date with bar codes. Each shipment is equipped with a temperature-monitoring device. The packaged product is shipped to the USA by (b) (4) (SOP 48SD-030, "International Shipments Packing Exceptions") and can be delivered to one of the PR5I distribution centers in the USA.

3.2.P.3.4 - Controls of Critical Steps and Intermediates Critical Steps

(b) (4)

successfully met. The critical quality attributes (or test results) were also satisfactory. The PR5I formulation process is validated.

3.2.P.4 Control of Excipients

Review Comment: None of the changes fall under DMPQ review responsibilities.

3.2.P.5 Control of Drug Product

Review Comment: None of the new information falls under the review responsibility of DMPQ. I have included the information for Specifications for information only.

Section 3.2.P.5.1 – Specification(s)

Introduction

This document provides the specifications for release of PR5I Final Bulk Product, Filled Product, and Labeled Filled Product.

Specification of the Final Bulk Product

The specification applied for release and shelf-life of PR5I Final Bulk Product for commercial lots is provided in Table 1.

(b) (4)

Specification of the Filled and Labeled Filled Product

The specification(s) applied for release and shelf-life of PR5I Filled Product and Labeled Filled Product, are provided in Table 2 and Table 3.

Table 2: Release and Shelf-life Specifications for PR5I Filled Product (Unlabeled)

Test	Method Reference	Release Acceptance Criteria	Shelf-life Acceptance Criteria
Physical Appearance	In-house	Uniform, cloudy, white to off-white suspension	Same as Release
Sterility	(b) (4)	No microbial growth	Same as Release
(b) (4)	(b) (4)	(b) (4)	Same as Release
(b) (4)	(b) (4)	(b) (4)	NA
Aluminum Content	(b) (4)	(b) (4)	NA
Extractable Volume	(b) (4)	≥ 0.5 mL	NA
Pyrogen	(b) (4)	Non-Pyrogenic	NA
General Safety Test – Modified	In-house (Modified CFR 610.11)	(b) (4)	NA

Note: Exemption for General Safety Test is requested in the BLA, however the commercial launch lots will be tested until exemption granted by CBER upon approval of PR5I License, see 3.2.P.5.6 Justification of Specifications.

Table 3: Release Specification for PR5I Labeled Filled Product

Test	Method Reference	Acceptance Criteria
Identity - (b) (4)	In-house	HBsAg and OMPC components detected
Alternate Identity Test		
Identity - PRP-OMPC (b) (4)	In-house	PRP-OMPC Detected
Identity - HBsAg (b) (4)	In-house	HBsAg Detected

3.2.P.6 Reference Standards or Materials

Review Comment: None of the information in this section falls under the review responsibilities of DMPQ.

3.2.P.7 Container Closure System

Review Comment: There is only the minor change of the flip-off cap color for PR5I. All of the other components for the final container closure (vials and stoppers) are currently used for the already licensed Pentacel. Information about the final container closure is provided in Part II for information only.

3.2.P.8 Stability

Review Comment: I performed a high-level review of the stability data presented in the application. I specifically reviewed the data from the hold times and found it to be acceptable. I do not have any comments.

3.2.P.8.1 - Stability Summary and Conclusion

Introduction



Several sets of stability studies were performed on PR5I and are summarized in this document. These stability studies included (b) (4) PR5I Final Bulk Product lots (b) (4) (b) (4) and (b) (4) Finished Product lots ((b) (4) (b) (4)). The assessment of the PR5I Final Bulk Product and the Finished Product shelf-life were conducted in (b) (4) containers and 2.0-mL single-dose (b) (4) glass vial, (b) (4) stopper and 13 mm aluminum seal with plastic flip-off cap, respectively at (b) (4). An overview of these stability studies is presented in the submission in Table 1: Overview of the Stability Studies.

Stability Summaries

The stability data presented provide evidence of the quality of the PR5I (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine) over time under the influence of environmental factors.

PR5I Final Bulk Product

(b) (4)



(b) (4)

PR5I Filled Product

The PR5I Vaccine is filled in primary packaging components conventionally used for other products manufactured by Sanofi Pasteur Limited (Canada). The PR5I Vaccine is filled in the 2.0-mL single-dose (b) (4) glass vial, (b) (4) stopper and 13 mm aluminum seal with plastic flip-off cap. The container closure system is described in 3.2.P.7 Container Closure System. In support of the vial presentation, four PR5I Vaccine lots produced at commercial scale are currently being studied for stability. The shelf life is 36 months from the date of the Final Bulk Product formulation.

The PR5I Final Bulk Product can be held for up to (b) (4) prior to filling (b) (4) Finished Product at 2°C to 8°C is 36 months.

Analysis of the stability of PR5I Finished Product is being performed through the study B014063 for lots (b) (4) and study B015684 for lot (b) (4) in the single-dose vial presentation at 2°C to 8°C. The stability studies for these lots are on-going and complete results are available for up to and including 36 months of testing and partial results are available at the 42 month time-point for lots (b) (4) and up to and including 30 months of testing for lot (b) (4).

All stability data obtained from proposed US release tests for the (b) (4) stability lots met the acceptance criteria when stored at 2°C to 8°C for up to 36 months. An out of specification (OOS) was obtained for the (b) (4) test for lot (b) (4) at the 42-month time point. An investigation is on-going to identify the reason for the OOS for this test at that time point. For this investigation, lot (b) (4) was tested (b) (4) times post the 42-month time-point and the results are provided in 3.2.P.5.6 Justification of Specifications.

The stability protocols included assays that addressed the physiochemical characteristics, safety, potency and/or immunogenicity of the PR5I Vaccine. Furthermore, test procedures identified in the current on-going stability studies for the PR5I Vaccine were validated. The (b) (4) methods are compendial Ph. Eur., methods and are therefore considered validated. The sensitivity of the mouse strain used in the test is verified periodically and meets the criteria for strain sensitivity as per (b) (4). Tests included in the release specifications but not in the stability study were deemed to not be stability indicating (i.e., Formaldehyde and Aluminum Content tests). In other cases, some tests were included in the stability studies that are required by some countries and not by others or to collect data for development purposes (e.g., (b) (4)).

Some tests that were in place at the time of manufacturing the lots for the ongoing stability studies have since been deleted or replaced with updated or more appropriate methods (refer to 3.2.P.2.3 Manufacturing Process Development) in order to improve the control testing of the product. This accounts for the differences between the tests described in the stability studies and the current specifications presented in 3.2.P.5.1 Specifications.

Stability Study Performed on Finished Product - Stability Studies B014063 and B015684

Stability Study Design

Stability studies B014063 and B015684 were designed to support the shelf-life period of PR5I Vaccine Finished Product in the 2.0-mL single-dose (b) (4) glass vial, (b) (4) stopper and 13 mm aluminum seal with plastic flip-off cap for a period of 36 months at 2°C to 8°C from the date of Final Bulk Product formulation (b) (4). Finished Product does not exceed 36 months). Study B014063 included (b) (4) PR5I Vaccine consistency lots ((b) (4)) while study B015684 included one PR5I Vaccine lot ((b) (4)). These lots were manufactured at commercial scale and their time zero was based on the date of final bulk product formulation. These lots were filled at Sanofi Pasteur Limited, (Canada). Refer to Table 1 for details on the date of final bulk formulation and filling. The stability program involves some of the testing to be performed at Sanofi Pasteur Limited, Canada, Sanofi Pasteur Inc. (USA), Sanofi Pasteur SA (France) and Merck & Co., Inc. (USA). As such, the stability samples are then shipped from Sanofi Pasteur Limited to Sanofi Pasteur Inc., Sanofi Pasteur SA and Merck & Co., Inc. Samples for the purpose of stability were stored in the (b) (4) orientation at 2°C to 8°C and each lot was tested at zero time (b) (4) Filled Product stages) and following 3, 6, 9, 12, 18, 24, 30, 36, 42 and 48 months of storage from the Final Bulk Product formulation. The testing parameters and frequencies of testing for lots (b) (4) are provided in Table 5.

Table 5: Test Schedule for Protocols B014063 and B015684, Stability Study for PR5I Lots (b) (4) Stored in the 2.0-mL single-dose (b) (4) glass vial, (b) (4) Stopper and 13-mm Aluminum Seal with Plastic Flip-off Cap at 2°C to 8°C

Test	Reference	Tentative Acceptance Criteria	Frequency (months)
Tests Performed by Sanofi Pasteur Inc.			
(b) (4)	(b) (4)	(b) (4)	0, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48
Physical Appearance	Non-compendial	Uniform cloudy, white to off-white suspension	0, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48
Tests Performed by Sanofi Pasteur Limited			
Specific Toxicity	Non-compendial	No symptoms of Diphtheria and/or Tetanus Toxicity	0, 18, 36, 42, 48
Container Closure Integrity	Non-compendial	The Container closure integrity test is acceptable if no presence of (b) (4) is detected in any of the tested vials	6, 12, 24, 36, 42, 48
D-antigen Content (b) (4) method‡	Non-compendial	Type 1: (b) (4) DU/0.5 mL Type 2: (b) (4) DU/0.5 mL Type 3: (b) (4) DU/0.5 mL	3, 6, 12, 18, 24, 30, 36, 42, 48
Sterility	(b) (4)	No microbial growth	0, 12, 18, 36,

			42, 48
Diphtheria Potency (USPHS)	USPHS	≥ 2 units/mL Diphtheria antitoxin	0, 6, 12, 24, 36, 42, 48
Tetanus Potency (USPHS)	USPHS	≥ 2 units/mL Tetanus antitoxin	0, 6, 12, 24, 36, 42, 48
Diphtheria Potency (b) (4)	(b) (4)	(b) (4)	0, 6, 12, 24, 36, 42, 48
Tetanus Potency (b) (4)	(b) (4)	(b) (4)	0, 6, 12, 24, 36, 42, 48
Immunogenicity – acellular Pertussis (b) (4)	Non-compendial	(b) (4)	0, 6, 12, 24, 36, 42, 48
		(b) (4)	
		(b) (4)	
		(b) (4)	
		(b) (4)	
Immunogenicity – acellular Pertussis (Mouse)	Non-compendial	Stage 1 Test (b) (4) animals	Stage 2: (b) (4) animals
		PT (GMU): (b) (4) PT (Resp) : (b) (4) FHA (GMU) : (b) (4) FHA (Resp) : (b) (4) PRN (GMU) : (b) (4) PRN (Resp) : (b) (4) FIM (GMU) : (b) (4) FIM (Resp) : (b) (4)	PT (GMU): (b) (4) PT (Resp) : (b) (4) FHA (GMU) : (b) (4) FHA (Resp) : (b) (4) PRN (GMU) : (b) (4) PRN (Resp) : (b) (4)

			FIM (GMU) (b) (4) FIM (Resp) (b) (4)	
(b) (4)	Non-compendial	(b) (4)		0, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48
(b) (4)	Non-compendial	(b) (4)		0, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48
(b) (4)	Non-compendial	(b) (4)		0, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48
(b) (4)	Non-compendial	(b) (4)		0, 18, 36, 42, 48
(b) (4)	Non-compendial	(b) (4)		0, 18, 36, 42, 48
(b) (4)	Non-compendial	(b) (4)		0, 18, 36, 42, 48
		(b) (4)		
		(b) (4)		
Immunogenicity – IPV (Rat)	(b) (4)	Type 1: Relative potency (b) (4)		0, 6, 12, 24, 36, 42, 48
		Type 2: Relative potency (b) (4)		
		Type 3: Relative potency (b) (4)		
Test Performed by Sanofi Pasteur SA				
(b) (4)	(b) (4)	(b) (4)		0, 18, 36, 42, 48
		(b) (4)		
Tests Performed by Merck & Co., Inc.				
(b) (4)	Non-compendial	(b) (4)		0, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48
HBsAg IVRP	Non-compendial	(b) (4)		0, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48
(b) (4)	Non-compendial	(b) (4)		0, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48
PRP Content	Non-compendial	(b) (4) 0.5mL		0, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48

(b) (4)	Non-compendial	(b) (4)	0, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48
Pyrogen	Non-compendial	Conforms	36, 42, 48

* For lot (b) (4) study started at 6 months as samples were not filled and available until after the 3-month time-point.

