Summary Basis for Regulatory Action

Date: December 18, 2018

From: Rana Chattopadhyay, PhD, Chair of the Review Committee

***BLA*/ STN#:** 125563.0

Applicant Name: MCM Vaccine Co.

Original Submission Date: August 13, 2014
2nd Cycle Submission Date: June 29, 2018

Goal Date: December 29, 2018

Proprietary Name/ Established Name: VAXELIS

Indication: Active immunization to prevent diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B and invasive disease due to *Haemophilus influenzae* type b in infants and children 6 weeks through 4 years of age (prior to fifth birthday)

Recommended Action:
The Review Committee recommends approval of this product.

Review Office(s) Signatory Authority(ies):
Marion F. Gruber, PhD, Director, Office of Vaccines Research and Review

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Office of Compliance and Biologics Quality Signatory Authority:
Mary A. Malarkey, Director, Office of Compliance and Biologics Quality

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA

Document title	Reviewer name, Document date	
CMC Review(s)		
• *CMC (product office)*		
Drug Substance/Drug product (OVRR/DBPAP)	Michael Schmitt, PhD	06/19/2015
	Tod Merkel, PhD	06/25/2015 11/07/2018
	Wei Wang, PhD	10/23/2015
	Juan Arciniega, PhD	10/21/2015
	Leslie Wagner, BS	04/13/2015 11/05/2018
	Freyja Williams, BS	12/09/2014 09/11/2018 09/27/2018
	Mustafa Akkoyunlu, MD, PhD	04/13/2015
	Lisa Parsons, PhD	11/16/2018
Drug Substance/Drug product (OVRR/DVP)	Alla Kachko, PhD	09/24/2015
	Diana Kouiavskaia, PhD	10/20/2015 10/27/2015
	Dmitriy Volokhov, DVM, PhD	04/20/2015
	Marian Major, PhD	06/15/2015
	Dino Feigelstock, PhD	10/16/2015
	Sara Gagneten, PhD	10/23/2015
• *Facilities review (OCBQ/DMPQ)*	Nancy Waites	09/25/2014 04/16/2015
• *Establishment Inspection Report (OCBQ/DMPQ)*	None	
• *Inspection Waiver*	Wei Wang, Ph.D.	10/16/2018
Clinical Review(s)		
• *Clinical (product office)*	Ann Schwartz, MD	10/28/2015
• *Postmarketing safety epidemiological review (OBE/DE)*	Patricia Rohan, MD	03/10/2015
• *BIMO*	Erin McDowell	05/18/2015
Statistical Review(s)		
• *Clinical data*	Mridul Chowdhury, PhD	05/04/2015
• *Non-clinical data*		
o D-Antigen (b) (4)	Ye Yang	07/12/2018
Pharmacology/Toxicology Review(s)		
• *Toxicology (product office)*	Steven Kunder, PhD	04/08/2015

• *Developmental toxicology (product office)* • *Animal pharmacology*		
Clinical Pharmacology Review(s)	None	
Labeling Review(s) • *APLB (OCBQ/APLB)* • *Cartons and Containers*	Oluchi Elekwachi, PharmD, MPH Daphne Stewart	09/16/2014 06/11/2015 06/02/2015 12/07/2018
Other Review(s) • *Analytical methods and product testing (OCBQ/DBSQC)*	Marie Anderson, Ph.D. Alfred Del-Grosso, Ph.D. Hyesuk Kong, Ph.D.	11/07/2018 06/26/2015 10/01/2018 11/07/2018 06/24/2015 11/07/2018
Advisory Committee summary	No Advisory Committee Meeting	

1. Introduction

Sanofi Pasteur Inc. (henceforth referred to as Sanofi) and Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (henceforth referred to as Merck) established a partnership in 1992 to support the co-development and commercial manufacturing of a diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed, inactivated poliovirus, *Haemophilus influenzae* b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] vaccine (DTaP-IPV-Hib-HepB, V419). The name of the partnership is MCM Vaccine Company (henceforth referred to as MCM). Under this agreement, Merck is responsible for clinical matters. Sanofi Pasteur is the Applicant for the United States (U.S.) Biological License Application, on behalf of MCM as the U.S. Marketing Authorization License holder. The principal office of MCM is maintained at the Sanofi Pasteur US office located in Swiftwater, Pennsylvania.