† There is no time zero for lot (b) (4) for this test but the lack of result does not adversely impact the shelf life of the product.

‡ The D-antigen (b) (4) Assay using the (b) (4) method was used at the 18-month time-point for lot (b) (4) the 12-month time-point for lots (b) (4) and at the 3-month time-point for lot (b) (4). The fact that this test was initiated at this time-points for these lots does not adversely impact the shelf-life of the product.

Stability Study Results

The stability study for these lots is still on-going and complete results are available for testing up to and including 36 months at 2°C to 8°C and partial results for the 42 month time-point are available for the three consistency lots (b) (4) and up to 30 months for lot (b) (4) from the date of the Final Bulk Product formulation. The stability data are presented in 3.2.P.8.3 Stability Data.

Stability Study Evaluation

Stability results obtained up to and including 42 months at 2°C to 8°C for the three consistency lots (b) (4) and up to and including 30 months for lot (b) (4) at 2°C to 8°C met the acceptance criteria set at the time for release of PR5I Finished Product with some exceptions. The (b) (4) Test, which is a test for the European market, for lot (b) (4) at time zero and 36-month time-point and at time-zero for lot (b) (4) did not meet the acceptance criteria. The (b) (4)) for lot (b) (4) at the 42-month time point did not meet the acceptance criteria. An investigation is on-going to identify the root cause for the out of specification result. For this investigation, lot (b) (4) was tested five times post the 42-month time-point and the results are provided in 3.2.P.5.6 Justification of Specifications. In addition, the subsequent (b) (4) Test at the 48-month time-point met the acceptance criteria, which supports a conclusion of acceptable product safety. Four test methods are used in the stability studies to evaluate the potential (b) (4)

(b) (4) Tests use a model of (b) (4). Although there were failing results for (b) (4) Test at the zero time and 9-month time-point for the (b) (4) stability lots (b) (4) and at the 36 month time-point for the Finished Product lot (b) (4) it has met the acceptance criteria at the 18-, 42- and 48-month time-points for lot (b) (4) and at the 18-, 36-, 42- and 48-month time-points for lot (b) (4). These results highlight the variability of the test. As such, if (b) (4) were truly present, the subsequent time-points would not be expected to pass. The (b) (4) results for lots (b) (4) met the acceptance criterion up to and including the 36 month time-point. In addition, these lots, which were used for the US clinical trial, were released based on the (b) (4) Test.

The D-antigen (b) (4) Assay was not used until the 18-month time-point for lot (b) (4) and from the 12-month time-point for lots (b) (4) as the company was in the process of replacing the (b) (4) method with the (b) (4) method. Likewise, it was used at the 3-month time-point for lot (b) (4) as this lot was formulated at a later time (Table 1).

During the test development process of PR5I Vaccine, the test that was used to quantify the Inactivated Poliovirus Vaccine (IPV) was the D-antigen (b) (4) Assay using the (b) (4) method.

The D-Antigen (b) (4) is (b) (4) assay for the quantitation of Poliovirus Type specific D-antigen present in (b) (4), IPV Vaccine and other vaccines containing IPV. The D-antigen content is closely associated with the generation of a protective immune response in the animal models and thus, a reliable measurement of the total D-antigen content for each IPV type is critical. D-Antigen (b) (4) accurately measures (b) (4)

However, with using the (b) (4) method, it was demonstrated that interference caused by non-IPV components in the PR5I formulation may be causing suppression of (b) (4) results. This was the cause for the D-antigen content test failure for lots (b) (4) during the (b) (4) Product stability study. As a result, the company has switched to a more robust method for assessing D-antigen content, which is the (b) (4) method.

The assessment of the D-antigen content for PR5I Vaccine using the (b) (4) method was applied at stability for the (b) (4) Product lot (b) (4) for all the time-points indicated in the study protocol B015659 (Table 4). With respect to the Finished Product stability studies, the (b) (4) method was applied at the 18-month time-point and onwards for lot (b) (4) at the 12-month time-point and onwards for lots (b) (4) and at the 3-month time-point and onwards for lot (b) (4). Future lots of PR5I Vaccine will use the D-antigen (b) (4) method to assess the D-antigen content at release and stability monitoring. Additional information on the development of the D-antigen (b) (4) methods is provided in 3.2.P.2.3 Manufacturing Process Development.

Conclusion

Data from stability studies B014063 and B015684 for (b) (4) PR5I Vaccine lots, (b) (4) demonstrate that the Finished Product is stable for hold time of 36 months. The data presented in this document are supportive of the storage of PR5I Vaccine Finished Product for a period of up to 36 months at 2°C to 8°C.

Overall Conclusion

In conclusion, the studies described above support the stability of PR5I Vaccine Finished Product in a 2.0-mL (b) (4) glass single-dose vial, (b) (4) stopper and 13-mm aluminum seal with plastic flip-off cap for 36 months at 2°C to 8°C. The shelf-life of PR5I Vaccine is 36 months from the date of Final Bulk Product formulation (b) (4). Finished Product does not exceed 36 months).

PART II – INFORMATION ALREADY ON FILE AND APPROVED

DRUG SUBSTANCE - Diphtheria – Sanofi Pasteur

Part II – Information Already On File and Approved for Pentacel






Review Note: The following information is included in this review memo for information only since it is already approved for Pentacel and has not changed. No equipment or cleaning procedures have changed. All room classifications remain the same and all routine area and utility monitoring are the same as currently approved for Pentacel.

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

The company internal name of the Drug Substance is Diphtheria Toxoid Adsorbed.

(b) (4)



(b) (4)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

DRUG SUBSTANCE - 5-Component Acellular Pertussis Adsorbed - Sanofi Pasteur

Part II - Information Already On File and Approved for Pentacel

Review Note: The remaining information in this review memorandum is provided for information only since it has not changed from what is currently on file for Pentacel. I have included this information in my review memorandum only as a reference.

3.2.S.1 General Information


Nomenclature

The company internal name of the Drug Substance is 5-Component Acellular Pertussis Adsorbed and is comprised of the following five antigens:

- Fimbriae Types 2 and 3 (FIM) Adsorbed
- Pertactin (PRN) Adsorbed
- Pertussis Toxoid (PT) Adsorbed
- Filamentous Haemagglutinin (FHA) Adsorbed.

3.2.S.2 Manufacture

(b) (4)



(b) (4)



DRUG SUBSTANCE- Tetanus Toxoid - Sanofi Pasteur




Part II - Information Already On File and Approved for Pentacel

3.2.S.1 General Information

Nomenclature

The company internal name of the Drug Substance is Tetanus Toxoid Adsorbed.

(b) (4)



(b) (4)

DRUG SUBSTANCE – vIPV - Sanofi Pasteur


Part II – Information Already on File and Approved for IPOL

3.2.S.1 General Information

Section 3.2.S.1.1 - Nomenclature

- (b) (4)

(b) (4)



DRUG PRODUCT - PR5I Suspension for Injection – Sanofi Pasteur

Part II - Information Already On File and Approved for Pentacel

Review Note: The remaining information in this review memorandum is provided for information only since it has not changed from what is currently on file for Pentacel. I have included this information in my review memorandum only as a reference.

3.2.P.3 Manufacture

3.2.P.3.1 – Manufacturer(s)

Name and Address of the Manufacturer(s)

The Drug Product is manufactured at the Sanofi Pasteur Limited facility located in Canada at 1755 Steeles Avenue West, Toronto, Ontario, M2R 3T4.

Responsibilities of each Manufacturer

The responsibility of Sanofi Pasteur for each manufacturing stage for the Drug Product process is listed in the following Table 1:

Table 1: Operations

Operation	Building
Manufacturer of the PR5I Final Bulk Product	(b) (4)
Media Preparation (Phosphate Solution and Aluminum Phosphate) (b) (4)	(b) (4)
Filling, labeling, packaging, release of PR5I in vials	(b) (4)
Quality Control Testing, Stability Testing	(b) (4)

3.2.P.3.5 - Process Validation and/or Evaluation

Overview

The overall process validation for the production of PR5I assesses the critical steps to ensure adequate quality assurance of the drug product.

Site policy at Sanofi Pasteur ensures that all manufacturing processes must be appropriately validated. Site policy states that process validation consists of providing evidence of a state of knowledge and control to assure that a specific process will consistently provide a product that meets pre-determined specifications.

The current overall process validation approach for the production of PR5I consists of process qualification and continuous process verification. Process qualification studies are further categorized as concurrent validation or supportive studies. Thus process validation at Sanofi Pasteur Limited can be presented as three different types, described below.

1) Concurrent Validation Studies

Concurrent validation demonstrates that the current manufacturing processes are consistent and meet all the pre-defined process and intermediate material acceptance criteria defined in the protocol.

2) Supportive Studies

Supportive studies are conducted in addition to concurrent validation studies in order to further evaluate any gaps or deficiencies identified in the concurrent studies. In some cases, small-scale studies within specified ranges are used to challenge the robustness and/or capacity of the unit operation.

3) Continuous Process Verification

After a manufacturing process is qualified using concurrent and supportive studies, continuous process verification is used to maintain assurance that the process remains in a state of control during commercial manufacture. This is performed by statistical process verification (SPC) according to procedure Q_0235384, General SPC Procedure. Statistical process verification is an ongoing program to collect and statistically analyze manufacturing data related to product quality during commercial manufacture. This type of program ensures that processes remain in control by detecting unplanned departures from the process as designed, by identifying product and process problems and by determining if actions must be taken to correct, anticipate, and prevent problems. Trained personnel perform statistical analysis of the manufacturing data to monitor process capability, identify process outliers (batches that exceed established alert limits), and identify potential process shifts or trends. For processes used to manufacture marketed products, periodic review ensures process verification. Reports describing such reviews document that the processes have not changed from the validated states. Long term trends are monitored, excursions and process shifts which exceed established alert limits are addressed, and the data is analyzed to provide support for any revision of alert limits that may be appropriate.

For PR5I, an SPC program will also be developed and implemented post-licensure, to build on the concurrent and supportive validations studies. The scope of process validation at Sanofi Pasteur Limited for PR5I focuses primarily on Formulation of Final Bulk Product and Filling into vials.

The process validation covering the manufacturing steps and parameters studied for PR5I are listed in Table 1.

Table 1: Description of the Process Validation and/or Evaluation Studies

(b) (4)

(b) (4)

Information on the derivation of batches used in the validation studies are provided in the submission in Table 2: Drug Product Batch Derivation and Manufacturing Dates.

The results of the completed validation studies demonstrate that the manufacturing process can consistently yield drug product that is suitable for its intended purpose. Table 1 describes the list of process validation studies conducted to support the manufacturing steps of PR5I production with a cross-reference to the individual section of Process Validation and Evaluation Summaries provided in section 3.2.P.3.5.

All results of the release and validation specific tests met the specifications and acceptance criteria with the exception of IPV D-antigen content (b) (4) tests, refer to 3.2.P.3.5 Process Validation and/or Evaluation - Formulation, Section 1.11-Deviations and Discussions for details.

The process fulfills the requirements and ensures a reproducible product. The data indicates that the process met the conditions established in the validation protocol and the process is considered to be under control.

3.2.P.3.5 - Process Validation and/or Evaluation Aseptic Process Simulation

Aseptic Process Simulation Program

Aseptic process simulations, in conjunction with comprehensive environmental, facility, utility and personnel monitoring, are part of the holistic evaluation of aseptic processing performance.

A summary of the aseptic process simulation program at Sanofi Pasteur Limited for the formulation of Final Bulk Products and vial filling processes is described below.

The aseptic process simulation simulates the same exposure and process, as the product itself, particularly for steps that present contamination risk or challenge to the aseptic operation. All factors contributing to process capability and representative of worst-case challenge conditions are taken into consideration when defining the process validation/re-qualification protocol. For example, such elements as aseptic assembly, duration of production run, representative number and complexity of interventions, number of personnel and their activities (i.e. shift changes), line speeds, hold-times, transportation and container closure systems are considered.

For the aseptic process simulation, (b) (4)

(b) (4)

. The aseptic process simulation acceptance criteria are detailed in the Sanofi Pasteur Limited policy “Aseptic Process Simulations at Sanofi Pasteur Ltd., Connaught Campus” (Policy Q_0209706 version 26.0).

The aseptic process simulation is performed, as per the protocol, every (b) (4) for formulation and filling of products in vials. The aseptic process simulation studies are not only performed to evaluate and ensure aseptic processing of PR5I, but also for all the other vaccines that use the same processes and container closures.

The aseptic process simulation for the formulation was designed to represent the worst-case consolidated formulation, based on the specific worst-case parameters used in the formulation of all vaccines that use the same processes and container closures. The filling aseptic simulations are done using a matrix approach. (b) (4)

The (b) (4) test is performed according to (b) (4)

Environmental monitoring is also performed during all aseptic process simulations according to the area routine Standard Operating Procedure (SOP). Quality personnel, as required/ requested, may take additional environmental and surveillance monitoring samples.

The aseptic process simulation program is reviewed and modified when necessary to ensure that the worst-case challenge conditions are used.

Two examples of aseptic process simulation studies performed in May 2010, in the same year when the first 3 PR5I consistency lots were formulated and filled, are described. Table 1: Dates of the Aseptic Process Simulation Studies Relative to the Dates of Formulation and Filling of the First 3 PR5I Consistency Lots, located within the submission, shows the dates of the aseptic process simulation studies (APSS) relative to the dates of formulation and filling of the first 3 PR5I consistency lots.

Aseptic Process Simulation for the Formulation Process of PR5I Final Bulk Product

An aseptic process simulation study (APSS) was performed for the formulation activities relative to Intermediate and/or Final Bulk Product bacterial and viral combination vaccines that include PR5I. The APSS was performed within Grade (b) (4) environments of the formulation suites (Rooms (b) (4)) in Building (b) (4) (Report Q_0262907 version 1.0).

3.2.P.3.5 - Process Validation and/or Evaluation (b) (4) - Water for Injection (WFI)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]

[REDACTED]

(b) (4)

3.2.P.3.5 - Process Validation and/or Evaluation Filling

Filling Process Validation

Process Validation Study PV08-010 (Q_0265333) was conducted to verify the consistency of the manufacturing operations associated with filling, stoppering, capping and inspection of PR5I in the Filling and Packaging Department at Sanofi Pasteur Limited (Canada). This summarizes the results of (b) (4) consistency lots of PR5I lot (b) (4).

Refer to Table 1: Time Table and Filling Lot Size, located in the submission, for the filling time table and lot size used in this study.

The process validation approach assessed critical unit operations within the entire process train, as governed by Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs). The consistency lots of PR5I were filled and stoppered on the vial tunnel filling line and capped with the capper in the Filling and Packaging Department in Building (b) (4).

The validation study data verified the process parameters for filling, stoppering and capping of the PR5I vial presentation, and the support functions related to the fill, including vial washing and depyrogenation, stopper sterilization, set-up and cleaning of filling units and environmental monitoring. The capped vials were 100% visually inspected by the Automatic Vial Inspection System. The inspected vials were also checked for Major A Defects.

Release testing was performed to verify critical quality attributes, which included General Safety, Sterility, Volume Check, (b) (4) Aluminum content, (b) (4) Pyrogen and Appearance. All predefined acceptance criteria were met.

Three non-conformances were initiated during the execution, and successfully closed; refer to Section 1.4 for details. The PR5I filling process into vials is validated. The (b) (4) are critical process parameters for both the formulation and the filling processes; refer to 3.2.P.3.5 Process Validation and/or Evaluation – (b) (4) for details.

Process Parameters

(b) (4)

- (b) (4)

Section 3.2.P.7 - Container Closure System

PR5I Final Bulk Product

(b) (4)

(b) (4)

(b) (4)

PR5I Vaccine

2.1 Primary Packaging

The container closure system used for PR5I Filled Product consists of a single-dose glass vial, rubber stopper and an aluminum seal with a plastic flip-off cap. Refer to 1.4.1 Letter of Authorization for the information on the vial and stopper Drug Master File (DMF). There is no DMF available for the flip-off cap.

Identity of Materials of Construction

The container closure system used for PR5I Filled Product consists of a 2.0-mL (b) (4) borosilicate clear glass vial, (b) (4) rubber stopper and a 13-mm aluminum seal with a plastic flip-off cap.

Specifications and Suppliers

Refer, in the submission, to Figure 1: Representative Picture of the Container Closure System for PR5I Filled Product for a representative (black and white) picture of the container closure system for PR5I Filled Product.

Tables 7 to Table 9 summarize the container closure components used for the PR5I Filled Product. Please note that each Certificate of Analysis or Certificate of Compliance includes the test results for a representative lot.

Table 7: 2.0-mL (b) (4) Clear Glass Tubing Vial Component Summary

Composition	(b) (4) borosilicate clear glass tubing
	(b) (4) treated; (b) (4) Glass Tubing
Dimensions	Neck: inner diameter: (b) (4) Flange: outer diameter (b) (4) Flange: thickness (b) (4)

	Outer diameter: (b) (4) Height: overall: (b) (4) Height: base to shoulder: (b) (4)
Manufacturer	(b) (4)
Supplier and Address	(b) (4)

Table 8: (b) (4) Stopper Component Summary

Composition	Elastomer: bromobutyl rubber (not made with natural rubber latex) Reinforcement Filler: (b) (4) Curing Agent: (b) (4) Coloring Agent: (b) (4) Additives: (b) (4) (b) (4) Surface treatment: (b) (4)
Dimensions	Flange outer diameter (b) (4) Flange thickness (b) (4) Stopper outer diameter: (b) (4) Stopper diameter at ridge: (b) (4) Stopper overall height: (b) (4)
Manufacturer	(b) (4)
Supplier and Address	(b) (4)

Table 9: 13-mm Aluminum Seal with Plastic Flip-Off Cap Component Summary

Composition	Plastic flip-off cap: polypropylene 13-mm aluminum seal: Aluminum
Dimensions	Height overall: (b) (4) Inside cap diameter: (b) (4) Plastic flip-off cap outer diameter: (b) (4) Thickness of metal: (b) (4)
Manufacturer	(b) (4)
Supplier and Address	(b) (4) (b) (4)

Suitability

In addition to the container closure integrity test mentioned in Section 2.1.3.1, refer to 3.2.P.2.4 Container Closure System and 3.2.P.8.3 Stability Data for information regarding the suitability of the container closure system with the PR5I Filled Product.

Container Closure Integrity Testing

The container closure system is suitable for maintaining the sterility and the integrity of the PR5I Filled Product throughout its shelf-life. This was confirmed by the sterility testing and container closure integrity testing performed during the stability monitoring of PR5I Filled Product; provided in 3.2.P.8.3 Stability Data.

Quality Control Measures for Primary Packaging Components

Quality Control Measures Taken by Sanofi Pasteur

Each shipment of vials, stoppers and aluminum seals with flip-off caps are randomly sampled as described in Standard Operating Procedures. The samples are inspected, measured and tested to determine that the shipment conforms to the approved specifications. Shipments conforming to the defined standards are accepted, while those shipments whose samples are non-conforming are rejected. The tests performed by Sanofi Pasteur are listed in Table 10.

Table 10: Components and Specifications of the Container Closure System for PR5I for the Vial Presentation

(b) (4)

(b) (4)

Secondary Packaging

The secondary packaging components for PR5I Vaccine consist of an insert, a label (attached to the vial) and a carton. There will be one presentation for the PR5I Vaccine packaging consisting of 10 vials per carton.

Section 3.2.A.1 – Facilities and Equipment

Building (b) (4) Building (b) (4) - General Overview, Flows and Contamination Control

Building (b) (4) General Description

Building (b) (4) is a multi-level building consisting of (b) (4) floors. The (b) (4) floor (Level (b) (4)) comprises of the Formulations, Media production, and Washing and Sterilizing areas. The (b) (4) floors (Level (b) (4) and Level (b) (4)) house testing laboratories. Some of the testing laboratories conduct live testing for other products manufactured at the site including POLIOVAX® (Poliovirus Vaccine Inactivated (IPV)) and TheraCys® (Bacillus Calmette-Guerin (BCG) Live). The Formulations area located on Level (b) (4) is used to formulate the PR5I Final Bulk Product.