During clinical development the investigational product, V419, was identified as PR5I. Initial clinical development of PR5I was not done under U.S. IND. Four Phase 1/2 clinical studies were conducted outside the U.S. and completed in 2008. End of Phase 2/pre-IND meetings to discuss the Phase 3 clinical studies and Chemistry, Manufacturing and Control issues were held with CBER during this period. The proposed Phase 3 clinical development plan included two pivotal studies to evaluate safety and immunogenicity of PR5I (V419-005 and V419-006) to be conducted in the U.S. under IND and two studies (V419-007 and V419-008) to be conducted in the European Union which would be supportive for safety. On September 21, 2010, Sanofi submitted an Investigational New Drug Application (IND), 14496, for conducting Phase 3 development of the PR5I vaccine in the U.S.

On August 13, 2014, MCM submitted a Biologics License Application (BLA) for PR5I to CBER, FDA which was assigned the STN 125563. The proprietary name of the vaccine at the time of the BLA submission was proposed as (b) (4) On February 14, 2018 Sanofi submitted a request to IND 14496 for withdrawing that proprietary name of the

vaccine and on February 16, 2018, submitted a Proprietary Name Review (PNR) request to the same IND for changing the name of the product from (b) (4) to VAXELIS. The rationale for the proposed proprietary name change request from (b) (4) to VAXELIS was supported by approval in the European Union (EU) of the vaccine (16 February 2016) under the tradename VAXELIS®. CBER provisionally accepted VAXELIS as the proprietary name of the vaccine on June 19, 2018. MCM submitted a PNR request to the BLA on August 27, 2018.

VAXELIS consists of diphtheria toxoid adsorbed, tetanus toxoid adsorbed, 5-component acellular pertussis adsorbed (comprised of pertussis toxoid adsorbed, filamentous hemagglutinin adsorbed, pertactin adsorbed, fimbriae types 2 and 3 adsorbed), inactivated Vero trivalent polio vaccine (vIPV), PRP-OMPC and HBsAg (Table 1).

Table 1: Composition of VAXELIS Drug Product

Component*	**Amount on a per unit basis (0.5 mL)**
Haemophilus b conjugate (PRP-OMPC)	3 µg PRP covalently bound to 50 µg of OMPC†
Hepatitis B Surface Antigen (HBsAg)	10 µg
Component Acellular Pertussis (aP) Adsorbed Antigens: -Pertussis Toxoid (PT) -Filamentous Hemagglutinin (FHA) -Pertactin (PRN) -Fimbriae types 2 and 3 (FIM)	 20 µg 20 µg 3 µg 5 µg
Diphtheria Toxoid Adsorbed (D)	15 Lf
Tetanus Toxoid Adsorbed (T)	5 Lf
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
Aluminum§	319 µg
Water for injection (WFI)	q.s. 0.5 mL

*(b) (4)

† In each dose of VAXELIS, Haemophilus b conjugate is comprised of 3 µg of PRP of *Haemophilus influenzae* type b covalently bound to 50 µg of OMPC from a *Neisseria meningitidis* serogroup B strain.

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

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

As per CBER guidance, two separate For Further Manufacturing Use (FFMU) BLAs were submitted by Merck, documenting the use of the bulk Intermediates of hepatitis B surface antigen (HBsAg, STN 125581) and *Haemophilus influenzae* type b conjugate (PRP-OMPC, STN 125580), used in final drug product manufacturing of VAXELIS and

providing Chemistry, Manufacturing and Control (CMC) information which is specific to those two antigens.

The PRP-OMPC bulk material (AAHS PRP-OMPC conjugate bulk) is an amorphous Aluminum Hydroxyphosphate Sulfate Adsorbed Polyribosylribitol Phosphate-Outer Membrane Protein Complex that is manufactured at the Merck's (b) (4) site and shipped to Sanofi Pasteur's Toronto, Ontario, Canada site for final VAXELIS drug product manufacturing.

Merck is the manufacturer of the recombinant (b) (4) HBsAg Bulk Alum Product (BAP, (b) (4) P/Al) at the Merck (b) (4) site which is shipped to Sanofi Pasteur's Toronto, Ontario, Canada site for final VAXELIS drug product manufacturing.

Acellular Pertussis adsorbed, diphtheria and tetanus toxoid adsorbed drug substances are manufactured at Sanofi Pasteur's Toronto, Ontario, Canada site.

The Inactivated Vero Trivalent Polio vaccine Bulk is manufactured at the Sanofi Pasteur (b) (4) facility located at (b) (4) and shipped to Sanofi Pasteur's Toronto, Ontario, Canada site for final VAXELIS drug product manufacturing.

The VAXELIS drug product is formulated, filled, labeled, packaged and tested for stability and quality control at Sanofi Pasteur Limited, 1755 Steeles Avenue West, Toronto, Ontario M2R 3T4, Canada.

VAXELIS is supplied as single-use vials of 0.5 mL volume. Table 1 above lists the components present in the final VAXELIS drug product.

The vaccine does not contain preservatives. The proposed shelf-life of the final container product is 48 months at 2° to 8°C from the date of the Final Bulk Product formulation.