The areas on Level (b) (4) (Formulations, Media production and Washing and Sterilizing) are independent of the laboratory testing areas on Level (b) (4) and Level (b) (4) through the use of separate air-handling systems thus maintaining segregation. Additionally, the flow of materials and personnel through the first floor operations is by way of defined entries (Standard Operating

Procedures (SOPs)) that are separate from those entries used for the testing laboratories on Level (b) (4) and Level (b) (4)

The following flow drawing illustrates the layout of Building (b) (4) (Level (b) (4)). Table 1: Summary of Room Number and Use, located in the submission, provides a summary of the room numbers, room function and major equipment locations within Level (b) (4) of Building (b) (4). The use of all adjacent areas is illustrated in drawing (b) (4) – Department Allocation Plan, located in the submission.

General Description of the Flow Pattern

The movement of product, personnel, equipment and materials, and waste for the Formulations, Media Production, and Washing and Sterilizing areas are described in the submission in the following sections.

Movement of Product

The movement of product is illustrated in the following flow diagrams provided in 3.2.A.1:

- (b) (4) – Formulations, Product Flow
- (b) (4) – Formulations, Product Components Flow

Movement of Personnel

The movement of personnel is illustrated in the following flow diagram provided in 3.2.A.1:

- (b) (4) – Formulations, Personnel Flow
- (b) (4) – Media, Personnel Flow
- (b) (4) – Washing and Sterilizing, Personnel Flow
- (b) (4) – Washing and Sterilizing, Personnel Flow

Traffic and Gowning Procedures

Trained operators are designated to the specific production areas. Entry to the facilities is controlled by security card access. As per approved procedures (SOPs) Personnel don dedicated garments as well as dedicated shoes or impervious shoe covers prior to entering the production area. Personnel movement is from areas of lower classification to areas of higher classification and as such the requirements for gowning increase prior to accessing the areas of higher classification. (b) (4)

(b) (4). To mitigate risks of introducing contaminants into the production areas, as per defined procedures, personnel are restricted from movement between areas of different classification unless appropriate gowning or decontamination procedures are performed.






Movement of Equipment and Materials

Building (b) (4) (Level (b) (4)) is divided into three areas: Formulations, Media Production and Washing and Sterilizing.

For each area when sterile equipment is obtained for use it is surface disinfected or a packaging layer is removed in designated airlocks prior to use.

Clean equipment requiring sterilization is autoclaved. After autoclaving, sterilized equipment is removed under laminar flow and can be temporarily stored in a designated sterilized equipment area until required for use or transport to designated areas.

(b) (4)



The movement of equipment and materials in each of the three areas are illustrated in the submission in the following flow diagrams:

(b) (4)

Formulations (movement of clean and sterile equipment),
Formulations (movement of soiled equipment),
Media (movement of clean and sterile equipment),
Media (movement of soiled equipment),
– Media (movement of media and prepared reagents),
Media (movement of raw materials),
Washing and Sterilizing (movement of clean and sterile

Washing and Sterilizing (movement of soiled equipment).

Movement Waste

The movement of waste is illustrated in the submission in the following flow diagrams:

- (b) (4) – Formulations (movement of waste),
- (b) (4) – Media (movement of waste),
- (b) (4) – Washing and Sterilizing (movement of waste).

Containment and Prevention of Contamination

The Formulations, Media Production and Washing and Sterilizing areas are cleaned and disinfected according to approved SOPs, using approved cleaning, disinfecting, and (b) (4) agents. All room hardware and finishes in the Formulations, Media Production and Washing and Sterilizing areas are sealed and corrosion resistant to the cleaning and disinfecting agents used for routine facility cleaning/disinfection.

Surface-disinfection/decontamination or removal of outer packaging layers is performed when moving equipment or materials (including product) from an area of lower classification to one of higher classification. Pass-throughs are disinfected before each use. Gowning, personnel and equipment/materials flows in the Formulations, Media and Washing and Sterilizing areas are carried out in accordance with approved Standard Operating Procedures (SOPs).

Segregation Procedures

The intermediate concentrates used in the Final Bulk Product formulation are clearly labeled and held in Building (b) (4). Each antigen has its own unique identification material number and batch number. As part of the formulation process, the material number and batch number of each antigen material are independently checked by (b) (4) operators to ensure that the correct antigens and batch numbers are used for the formulation.

The *Haemophilus influenzae* type b conjugate concentrate and Hepatitis B surface antigen concentrates are the only antigens stored in Merck's (b) (4) containers and are uniquely identifiable. The other antigens, from Sanofi Pasteur, are stored in (b) (4) containers and are clearly labeled. The Vero IPV used for PR5I formulation is stored in a locked cage to segregate the lots designated for PR5I Vaccine formulation.

Environmental Monitoring

The manufacturing environment is routinely monitored to confirm that the production areas are under control with respect to cleaning/disinfecting, room classification and personnel gowning.

The environmental monitoring includes viable and non-viable monitoring of surfaces and the air under dynamic conditions and is performed according to an approved SOP. Monitoring also includes temperature, relative humidity and pressure differential of controlled environments.

The dispensing of samples is performed in the (b) (4). Formulation is done in the Grade (b) (4) environment using (b) (4). Locations for routine monitoring within areas and rooms are chosen based on the nature of the activities within the room (e.g., operations using the (b) (4)) and the location of these activities. Locations are subject to change based on the results of routine and

surveillance monitoring. Room air pressure differentials are monitored continuously by the facility monitoring system and are also verified prior to entry into the area. The pressure differential gauges on the Grade (b) (4) are verified prior to use, on each day that the (b) (4) are used.

The Department Manager or designate is responsible for ensuring all personnel who enter a controlled area in the Formulations, Media Production and Washing and Sterilizing areas are trained in and follow procedures for aseptic gowning and personnel flows. (b) (4)

Section 3.2.A.1 – Facilities and Equipment

Building (b) (4) – Equipment

Major Process Equipment Overview

The major equipment used during final formulation of PR5I is summarized in Table 1. The equipment listed includes those used directly in vaccine formulation (product contact equipment) and ancillary systems/equipment which support the formulation process (non-product contact equipment). Product contact equipment includes the formulation (b) (4) which are non-dedicated.

Refrigerators, sterile connecting devices (b) (4) tubing in contact with the product) and tube sealers are examples of ancillary equipment. Supporting validation of the equipment used in the manufacturing process is also referenced in the 3.2.P.3.5 Process Validation and/or Evaluation - Mixing and 3.2.P.3.5 Process Validation and/or Evaluation – Aseptic Process Simulation.

Cleaning and sterilization validation for equipment identified as having product contact can be referenced in the 3.2.A.1 Facilities and Equipment – Cleaning (Building (b) (4) and 3.2.A.1 Facilities and Equipment – Sterilization (Building (b) (4)


Table 1: Major Equipment for Building (b) (4) - Final Formulation

(b) (4)


Major Equipment Description and Qualification

Sanofi Pasteur Limited certifies that the Installation Qualification and the Operational Qualification for the equipment listed in Table 1 (where applicable) have been completed and based on the documentation review and data generated during the execution of the validation studies, the conclusion is that the equipment have been installed and are operating in accordance with the manufacturer's and Sanofi Pasteur Limited's specifications.


(b) (4)

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(b) (4)

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(b) (4)

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(b) (4)



Section 3.2.A.1 – Facilities and Equipment

Building (b) (4) – Cleaning

Cleaning of Product Contact Equipment

In general, equipment used in manufacturing is decontaminated, cleaned, sterilized where applicable, and prepared for reuse. The program for decontamination and sterilization is outlined in 3.2.A.1 Facilities and Equipment – Sterilization (Building (b) (4) Equipment used in Building (b) (4) are washed and sterilized in the Building (b) (4) Washing and Sterilizing area. Additionally, equipment from Building (b) (4) (5-Component Acellular Pertussis) and Building (b) (4) (Diphtheria Toxoid Adsorbed and Tetanus Toxoid Adsorbed) can be washed and sterilized in the Building (b) (4) Washing and Sterilizing area as an alternate to the Washing and Sterilizing areas in Building (b) (4) and Building (b) (4).

Cleaning of the bioprocess equipment is important in maintaining lot-to-lot segregation of material as well as the elimination of product-to-product carry-over. In consideration of these reasons, Sanofi Pasteur Limited takes into account the material of construction for all equipment and the types of residual materials that may adhere during the manufacturing process. These residual materials may include media components, reagents, biomass, product, by-product, product impurities, as well as the potential build-up/accumulation of any one or combination of these materials. The factors mentioned are therefore considered when establishing the cleaning procedures.

Both automatic and manual cleaning methods are used to perform cleaning operations. These processes may consist of dismantling the equipment and cleaning of the individual components.

Cleaning Overview

Table 1 provides a summary of the cleaning validation for the Washing and Sterilizing area of Building (b) (4)

(b) (4)

(b) (4)

(b) (4)

Section 3.2.A.1 – Facilities and Equipment

Building (b) (4) – Sterilization

Equipment Sterilization

(b) (4) sterilization of equipment and materials in Building (b) (4) is carried out using (b) (4) autoclaves located in the Washing and Sterilizing facility.

Autoclave Sterilization

(b) (4)

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(b) (4)

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Section 3.2.A.1 – Facilities and Equipment

Building (b) (4) - Building Utilities (Water and Clean Steam)





Water and Clean Steam

City or source water is supplied to Building (b) (4) through a main located in the basement mechanical room. There are three systems that will be described in this section. These include Pre-treatment Systems, the Water for Injection System (WFI) and the Clean Steam System.

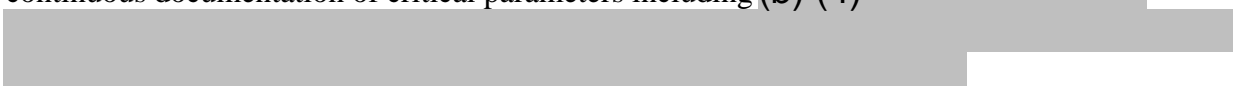
Water for Injection (WFI) System (WFI (b) (4))

The Water for Injection (WFI) System (WFI (b) (4)) in Building (b) (4) is produced by a multi-effect

(b) (4)



The WFI distribution system is controlled by a central PLC-based panel with a chart recorder for continuous documentation of critical parameters including (b) (4)




The WFI system is designed to produce WFI-quality water to current (b) (4) specifications.