The original PDUFA due date was August 12, 2015; however, this was extended to November 11, 2015 for a major amendment, submitted by MCM to the BLA on June 25, 2015. The major amendment resulted from of an extensive investigation into several Out-of-Specification (OOS) results for drug product during the stability monitoring program for (b) (4).

CBER issued a two-item CR letter on November 01, 2015, which contained comments on (1) OOS pertactin (PRN) potency assay data for multiple manufactured lots of VAXELIS and (2) proposed use of expired lot of PRP-OMPC as a reference standard.

The (b) (4) and PRN potency assay issues were further investigated by Sanofi utilizing their IND 14496. On May 25, 2017, Sanofi submitted an amendment to their IND 14496 which contained information about the investigations of the (b) (4) and PRN potency assays as well as Aluminum Phosphate (AlPO4) release test and questions regarding CBER agreement on submission of Quality Amendments to the BLA in order to address the CR letter.

On August 01, 2017, CBER responded to the questions included in the above-mentioned amendment, to IND 14496 and allowed MCM to submit a number of quality amendments to the BLA in order to resolve the issues mentioned in the CR letter.

MCM submitted a response to the CR letter on June 29, 2018 addressing both of the issues cited in the CR Letter. This submission initiated a new 6-month review clock with a Resubmission Action Due date of December 29, 2018.

2. Background

VAXELIS is a hexavalent vaccine developed for active immunization to prevent diseases caused by *Corynebacterium diphtheriae, Clostridium tetani, Bordetella pertussis*, poliovirus types 1, 2, and 3, *Haemophilus influenzae* type b, and hepatitis B virus. All components of the vaccine are currently licensed in the U.S. Table 2 below shows the relationship between VAXELIS and other related vaccines licensed in the U.S.

Table 2: Antigen composition of VAXELIS, Pentacel, Daptacel, PedvaxHIB, Recombivax and IPOL (per dose)

Antigens	VAXELIS	Pentacel[1]	Daptacel[2]	PedvaxHIB[3]	Recombivax[4]	IPOL[5]
PRP‡ conjugate	3µg (+ 50 µg OMPC*)	10µg (+ 24µg tetanus toxoid)	-	7.5µg (+ 125 µg OMPC)	-	-
Hepatitis B Surface Antigen (HBsAg)	10µg	-	-	-	5µg	-
Diphtheria toxoid	15 Lf	15 Lf	15 Lf	-	-	-
Tetanus toxoid	5 Lf	5 Lf	5 Lf	-	-	-
Pertussis toxoid	20µg	20µg	10µg	-	-	-
Filamentous hemagglutinin	20µg	20µg	5µg	-	-	-
Fimbriae 2 & 3	5µg	5µg	5µg	-	-	-
Pertactin	3µg	3µg	3µg	-	-	-
Poliovirus 1	29 DAU†	40 DAU§	-	-	-	40 DAU†
Poliovirus 2	7 DAU†	8 DAU§	-	-	-	8 DAU†
Poliovirus 3	26 DAU†	32 DAU§	-	-	-	32 DAU†
Aluminum Content	319µg	330µg	330µg	225µg	250µg	-

[1]Pentacel: DTaP-IPV, manufactured by Sanofi Pasteur Limited, licensed in the U.S.
[2]Daptacel: DTaP, manufactured by Sanofi Pasteur Limited, licensed in the U.S.
[3]PedvaxHIB: Haemophilus b conjugate vaccine, manufactured by Merck & Co., Inc., licensed in the U.S.
[4]Recombivax: Hepatitis B vaccine (recombinant), manufactured by Merck & Co., Inc., licensed in the U.S.
[5]IPOL: Poliovirus Vaccine Inactivated, Sanofi Pasteur S.A., licensed in the U.S.
‡ PRP: Polyribosylribitol phosphate of *Haemophilus influenza* type b
* OMPC: Outer membrane protein complex of *Neisseria meningitidis* serogroup B
† Poliovirus propagated on Vero cells (DAU: Poliovirus D-Antigen Unit)
§ Poliovirus propagated on MRC-5 cells

The applicant has requested licensure for administration of VAXELIS to infants and children 6 weeks through 4 years of age (up to the fifth birthday). VAXELIS is administered intramuscularly (IM) as a three-dose (0.5 mL each) series at 2, 4, and 6 months of age.