Materials in contact with the WFI are (b) (4)


The exception to this is the WFI distribution pump that has mechanical seals composed of (b) (4).
All components on the WFI distribution system are capable of being (b) (4)
at a temperature of at least (b) (4)

Water for Injection System Installation Qualification

(b) (4)




(b) (4)

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Clean Steam ((b) (4))

Water from the Pre-treatment system ((b) (4)) described in Section 1.1 is used to feed the clean steam generator located in Mechanical Room (b) (4)

The generator is used to supply clean steam to Building (b) (4) The generator also (b) (4)

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(b) (4)

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All piping in contact with product clean steam is (b) (4) either (b) (4)

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(b) (4)

Clean Steam System Specifications

The clean generator receives (b) (4) water that conforms to established procedures. The (b) (4) of the clean steam production rate at full capacity and (b) (4) feed water temperatures. The nominal capacity is (b) (4)

The clean steam distribution system is designed to the (b) (4)

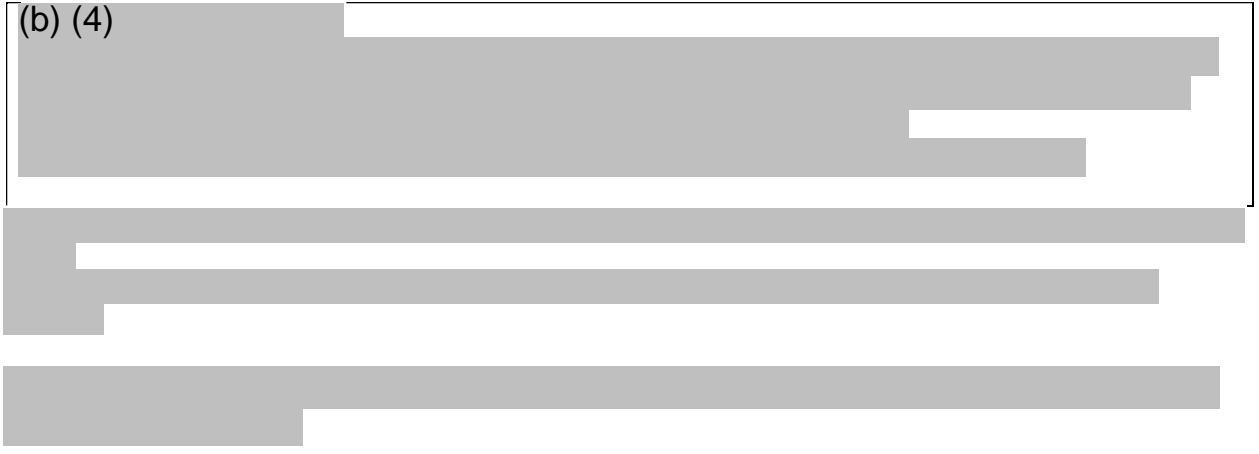
The piping, valves, and components in contact with the steam are composed of (b) (4). Valves on the steam distribution system are the (b) (4)

Clean Steam Installation and Operational Qualification

Sanofi Pasteur certifies that the IQ and OQ for the Clean Steam System serving Building (b) (4) have been successfully completed.

(b) (4)

(b) (4)



(b) (4)

Section 3.2.A.1 – Facilities and Equipment

Building ^{(b) (4)} – Building Utilities (Pharmaceutical Gas)

Pharmaceutical Gases

Compressed Air System

Description of the Compressed Air System

The Compressed Air system serving Building ^{(b) (4)} consists of ^{(b) (4)} compressors that are located in the Building ^{(b) (4)} penthouse. The compressed air system supplies compressed air to the Formulations, Media and Washing and Sterilizing areas. Compressed air is used in the operation and control of production equipment including (b) (4). Compressed air is also used in media production for (b) (4).

(b) (4)). Compressed air is also used in the Washing and Sterilizing area for equipment set-up.

(b) (4) compressors supply compressed air. A control system alternates operation (b) (4) compressors. Prior to distribution to the points of use, (b) (4) .

The system is equipped with electronic pressure sensors with displays and user adjustable set points and hour meters for the (b) (4) compressors. The system is designed to operate with (b) (4) compressors depending on demand.

The distribution piping is comprised of (b) (4) (conforms to (b) (4)). Valves on the system are primarily (b) (4) used at the points of use. The system normally operates between (b) (4) , but is regulated down where required by using pressure-regulating valves. Each air compressor is rated at (b) (4) . The system meets the requirements for (b) (4)

Compressed Air System Validation

Sanofi Pasteur Limited certifies that the Installation Qualification (IQ) and the Operational Qualification (OQ) for the compressed air system serving Building (b) (4) are completed.

Performance Qualification Summary

(b) (4)

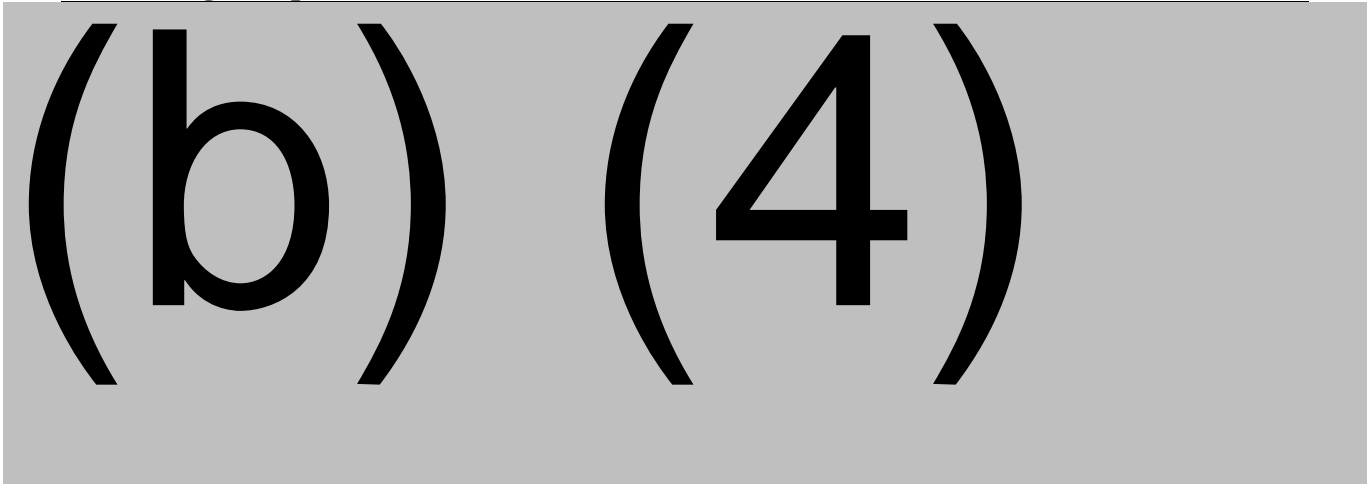
Routine Monitoring

The monitoring of compressed air systems at Sanofi Pasteur is governed by the requirements outlined in policy level SOPs. These SOPs also reflect the action limits that are applied to all compressed air systems at Sanofi Pasteur. Additionally, there are additional approved procedures

that outline the reporting requirements and the investigational requirements when a reported out-of-specification test result occurs.

For the tests performed, the frequency of sampling monitoring, and the action levels for monitoring compressed air systems, refer to Table 2.

Table 2: Tests Performed, Minimum Routine Sampling Frequency, and Action Levels for Monitoring Compressed Air



Section 3.2.A.1 – Facilities and Equipment

Building (b) (4) - Building Utilities (HVAC)

Heating, Ventilation, and Air Conditioning (HVAC)

The HVAC system serving Washing and Sterilizing, Media Production and Formulation in Building (b) (4) consists of (b) (4) air-handling units (b) (4) that are located in Mechanical Rooms (b) (4). The units provide recirculated air to the classified areas. All units use (b) (4) for preheating the fresh air, while (b) (4) provide both cooling and dehumidification. Each unit is also equipped with a clean steam humidifier for humidification. Pre-filtration is provided by (b) (4) of pre-filters (b) (4) efficient) while all classified rooms are supplied with terminal High Efficiency Particulate Air (HEPA) filters. Final temperature control is achieved using (b) (4).

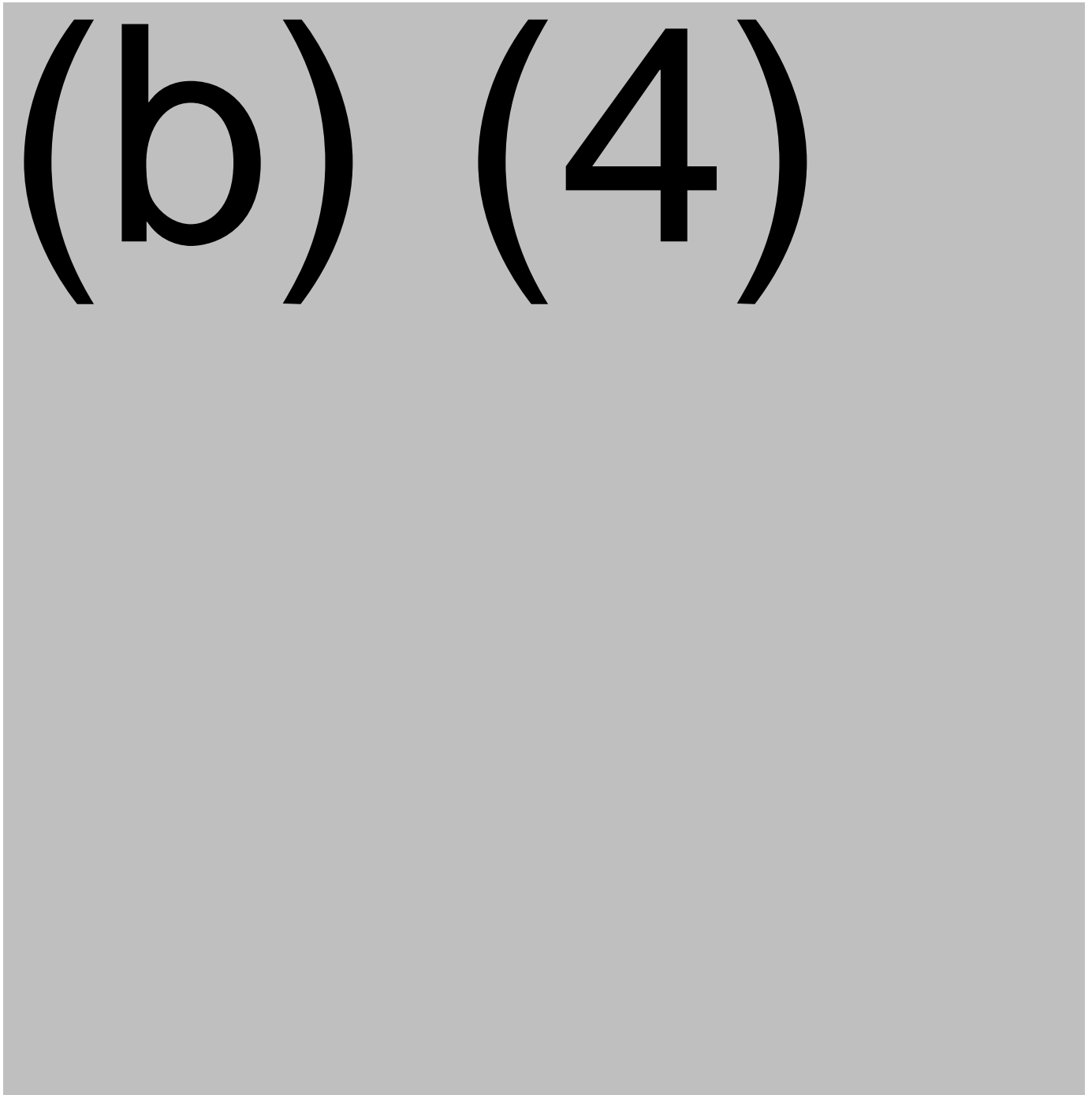
Air-return ducts in rooms with Grade (b) (4) classifications are mounted at low level. All air-handling units are connected to a central (b) (4) Building Management System that maintains, controls, and monitors temperature, humidity, and pressures within the classified areas.