Three doses of VAXELIS constitute a primary immunization course against diphtheria, tetanus, *Haemophilus influenzae* type b invasive disease, and poliomyelitis and a complete immunization series against hepatitis B. The primary immunization course for the pertussis component of VAXELIS is four doses which should be completed with a fourth dose of a vaccine containing the same pertussis antigens manufactured by the same process (i.e., DAPTACEL or Pentacel). Although a serologic correlate of protection for pertussis has not been established, the antibody responses to pertussis antigens in North American infants after 4 doses of DAPTACEL given at 2, 4, 6 and 15-20 months of age were shown to be comparable to those achieved in Swedish infants in whom efficacy was demonstrated after 3 doses of DAPTACEL given at 2, 4 and 6 months of age (Ref: Section 14.3, Prescribing Information, DAPTACEL, Sanofi Pasteur Limited).

3. CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

The review of CMC information submitted in the original BLA resulted in a number of Information Requests to the Applicant in 2014-2015. Due to unresolved issues, a CR letter was issued on November 01, 2015. These issues were resolved through a number of Quality Amendments submitted to IND 14496 and BLA during 2017-2018, with a final response to the CR letter submitted to the BLA on June 29, 2018. After reviewing all the information, CBER concluded that no CMC issues precluded approval of this BLA.

a) Product Quality

A. Drug Substances (DS):

(b) (4)

7 Pages Determined to be Not-Releasable: (b)(4)

(b) (4)

B. Drug Product (DP):

Formulation of VAXELIS Final Bulk Product

The VAXELIS formulation process begins with the formulation of the (b) (4)

(b) (4)

Differences in the formulation of the drug product between VAXELIS and Pentacel®:

- (b) (4)

Filling

The Bulk Product is transferred to the filling area and (b) (4) . The Bulk Product is (b) (4) during filling. It 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. The inspected unlabeled vials are stored at (b) (4) until released for labeling and secondary packaging. 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.

Stability of the DP and Proposed Shelf-life

On November 20, 2018, MCM submitted an amendment to the BLA which included information on several stability studies performed on (b) (4) DP lots ((b) (4) (b) (4) DP shelf-life were (b) (4) 2.0-mL single-dose (b) (4) glass vial, (b) (4) stopper and 13 mm aluminum seal with plastic flip-off cap, respectively at 2°C to 8°C. A stability study was conducted on an additional VAXELIS (b) (4)

In addition, accelerated stability studies were also performed (b) (4)

An accelerated (b) (4) .

(b) (4)

In addition, a routine stability study is being performed on (b) (4) VAXELIS vial lots ((b) (4)) stored 2°C to 8°C until expiry to support the 2017 routine stability study in the vial presentation.

Results from the studies described above support the stability of VAXELIS 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 48 months at 2°C to 8°C. The shelf-life of VAXELIS Vaccine is 48 months from the date of Final Bulk Product formulation (b) (4) Finished Product does not exceed 42 months).

The company agreed to place (b) (4) commercial scale lots of VAXELIS per year on the stability program, for at least three years. After data are accrued and reviewed for those (b) (lots, the results will be evaluated by CBER and a decision to test only one lot per year on the stability program may be made in consultation between CBER and the Applicant.

The samples for this stability program will be tested at time points 0, 12, 24 and 36 and 48 months (from the date of formulation) while stored at 2°C to 8°C.

Release Testing

The analytical methods and their validations and/or qualifications reviewed for the VAXELIS vaccine drug product were found to be adequate for their intended use. Table 3 below shows the Release Specifications for VAXELIS (b) (4) Product and Shelf-life Specifications for VAXELIS Final Filled Product.

Table 3: Release Specifications for VAXELIS (b) (4) Product and Shelf-life Specifications for VAXELIS Drug Product

Test	Method Reference	Release Acceptance Criteria (b) (4)	Shelf-life Acceptance Criteria (Filled Product) #
Sterility	(b) (4)	(b) (4)	Same as Release
(b) (4)			Same as Release
Aluminum Content*			NA†
Formaldehyde	In-house		NA
(b) (4)	In-house		NA
	In-house		(b) (4)

(b) (4)	In-house	(b) (4)	(b) (4)
	In-house		Same as Release
HBsAg IVRP‡**	In-house		(b) (4)
PRP Content**	In-house		Same as Release
IPV Immunogenicity (Rat)	(b) (4)		Same as Release
			Same as Release
			Same as Release
D-antigen Content§	In-house		Same as Release
			Same as Release
			Same as Release
Acellular Pertussis Immunogenicity (Mouse)	In-house		Same as Release
(b) (4)	In-house		(b) (4)
Specific Toxicity*	(b) (4) USPHS		Same as Release
Diphtheria potency	USPHS		Same as Release
Tetanus Potency	USPHS		Same as Release

* Test site changed from Sanofi Pasteur Inc. to Sanofi Pasteur Ltd.
** Test site changed from Merck to Sanofi Pasteur Ltd.
# VAXELIS Filled Product stability indicating acceptance criteria
† NA – Not Applicable
‡ HBsAg IVRP - *In Vitro* Relative Potency
§ vIPV D-antigen Units (DU) are calculated using the (b) (4) test method

Adventitious Agents Safety Evaluation for the DP: No risk identified.

Exemption from the General Safety Test (GST): In the original BLA submission of 2014 MCM included results of a modified GST on (b) (4) VAXELIS lots and requested an exemption for the General Safety Test according to the Federal Register Volume 68, Number 42 (04 March 2003) and the final ruling in the Code of Federal Regulations (CFR) Title 21 Part 610.11 paragraph (g)(2) for all future lots of VAXELIS. CBER concurred.

Extractables and Leachables: No risk identified.

Analytical Procedures

The BLA includes the procedures for all analytical methods and related changes used for testing of the drug product. Most of these methods and changes were found to be adequate either in the BLA or in the responses to several CBER IRs to MCM regarding analytical validations during the review of the BLA.

(b) (4) ***HBsAg on the alum adjuvant*** in the VAXELIS (b) (4) Product is determined using a (b) (4) Assay ((b) (4) The assay for the (b) (4) of Hepatitis B is performed on the HBsAg (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) and may be performed on the Labelled Filled Product. The assay is validated for specificity, accuracy, linearity, intermediate precision, repeatability, range, limit of quantitation, and reproducibility at Merck. Reproducibility was tested in a supplemental validation during the transfer to Sanofi Pasteur Limited.

In Vitro Relative Potency (IVRP) of HBsAg in (b) (4) product is determined using a (b) (4) by measuring (b) (4) The assay was validated for specificity, accuracy, linearity, precision (repeatability and intermediate precision), reproducibility, and range by Merck and then transferred to Sanofi Pasteur where supplemental validation of minor changes pertains to pipetting and data analysis was done and the equivalence of the results from both calculation methods was established.

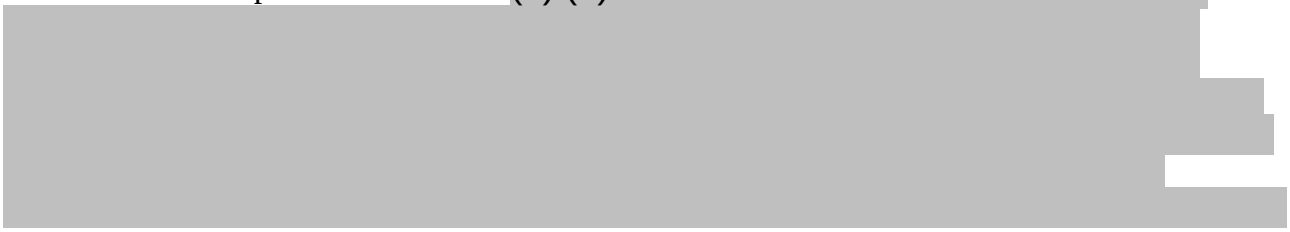
(b) (4) is used to detect the presence of HBsAg and PRP-OMPC (b) (4) in VAXELIS labelled filled product. These two components are present in VAXELIS and absent in other products manufactured at Sanofi Pasteur. This identity test is developed, validated and performed at Sanofi and is used to verify that VAXELIS labeled filled product manufactured at Sanofi Pasteur Limited has been labeled correctly.

The (b) (4) ***Test*** is used as a safety test to detect any (b) (4) in final bulks of VAXELIS.

(b) (4)

(b) (4)

Acellular Pertussis Mouse Immunogenicity Assay [Pertactin (PRN) Potency Assay] is used to confirm that each commercial lot of VAXELIS induces antibody responses in mice to each of the pertussis antigens, consistent with the responses induced by the lots used in the pivotal Phase 3 clinical studies. The proposed acceptance specifications for the Acellular Pertussis Mouse Immunogenicity Assay for VAXELIS were based on the acceptance criteria for (b) (4)



(b) (4)

During a communication between MCM and CBER in 2015, MCM revealed that several of VAXELIS (b) (4) , finished product and commercial lots failed PRN potency assay both at release and Stability time points. MCM could not confirm the root cause for these OOS results which prompted CBER to issue a Complete Response (CR) Letter on November 01, 2015.

On June 29, 2018, in response to the CR Letter comment, MCM provided information supporting the age and weight of the mice used in the Acellular Pertussis Mouse Immunogenicity Assay as the cause for the out of specification (OOS) results observed for the pertactin antigen in VAXELIS. In addition, they referenced STN# 125145/483 +1, the prior approval supplement that requested an increase in the age and weight of the mice to be used in the assay when testing Quadracel and Pentacel. The criteria proposed in STN# 125145/483 +1 will be adopted for the release testing of VAXELIS. The response was adequate. The data provided and cross referenced indicated that the OOS results for the pertactin potency were likely due to the use of immature mice. The implementation of the proposed criteria of (b) (4) for the potency test is appropriate. The data support approval of the product using the proposed criteria for the age and weight of the mice, and the release and stability limits currently applied to the pertussis components of Quadracel.