The facility is designed to maintain (b) (4) relative humidity in all classified rooms. Pressure differentials across adjacent doorways in classified areas are (b) (4) between rooms with the same classification, (b) (4) between rooms with differing classifications, and (b) (4) between classified and unclassified rooms.

For information on room classifications and airflow directions, refer to the following drawings provided in the submission in 3.2.A.1:

- Formulation: Air Flow and Room Classification Level ^{(b)(4)} Plan ((b) (4)),
- Media: Air Flow and Room Classification Plan Level ^{(b)(4)} ((b) (4)),
- Washing and Sterilizing: Air Flow and Room Classification Plan Level ^{(b)(4)} ((b) (4) - (b) (4))

Table 1 lists the Building ^{(b)(4)} Level ^{(b)(4)} AHUs and the areas serviced by the units.



(b) (4)

Heating, Ventilation, and Air Conditioning (HVAC) Validation Installation Qualification and Operation Qualification

Sanofi Pasteur certifies that the Installation Qualification (IQ) and Operational Qualification (OQ) for the HVAC system servicing the Media, Formulation, and Washing and Sterilizing areas in Building (b) (4) were successfully completed.

Heating, Ventilation, and Air Conditioning (HVAC) Validation Performance Qualification

(b) (4)

- (b) (4)

Routine Environmental Monitoring

The manufacturing environment is routinely monitored to detect any air quality issues in order to prevent potential product contamination. All environmental monitoring (EM) is performed under dynamic conditions, except for Grade (b) (4) total airborne particulate monitoring. Monitoring also includes temperature, relative humidity and pressure differentials of controlled environments.

Environmental monitoring frequency for each classification area and types of sampling is provided in site and area procedures and include action and alert levels. Environmental control decisions are based on monitoring data. In the event of an action limit excursion, an investigation is initiated.

The program encompasses monitoring of total airborne and non-viable particles, pressure differentials, temperature and humidity with the limits and frequencies shown in Table 4. In this table and in the remainder of this document, air classifications are listed by Grade.

Locations for routine monitoring within areas and rooms are chosen based on the results of Performance Qualification (PQ) studies and on the nature of the process. Locations are subject to change based on the results of routine and surveillance monitoring.

All limits shown in Table 4 are site policy limits. Limits may be lowered as a result of trending, but limits are never raised above the policy limits. Alert limits are trended on an (b) (4) basis. When environmental monitoring action limits are exceeded in an aseptic processing area, the isolates are identified to a genus and species level, where possible. In other classified areas, representative colonies are identified when action limits are exceeded. Quality Operation Sterility Assurance – Contamination Control (QOSA-CC) is notified of the failure and a decision on further identification is documented. A notification is generated in the Event Reporting

system for all exceeded action limits. QOSA-CC initiates an investigation in collaboration with Quality Control and the relevant production area(s).

Table 4: Routine Monitoring Limits and Sampling Frequency

(b) (4)

(b) (4)

Building (b) (4) - Filling

Building (b) (4) - General Overview, Flows and Contamination Control

Building (b) (4) General Description

Building (b) (4) is a multi-purpose, multi-level facility utilized to fill, inspect, label, and package the final PR5I Vaccine Drug Product. The operations all occur on the (b) (4) floor (Level (b) (4))

Clean utility support systems for the (b) (4) floor are located on the (b) (4) floor and the roof (HVAC units), Level (b) (4) and Level (b) (4) respectively. Refer to 3.2.A.1 Facilities and Equipment – Building Utilities (HVAC) – Building (b) (4) 3.2.A.1 Facilities and Equipment – Building Utilities (Water and Clean Steam) – Building (b) (4) and 3.2.A.1 Facilities and Equipment – Building Utilities (Pharmaceutical Air) – Building (b) (4) for further details regarding the clean utilities supporting Building (b) (4)

The Building (b) (4) Level (b) (4) and Level (b) (4) floor plans are illustrated in the following drawings provided in 3.2.A.1:

- (b) (4) Architectural Level (b) (4) Floor Plan
- (b) (4) Architectural Level (b) (4) Floor Plan

The Building (b) (4) area allocations within Level (b) (4) and Level (b) (4) are illustrated in the following drawings provided in 3.2.A.1:

- (b) (4) Department Allocation Level (b) (4) Plan
- (b) (4) Department Allocation Level (b) (4) Plan

The Building (b) (4) area/room classifications and air flows for Level (b) (4) are illustrated in the drawing provided in 3.2.A.1 (b) (4) Air Flow and Room Classification Level (b) (4) Plan. A Level (b) (4) drawing is not presented as there are no classified areas on that floor.


The Level (b) (4) filling and packaging rooms (including unclassified and classified rooms) are summarized in the submission in Table 1: Building (b) (4) (Level (b) (4) - Filling Area, Table 2: Building (b) (4) (Level (b) (4) - Washing / Sterilization Area, Table 3: Building (b) (4) (Level (b) (4) - Labeling / Packaging Area, and Table 4: Building (b) (4) (Level (b) (4) - General / Mechanical / Support Areas. These rooms are utilized for the Drug Product unless otherwise noted.

General Description of the Flow Pattern

The movement of product, personnel, equipment, materials, and waste within Building (b) (4) is described in this section.

Movement of Product

(b) (4)








The labeled and packaged Drug Product is stored in Refrigerator Room (b) (4) until it is transferred to Building (b) (4)

Movement of Personnel

The movement of personnel on Level (b) (4) is illustrated in the drawing provided in 3.2.A.1 (b) (4) Personnel Flow Level (b) (4) Plan.

Personnel movement includes passage through the unclassified and classified rooms detailed in Table 1, Table 2, Table 3, and Table 4. Personnel attire and gowning restrictions apply with transit in/out of the unclassified and classified rooms as specified in Section 2.2.1.

(b) (4)



(b) (4)

Traffic and Gowning Procedures

Personnel traffic and gowning procedures for Building (b) (4) are established to manage product and facility contamination prevention. Gowning is required to work and/or move through the classified rooms of the aseptic processing area (Grades (b) (4)), whereas reduced personnel attire restrictions (without gowning) is required for the unclassified (e.g. labeling, packaging, inspection) or classified washing and sterilization/depyrogenation rooms (Grades (b) (4)). Work in unclassified areas requires the donning of disposable covers (head, beard, moustache as applicable) and safety shoes/glasses. In some instances, lab coats and gloves are also worn, all as procedurally specified for each work area. Work in all classified areas requires hand sanitization and the donning of controlled, company uniforms (scrubs), dedicated shoes, and shoe covers. Entry into the classified washing and sterilization areas requires gloves and coveralls. Work in the classified aseptic processing area requires sterile attire (hood, coverall, boot covers, goggles, gloves) and glove sanitization.

Movement of Equipment and Materials

The movement of equipment and materials is illustrated in the following flow diagrams provided in 3.2.A.1:

- (b) (4) Clean and Sterile Equipment Flow Level (b) (4) Plan
- (b) (4) Soiled Equipment Flow Level (b) (4) Plan
- (b) (4) Soiled Equipment Flow Level (b) (4) Plan
- (b) (4) Packaging Components Flow Level (b) (4) Plan
- (b) (4) Packaging Components Flow Level (b) (4) Plan

The materials and equipment utilized for Drug Product final container filling and packaging operations include disposable (single-use) and reusable materials/equipment. Disposable materials are cleaned and/or sterilized prior to use in Building (b) (4). Reusable equipment is cleaned and sterilized in Building (b) (4) (e.g. product contact filling parts) or in Building (b) (4) (e.g. Formulation Bulk (b) (4)). Refer to 3.2.A.1 Facilities and Equipment – General Overview, Flows, and Contamination Control (Building (b) (4)) for details regarding the cleaning of the Final Bulk Product (b) (4).

(b) (4)

Disposable Materials

Disposable materials are transported from Room (b) (4). The specific transit of disposable materials is dependent on whether the materials are ready-to-use or require cleaning, sterilization/depyrogenation, and/or assembly within Building (b) (4) prior to use.

- (b) (4)

Reusable Equipment

The movement of reusable equipment includes clean, soiled, and sterilized equipment. Reusable equipment soiled during filling and packaging operations is cleaned and sterilized in Building (b) (4) or Building (b) (4) prior to reuse. The Final Bulk Product (b) (4) are cleaned and sterilized in Building (b) (4). Refer to 3.2.A.1 Facilities and Equipment – Cleaning (Building (b) (4) and 3.2.A.1 Facilities and Equipment – (b) (4) (Building (b) (4) for equipment cleaning and sterilization, respectively in Building (b) (4). For details regarding the return of the (b) (4) to Building (b) (4) refer to Section 2.1.

- (b) (4)

The transport of clean and/or sterilized materials/equipment from a lower room classification area to a higher room classification (e.g. Grade (b) (4)) are subjected to a treatment of exposed surfaces. The treatments include the use of disinfectants to ensure the materials/equipment do not introduce contaminants into the critical, Grade (b) (4) areas of the aseptic processing area. A disinfectant treatment is performed at each transition point through the classified rooms/area (i.e. from Grade (b) (4) and from Grade (b) (4) From a Grade (b) (4) area to Grade (b) (4) area (limited to Room (b) (4) within the filling cabinet), the outer wrapping of the sterile, double bagged item is removed and the now single bagged item is passed into the Grade (b) (4) area.

Movement Waste

The movement of waste is illustrated in the following flow diagrams provided in 3.2.A.1:

- (b) (4) Waste Flow Level (b) (4) Plan
- (b) (4) Waste Flow Level (b) (4) Plana

Refer to 3.2.A.1 Facilities and Equipment – Waste (Building (b) (4) for further details regarding the handling of waste generated from the filling, labeling, and packaging operations on Level (b) (4) of Building (b) (4)

Prevention of Contamination

Sanofi Pasteur utilizes the facility design and system features of Building (b) (4) in addition to procedural controls to minimize the potential for contamination around the filling and packaging operations. This section contains an overview of the contamination prevention measures taken within Building (b) (4)

Facility Design Features

The Building (b) (4) facility utilizes architectural design and qualified systems to manage contamination control. The control features include:

- Defined unclassified and classified rooms/areas
- Air pressure differentials to maintain room classifications
- Restricted access to critical, classified areas
- Qualified heating, ventilation, and air conditioning systems (HVAC) to control room temperature, humidity and air quality

- Qualified facility management system (FMS) to continually monitor environmental conditions in classified areas and clean utility conditions
- Cleaning and sterilization / depyrogenation systems for process equipment
- (b) (4) (Grade (b) (4) air) in the filling area

The design of Building (b) (4) includes segregated, unclassified and classified airlocks, corridors, and rooms which cascade from the most critical to the least critical air classification (i.e. Grades (b) (4) to unclassified). The cascade is designed to prevent ingress of potential contaminants from the least critical into the most critical areas. Airlocks in the aseptic processing areas also provide additional assurance against potential contamination in classified areas with the use of dedicated personnel versus material/equipment specific airlocks. The personnel entry airlock to the aseptic processing area is access restricted by use of authorized cards. Airlocks are also utilized for passage in/out of the classified washing and sterilization areas.