D-Antigen Potency Tests based on the Rat Potency Test (for stability) and D-Antigen (b) (4) (for quantitation) have been used for release of vaccines containing IPV which are licensed in the U.S. Differences between the D-Antigen (b) (4) for VAXELIS and other IPV Trivalent Concentrate-containing U.S. licensed vaccines are shown in Table 4 below.

Table 4: Differences in D-Antigen (b) (4) between VAXELIS and IPOL

(b) (4)

(b) (4)

(b) (4)

(b) (4)

CBER requested that MCM provide additional support demonstrating that (b) (4) antigen units/dose for types 1, 2, and 3, respectively in VAXELIS are as immunogenic as the currently licensed vaccines containing IPV. In response, MCM provided clinical data to support the conclusion that immunogenicity of VAXELIS is non-inferior to the currently licensed component vaccine controls for IPV. It also stated that the D-antigen content targets used for DTaP-IPV (manufactured with MRC-5 IPV) and VAXELIS (manufactured with Vero IPV) are different, due to the different D-Antigen (b) (4) methods and reference standards used to formulate and test the two types of Inactivated Poliovirus (IPV) Trivalent Concentrates (see Table 5). As such, it is not expected that the two products have the same IPV content. Importantly, both products have been shown to be immunogenic in the same clinical studies as discussed in Section 1.1 and thus the different acceptance criteria based on these different methods are justified. (b) (4)

In the original BLA, the acceptance criterion for the **Formaldehyde Content Test** (b) (4)) was based on the (b) (4) . CBER requested MCM to establish a specification reflective of the capacity of the manufacturing process to remove formaldehyde and report the actual results of the test in the certificates of analysis

and lot release protocols for (b) (4) Product lots. CBER further instructed MCM to modify this test method and validation to serve the purpose of a quantitative procedure. In response, MCM submitted to the BLA updated release specification for VAXELIS Labeled Filled Product, a summary of the revised quantitative procedure for formaldehyde, a summary of the method validation, a justification for a revised formaldehyde specification and a representative Certificate of Analysis for the (b) (4) Formaldehyde, (b) (4) used as a standard. The modification of the test for residual formaldehyde in the VAXELIS (b) (4) to a quantitative procedure is acceptable along with the revised formaldehyde specification of (b) (4) .

b) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of VAXELIS are listed in the table below. The activities performed and inspectional histories are noted in Table 5.

Table 5: Manufacturing Facilities for VAXELIS

Name / Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification/ Results
Drug Substance Manufacturing (Diphtheria Toxoid Adsorbed, 5-Component Acellular Pertussis Adsorbed, and Tetanus Toxoid Adsorbed). *Final Bulk Product Formulation.* *Filling and Packaging.* *Quality Control and Stability Testing* Sanofi Pasteur Limited 1755 Steeles Avenue West Toronto, ON, Canada	3002888623	208206623	Waived	Team Biologics 09/06/2017 – 09/22/2017 VAI
Drug Substance Manufacturing (Inactivated Vero Trivalent Polio vaccine Bulk). *Final Bulk Product Formulation.* *Quality Control and Stability Testing.* Sanofi Pasteur (b) (4)	(b) (4)	(b) (4)	Waived	Team Biologics (b) (4) VAI

Drug Substance Manufacturing (Amorphous Aluminum Hydroxyphosphate Sulfate Adsorbed Polyribosylribitol Phosphate - Outer Membrane Protein Complex (AAHS PRP-OMPC) Conjugate Bulk intermediate and Hepatitis B Surface Antigen Bulk Intermediate) Merck Sharp & Dohme Corp. (b) (4)	(b) (4)	(b) (4)	Waived	ORA (b) (4) VAI

CBER waived the pre-license inspections based on the following Team Biologics and ORA surveillance inspections of the manufacturing facilities involved with the manufacture of VAXELIS.

Team Biologics performed a surveillance inspection of Sanofi Pasteur Limited in Toronto, Canada from September 06 - 22, 2017. All 483 issues were resolved and the inspection was classified as voluntary action indicated (VAI).

Team Biologics performed a surveillance inspection of Sanofi Pasteur (b) (4) in (b) (4) from (b) (4) All 483 issues were resolved and the inspection was classified as VAI.