(b) (4) Heating, Ventilation, and Air Conditioning (HVAC) units support the Level (b) (4) areas in Building (b) (4) that are used in the Filling and Packaging operations. (b) (4) HVAC systems service the classified areas, while (b) (4) additional HVAC systems service the unclassified areas. The control of HVAC systems provide a maintained, minimum air pressure differential within classified areas and between classified and unclassified areas with the air gradient flowing from the most critical to the least critical room. Air pressure differentials are continually monitored through a facility management system (FMS) as are room temperature and relative humidity. Local magnehelic gauges provide additional confirmation of air differentials, the data of which can be manually logged. The FMS is equipped with alarms to notify operations personnel of out of tolerance events. The reaction to out of tolerance events is procedurally managed, complete with appropriate response instructions. All product contact equipment is cleaned and sterilized/depyrogenated in preparation for the filling operations in the aseptic processing areas. Systems utilized to execute cleaning and sterilization/depyrogenation processes are qualified for repeatable, reliable use and are located within classified areas to decrease the contamination potential around such operations.

The filling and stoppering machine in Room (b) (4) utilizes a (b) (4) final container filling and stoppering operation to prevent product contamination.

The (b) (4) provides Grade (b) (4) air over the filling and stoppering operation.

Contamination Control Procedures

The Building (b) (4) facility utilizes procedural programs to complement facility design features for contamination control. The programs include:

- Defined personnel, equipment/materials, product, and waste flow patterns
- Personnel attire/gowning instructions
- Segregation of attenuated, inactivated, and detoxified products
- Dedicated or campaigned product contact equipment
- Segregation of clean, sterile, and soiled equipment
- Filling line clearances
- Defined facility cleaning procedures and frequencies
- Qualified routine environmental monitoring program

- Personnel training

The flow of product, personnel, equipment/materials and waste is procedurally controlled throughout Building (b) (4) as detailed in Section 2. The flows are complemented with procedural restrictions in passage of clean/sterile/depyrogenated versus soiled equipment, segregation of attenuated versus inactivated/detoxified products, segregation of in-process product batches (e.g. unlabeled, labeled, packaged, unreleased, released, quarantined, rejected), and restrictions on personnel attire/gowning relative to work performed in unclassified versus classified areas.

Since Building (b) (4) is a multi-product facility, segregation of attenuated versus inactivated/detoxified product is necessary to avoid cross contamination. Refer to 3.2.A.1 Facilities and Equipment – General Information on Facilities for an indication of the other biologic products handled in Building (b) (4). No attenuated product filling operations occur in Building (b) (4) as filling of final container product is restricted to inactivated/detoxified products. Processing of attenuated product is restricted to inspection, labeling, and packaging. Filling operations for inactivated/detoxified product is executed on a campaign basis with (b) (4) filled, capped, and inspected at a time. Product contact filling equipment is also either product dedicated or campaigned to further minimize or prevent product cross contamination. Waste procedures are in place to appropriately segregate and dispose of attenuated and inactivated/detoxified waste. Procedures governing waste disposal include instructions for managing product spills. All products processed in Building (b) (4) are segregated under storage to ensure separation of individual products and in-process products.

Clean and sterile product contact equipment is appropriately segregated from soiled equipment and is stored to ensure cleanliness/sterility until used during filling operations. All cleaning and sterilization/depyrogenation operations are procedurally controlled and documented. Refer to 3.2.A.1 Facilities and Equipment – Cleaning (Building (b) (4)) and 3.2.A.1 Facilities and Equipment – Sterilization (Building (b) (4)) for further details on the cleaning and sterilization of product contact equipment. Line clearances for the vial washer, vial depyrogenation tunnel, filling and stopper machine, capping machine, inspections, labeling, and packaging machines are also performed to ensure Filled Product, final container components (e.g. stoppers, vials, caps), labels, and packaging are clear of the machines in advance of the next processed product batch.

The facility is cleaned/disinfected using appropriate cleaning/disinfecting agents that have been qualified for use as bactericidal, fungicidal, and/or sporicidal agents. The frequency and rotation of disinfectant use is procedurally controlled. Both before and after the completion of an operation all work surfaces are cleaned and disinfected. Cleaning of the facility is progressive with cleaning beginning within the most critical, classified areas down to the unclassified areas.

Logbooks are used to document the cleanings and are checked daily and/or prior to initiating each batch to verify completion of the cleaning. The procedures specify the frequency for each cleaning (e.g. daily, weekly or monthly) and vary relative to unclassified versus classified rooms with the stringency and frequency of the cleanings increasing with the criticality of the room classification.

The manufacturing environment is routinely monitored according to site procedure to detect any air quality issues in order to reduce any risks of contamination. Environmental monitoring frequency and sampling types for each classified room is managed per site and area procedures.

The monitoring program includes established action and alert levels. In the event of an action limit excursion, an investigation is initiated.

Personnel training is conducted, documented, and maintained relative to all filling and packaging operations.

Section 3.2.A.1 – Facilities and Equipment

Building (b) (4) - Equipment

Major Process Equipment Overview

Major equipment used for the filling, stoppering, capping, and inspection of PR5I Vaccine in Building (b) (4) is described in this section. Product contact equipment is dedicated to Building (b) (4) the only exception are the (b) (4) that are used for the Final Bulk product for filling.

The equipment is shared for the filling of other products listed in section 3.2.A.1 Facilities and Equipment – General Information on Facilities.

Major pieces of equipment used are included in Table 1. The table does not include utility related equipment or building support systems as they are described in other sections, see 3.2.A.1 Facilities and Equipment – Building and Utilities (Water and Clean Steam) – Building (b) (4) 3.2.A.1 Facilities and Equipment – Computer Systems (Building (b) (4) 3.2.A.1 Facilities and Equipment – Building and Utilities (Pharmaceutical Gas) – Building (b) (4) and 3.2.A.1 Facilities and Equipment – Building and Utilities (HVAC) – Building (b) (4)

The PR5I Vaccine Final Bulk is filled into final containers (vials) on an automated production line in the Filling and Packaging Department (Building (b) (4) Rooms (b) (4)). The automated production line is comprised of the following equipment: a (b) (4) vial tunnel line ((b) (4)). After filling and stoppering, the product continues to the (b) (4) capping machine, then the (b) (4) Vial Inspection system, then to the (b) (4) labeling system and the product is packaged on the (b) (4) Line.

The vial tunnel washer, sterilizer and filling and stoppering machines are (b) (4)

(b) (4)

(b) (4)

[REDACTED]

Age Group	Percentage
18-24	18%
25-34	25%
35-44	22%
45-54	15%
55-64	10%
65-74	8%
75-84	5%
85+	3%

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[REDACTED]

Section 3.2.A.1 – Facilities and Equipment

Building (b) (4) – Cleaning

Cleaning of Product Contact Equipment

Building (b) (4) product contact equipment includes filling equipment and final containers (vials), all used in the filling of Drug Product, PR5I Vaccine. The equipment is cleaned using

(b) (4) technology (vial washer) and manual cleaning processes (filling product contact equipment). Refer to 3.2.A.1 Facilities and Equipment – Sterilization (Building (b) (4) for information on vial depyrogenation and moist heat sterilization of manually cleaned parts.

Vial Washer (b) (4)

Vial Washer Description

The vial washer, manufactured by (b) (4), is located in Room (b) (4)

(b) (4)

(b) (4) is further detailed in 3.2.A.1 Facilities and Equipment – Sterilization (Building (b) (4)

(b) (4)

(b) (4)

Vial Washer Qualification


Installation / Operational Qualification

(b) (4)


(b) (4)

(b) (4)

(b) (4)



(b) (4)



Manual Cleaning

Manual Cleaning Description


A manual cleaning process is utilized to clean product contact parts used in the filling of the Drug Product final container. The cleaning process begins within a controlled dirty hold time and includes a (b) (4)

step is executed to minimum time requirement.

Following each cleaning process, clean parts are visually inspected with final rinse (b) (4) being analyzed for (b) (4). The cleaning process is executed in Rooms (b) (4).

Manual Cleaning Validation

(b) (4)



(b) (4)

Section 3.2.A.1 – Facilities and Equipment

Building (b) (4) – Sterilization

Equipment Sterilization

Equipment utilized in the filling of the Drug Product final container is sterilized prior to use in Building (b) (4) with the exception of the filling (b) (4) (Final Bulk (b) (4)). The filling (b) (4) is sterilized prior to use in Building (b) (4) (3.2.A.1 Facilities and Equipment – Sterilization (Building (b) (4)). Building (b) (4) utilizes (b) (4) systems to sterilize single-use and/or multi-use equipment as summarized in Table 1.

Table 1: Sterilized Filling and Inspection Process Equipment

Equipment	Use	Sterilization Method
Stoppers	Final container (single use components)	(b) (4)
Vials		(b) (4)
Filling Equipment	Filling and final container stoppering equipment (single and multi-use equipment)	(b) (4)

(b) (4)

(b) (4)

Section 3.2.A.1 - Facilities and Equipment

Building (b) (4) - Computer Systems

Computer Systems Overview


There are (b) (4) computer-controlled equipment systems used for the filling and packaging of the Drug Product in Building (b) (4). The equipment systems are as follows:

- (b) (4)

Additional computer-controlled systems are utilized for environmental, cleaning, and sterilization controls/processes. Refer to 3.2.A.1 Facilities and Equipment – Building Utilities (HVAC) – Building (b) (4), 3.2.A.1 Facilities and Equipment – Cleaning (Building (b) (4)) and 3.2.A.1 Facilities and Equipment – Sterilization (Building (b) (4)) for details specific to the environmental, cleaning, sterilization/depyrogenation computer-control systems, respectively.

(b) (4)

(b) (4)

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Section 3.2.A.1 – Facilities and Equipment

Building (b) (4) - Building Utilities (Water and Clean Steam)

Water and Clean Steam

Description of the Water Systems

Building (b) (4) contains systems for the generation and storage of Water for Injection (WFI) and generation of Clean Steam (CS). The terms Clean Steam and Pure Steam are considered equivalent and therefore may be used interchangeably throughout this document. The Process Feed Water generation and distribution systems are located in Building (b) (4) and are piped into Building (b) (4) to supply purified water (i.e. (b) (4) refer to 3.2.A.1 Facilities and Equipment – Building Utilities (Water and Clean Steam) – Building (b) (4)

Water for Injection

The WFI System supplies WFI quality water on a continuous basis to the Filling and Packaging Department in Building (b) (4). There is no formulation performed in Building (b) (4). The WFI is used as the (b) (4). The WFI System consists of a (b) (4)

are located on the (b) (4) floor within Mechanical Room (b) (4) in Building (b) (4). The distribution loop circulates from (b) (4). The cooling exchanger is located on the (b) (4) floor in the Filling and Packaging Department.