ORA performed a surveillance inspection of the Merck Sharp & Dohme Corp. facility in (b) (4) from (b) (4) . All 483 issues were resolved and the inspection was classified as VAI.

Container/Closure System:
The drug product is filled into the 2.0-mL single-dose (b) (4) borosilicate clear glass vial (b) (4)) with bromobutyl rubber (not made with natural rubber latex) 13 mm stopper ((b) (4)), aluminum seal (b) (4) , and plastic flip-off cap. Each vial contains a single (≥0.5-mL extractable volume) dose of VAXELIS Suspension. Sanofi Pasture Limited conducted the container closure integrity testing at the Toronto, Canada facility, employing the (b) (4) method; all acceptance criteria were met.

d) Environmental Assessment

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

e) Product Comparability

Not Applicable

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

A single dose toxicology study was conducted under Good Laboratory Practice in (b) (4) rats to confirm the safety profile of D, T, aP, IPV, Hib, and Hepatitis B antigens when combined in VAXELIS and was focused on local tolerance. Repeat-dose Toxicity, Genotoxicity, Carcinogenicity, Reproductive and Developmental toxicity studies are not performed for VAXELIS as there is a large amount of pre- and post-licensure data available that show that the component licensed vaccines of VAXELIS are well tolerated in humans.

Single-dose Toxicity Study

A total of 20 male and 20 female (b) (4) rats each were administered VAXELIS or saline for injection. A dose that matched or exceeded the full human dose (HD) and the human dose volume (0.5 mL) was given to the animals to support the single dose Phase I clinical schedule. VAXELIS was administered at 2 injection sites (left and right thigh muscle), 0.25 mL per injection site. After injection, the animals were maintained for a 1- or 14-day period to evaluate the recovery of any findings.

This study showed that IM injection of VAXELIS was well tolerated. Some minor changes were observed which were transient and of low toxicological significance, including: transient effects on female body weight and slightly higher neutrophil levels associated with slightly lower lymphocyte count, when compared to concurrent controls. These changes were all reversible within 2 weeks. At the injection sites, an expected foreign body reaction (in the form of an inflammatory reaction) was noted only at the histological level. This finding is typical of a vaccine-induced immune response (stimulation of the immune system) especially with multi-component vaccines adjuvanted with aluminum. Despite showing evidence of recovery after 14 days, local changes persisted. This is consistent with nonclinical and clinical data indicating that local changes induced by aluminum adjuvanted vaccines may persist for several months. In summary, the nonclinical safety profile of VAXELIS was similar to that expected with similar multi-component vaccines including an aluminum-based adjuvant.

All VAXELIS residuals, preservatives, excipients, and adjuvants resulting from and/or used in the VAXELIS manufacturing process have been qualified in Sanofi Pasteur's and Merck's licensed vaccines and as such, they are not expected to pose a risk to human safety.

5. CLINICAL PHARMACOLOGY

No clinical pharmacology or pharmacokinetic studies were performed in the clinical development program for VAXELIS vaccine. No studies were performed on special populations.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

Overview of Clinical Trials-Immunogenicity

The Phase 1/2 clinical development program for VAXELIS consisted of 4 clinical studies conducted from 2000 to 2006. These studies, involving more than 2,000 subjects, were conducted under approved Canadian Health Authority applications (file #'s 9427-A1564-31C and 9427-S2754\2-21C) following procedures that are in alignment with U.S. Food and Drug Administration (FDA) Investigational New Drug (IND) requirements. The early clinical development program supported the initiation of the Phase 3 program.

The Phase 3 clinical development program included four pivotal immunogenicity and safety studies conducted in the U.S. and EU. Two of these studies, V419-005 (Protocol 005) and V419-006 (Protocol 006), were conducted in the U.S. and served as the basis for licensure (Table 6). This approach to licensure was in alignment with the guidance provided at the End of Phase 2 Clinical Meeting with the CBER on January 25, 2008. Two other Phase 3 studies (Protocol 007 and Protocol 008) were conducted in several countries in the EU (Belgium, Finland, Germany, Italy and Sweden) and were designed to evaluate immunization schedules that are utilized in those areas. The immunogenicity data from these trials were not integrated with the U.S. studies due to differences in study design, including vaccination schedules, but listings of serious adverse events occurring in these studies were provided in the BLA. Additionally, two supportive immunogenicity and safety studies were conducted with VAXELIS in the United Kingdom (UK) and Spain (i.e., PRI01C and PRI02C, respectively) to evaluate the use of VAXELIS in those country-specific immunization schedules, including co-administration with meningococcal C vaccine. A summary of the study design and objectives for all studies conducted with VAXELIS was included in the BLA.