The WFI still uses (b) (4) steam as a heat source and produces WFI at (b) (4). The filling of the WFI storage tank is automated based on preset tank levels. The WFI tank level is determined by (b) (4)

The WFI holding tank is equipped with a (b) (4)) to control the temperature of the WFI to (b) (4) to measure the amount of WFI in the tank. (b) (4)

WFI system piping is (b) (4) inspection. (b) (4)

The WFI System uses a loop-based controller panel mounted in Room (b) (4). The panel maintains WFI temperature at (b) (4), monitors WFI (b) (4), monitors WFI temperatures (at the WFI tank and at the reheat exchanger inlet) and controls alarms if the

following conditions exist: (b) (4)

The WFI distribution system can be (b) (4) at a temperature (b) (4), as measured by the WFI system temperature probes. (b) (4) sanitization is performed (b) (4) at a minimum and following preventive maintenance work on the WFI system.

Installation and Operational Qualification of Water for Injection

(b) (4)

Clean Steam (Pure Steam)

The Pure Steam System (equipment #(b) (4)) provides pure steam to the (b) (4) floor. The system consists of a pure steam generator located in Mechanical Room (b) (4) and the associated distribution piping. The generator uses (b) (4) steam as a heat source and uses a Programmable Logic Controller (PLC) to control steam pressure and water level. The generator is fed by a pretreatment system located in Building (b) (4) and is equipped with a (b) (4).

All tubing in contact with pure steam is (b) (4) either (b) (4) inspection, or (b) (4). Other components include (b) (4).

(b) (4) pure steam system drops are located in the mechanical rooms (b) (4) to Rooms (b) (4) (b) (4) to provide pure steam to the (b) (4) (equipment #(b) (4)). Use points are equipped with (b) (4) to ensure delivery of dry steam. Check valves are used to prevent migration of condensate into the steam system in case of a system shutdown. The system provides pure steam at approximately (b) (4).

(b) (4)

(b) (4)

Section 3.2.A.1 – Facilities and Equipment

Building (b) (4) - Building Utilities (Pharmaceutical Gas)

Pharmaceutical Gas

Pharmaceutical (Clean Compressed) Air System

Description of the Pharmaceutical (Clean Compressed) Air System

The compressed air system utilized in the Filling and Packaging areas of Building (b) (4) is located on Level (b) (4) in Room (b) (4) (Mechanical Room). The compressed air system is comprised of (b) (4)

(b) (4)

Compressed air is utilized for critical operations, product contact sites, and instruments/equipment. The compressed air system is designed to provide air which is (b) (4) and distributed to point of use sites. Table 1: Point of Use Drops for the Compressed Air System, located in the submission, provides a list of the point of use drops for the compressed air system.

Pharmaceutical (Clean Compressed) Air Validation

Installation and Operational Qualification

Sanofi Pasteur Limited certifies that the Installation Qualification (IQ) and the Operational Qualification (OQ) for the compressed air system serving Building (b) (4) are completed.

Performance Qualification

A Performance Qualification (PQ) for the compressed air system was performed in (b) (4) phases

(b) (4)

(b) (4)

Section 3.2.A.1 – Facilities and Equipment

Building (b) (4) - Building Utilities (HVAC)

Heating, Ventilation, and Air Conditioning (HVAC)

Description

(b) (4) HVAC systems support the classified areas (Grades (b) (4)) of the Drug Product filling and packaging operations on Level (b) (4) floor) in Buildin (b) (4)

The HVAC systems AHUs physically reside in mechanical rooms located on Level (b) (4) floor). Additional HVAC systems supply conditioned air to Level (b) (4) however, the supply is limited to unclassified areas. Additional details regarding these systems and their supplied rooms are therefore not provided since there is no association with classified areas.

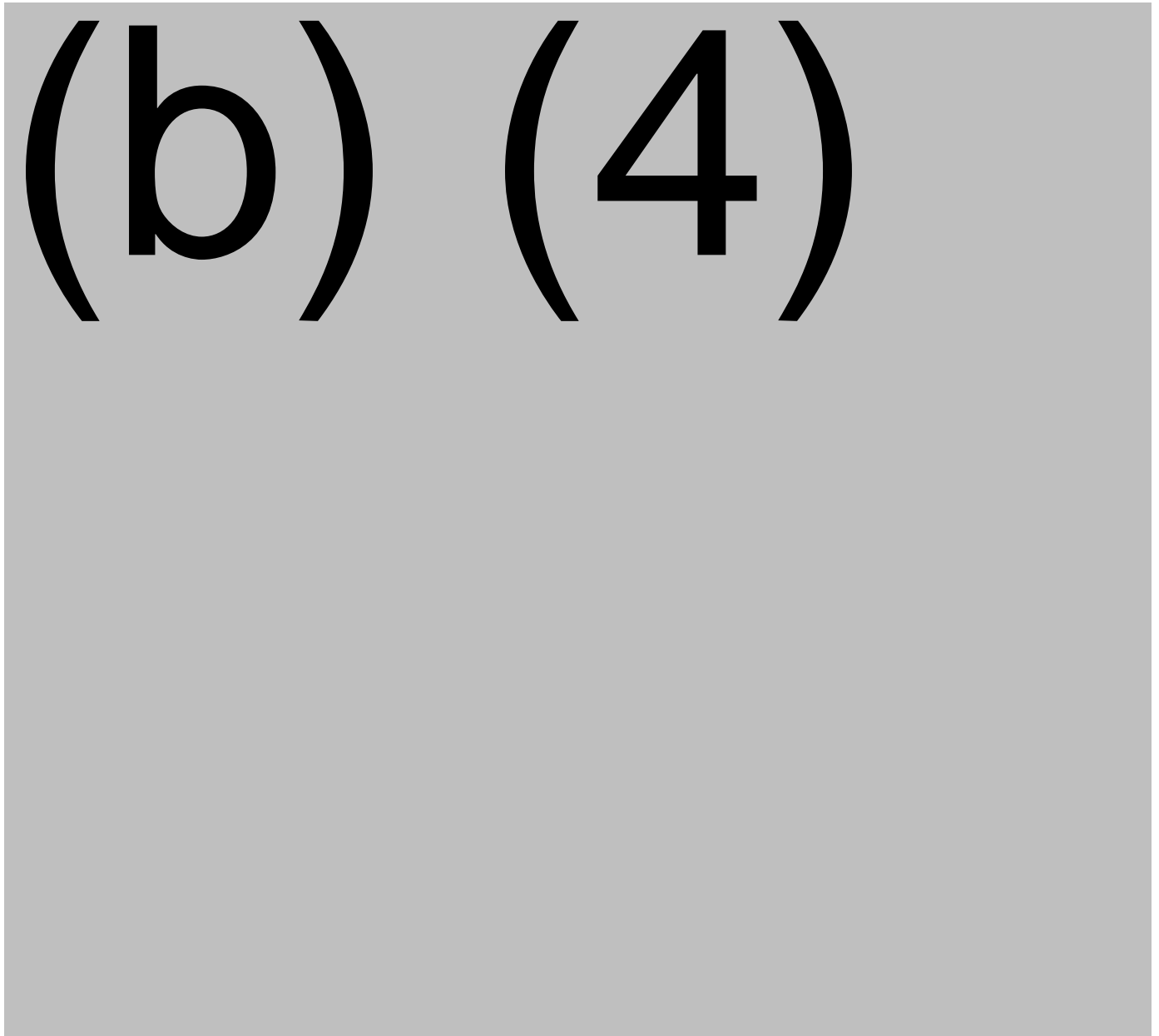
The filling facility is designed to minimize the potential for contamination. The facility is segregated into classified rooms (Grades (b) (4)) and unclassified rooms. Between rooms an air pressure cascade is maintained to prevent the ingress of contaminants from the least critical to most critical room. Minimum pressure differentials, measured in (b) (4) between areas of parallel classification and (b) (4) between rooms with differing

classifications. The minimum air pressure differential between classified and unclassified rooms is (b) (4) . Refer to Table 1 for a summary of the rooms serviced by each HVAC system and the corresponding classifications.

(b) (4) are utilized to provide Grade (b) (4) operation in Room (b) (4) supplies conditioned air to the (b) (4)

The area classifications, directional air flows, and minimum air pressure differentials are illustrated in the following drawing provided in 3.2.A.1: (b) (4) – Air Flow and Room Classification Level (b) (4) Plan.

Table 1: Rooms Controlled by Air Handler Units (b) (4) ,



(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Routine Environmental Monitoring

The manufacturing environment is routinely monitored according to site procedure to detect any air quality issues in order to reduce any risks of contamination. The environmental monitoring includes (1) viable and total airborne particulates monitoring under dynamic conditions for all grades (with the exception of Grade (b) (4) where total airborne particulates are monitored under static conditions, (2) temperature, (3) relative humidity, and (4) pressure differentials of controlled classified environments.

All limits shown in Table 7 are site policy limits. Limits may be lowered as a result of trending, but limits are never raised above the policy limits. Alert limits are trended on an (b) (4) basis. Environmental monitoring frequency and sampling types for each classified room is managed per site and area procedures. The monitoring program includes established action and alert levels. In the event of an action limit excursion, an investigation is initiated.

When environmental monitoring action limits are exceeded in an aseptic processing area, the isolates are identified to a genus and species level, where possible. In other classified areas, representative colonies are identified when action limits are exceeded. Quality Operation Sterility Assurance – Contamination Control (QOSA-CC) is notified of the failure and a decision on further identification is documented. A notification is generated in the Event Reporting system for all exceeded action limits. QOSA-CC initiates an investigation in collaboration with Quality Control and the relevant production area(s).

Together with the continuous monitoring provided by a Facility Monitoring System (refer to Section 3 below for further details), controlled areas are routinely monitored as specified by process or area specific requirements. Room release is conducted before operations begin and is documented.

(b) (4)

Facility Monitoring System (FMS)

Description

The Facility Monitoring System (FMS) provides continuous monitoring of critical environmental conditions specific to classified and unclassified room temperature, relative humidity, and

differential pressure. The system monitors conditions via field sensors in the rooms which are connected to a dedicated (b) (4)) System. Should any monitored variables be detected outside of specified alarm limits, an alarm is communicated locally or remotely to user workstations in order to alert monitoring personnel. All critical, logged data by the system is automatically archived within the system on a (b) (4) basis. All data, real time and archived can be accessed for review via the operator interface. The monitoring and recording operations are conducted at a designated computer workstation located on Level (b) (4) floor).

The FMS system is a restricted access system using multi-level security access control using password protection. The security is based on configurable user groups with definable access privileges and individual user password definition. The system is also equipped with an audit trail feature. The audit trail records the operator identity, the nature of a modification, a date / time stamp, and the new value of the modified information. The audit trail is maintained by alarm and system event logs.