Immunogenicity of VAXELIS was evaluated in the Phase 3 studies, 005, and 006, described previously, that served the basis for licensure. Immunogenicity analyses were based on a per-protocol (PP) approach, excluding subjects based on certain pre-specified criteria. Two PP populations, PP-Revised Windows (PP-RW) and PP-Original Windows (PP-OW), were used in both studies. The PP-RW population allowed for more subjects to be included in the statistical analyses by extending the windows for blood draws. As pre-specified and in agreement with CBER, the success of the primary endpoints for the pivotal studies was based on the results from the PP-RW population.

For study V419-005, in infants who received 3 doses of VAXELIS at 2, 4, and 6 months (concomitantly with Prevnar 13 and RotaTeq) followed by DAPTACEL and PedvaxHIB at 15 months of age, the immune responses following three doses of VAXELIS were non-inferior to those of the control vaccine (see Table 6 for details), except for the Geometric Mean Titer (GMT) of the pertussis antigen FHA at one month post-dose 3, which missed the non-inferiority criterion marginally. Following the fourth dose of a DTaP vaccine, the pertussis responses of infants who had received three doses of VAXELIS were non-inferior to those who had received the control vaccine. The IPV response rate was 100% following the 3 dose infant series of VAXELIS.

The immunogenicity findings in study V419-006 (lot consistency study) were similar to those seen in V419-005 in terms of the prespecified success criteria for non-inferiority.

Lot consistency was demonstrated with respect to GMTs and response rates for all antigens contained in VAXELIS. As seen in V419-005, the immune responses following three doses of VAXELIS were non-inferior to those of the control vaccine (see table 6 for details) except for the GMT of the pertussis antigen FHA at one month post-dose 3. Due to acceptable immunogenicity against multiple pertussis antigens elicited by the VAXELIS vaccination series that begins with an infant series, and the non-inferiority demonstrated for FHA responses after the Toddler dose, the missed FHA GMT endpoint at Post-dose 3 is considered of limited clinical significance. After the Toddler dose, the pertussis responses and GMTs in subjects who received a 3-dose infant series of VAXELIS were comparable to subjects who received an infant series of a licensed control vaccine, except for the GMT for PRN antigen. In study 006, the post-toddler PRN GMT ratio [0.74 (95% CI: **0.66**, 0.83)] marginally missed the prespecified non-inferiority criterion [lower limit of the 2-sided 95% CI of the GMT ratio (VAXELIS group/Control group) > 0.67]. However, integrated results across studies 005 and 006 [GMT ratio 0.76 (95% CI: **0.70**, 0.83), met non-inferiority criteria prespecified for the individual studies. Since infant/toddler vaccination against pertussis requires 4 doses, the results from the 2 pivotal US studies, taken together, support the use of an infant series of VAXELIS within the pertussis vaccination series.

An evaluation of immune responses following concomitant vaccination of VAXELIS with Prevnar 13 demonstrated immune responses that were non-inferior to those seen when Prevnar 13 was given concomitantly with the control vaccines for 12 out of the 13 antigens, with the GMT for serotype 6B included in Prevnar 13, falling outside the pre-specified immunogenicity criterion. The immune responses demonstrated to RotaTeq (concomitant vaccine) were comparable between the control vaccine and VAXELIS cohorts.

Table 6: Pivotal Phase 3 study protocols for VAXELIS vaccine in the U.S.

	V419-005/Phase 3	**V419-006/Phase 3**
Study Design and Treatment Duration	Open-label, multicenter, randomized, active-comparator controlled Phase 3 study to evaluate the safety, tolerability and immunogenicity of VAXELIS All subjects were to receive a dose of monovalent hepatitis B vaccine at birth (outside of the context of the study). Subjects in the VAXELIS group received a 0.5 mL dose of VAXELIS at 2, 4, and 6 months followed by DAPTACEL™ and PedvaxHIB™ at 15 months. Subjects in the Control group received a 0.5 mL dose of PENTACEL™ at 2, 4, and 6 months and a 0.5 mL dose of RECOMBIVAX HB™ at 2 and 6 months followed by DAPTACEL™ and ActHIB™ at 15 months.	Partially double-blind, multicenter, randomized, active-comparator controlled, lot-to-lot consistency Phase 3 study to evaluate the safety, tolerability and immunogenicity of VAXELIS. All subjects were to receive a dose of monovalent hepatitis B vaccine at birth (outside of the context of the study). Subjects in each of the VAXELIS groups received a 0.5-mL dose of VAXELIS (3 different lots to assess lot consistency) at 2, 4, and 6 months and a 0.5-mL dose of PENTACEL™ at 15 months. Subjects in the Control group received a 0.5-mL dose of PENTACEL™ at 2, 4, 6, and 15 months and a 0.5-mL dose of RECOMBIVAX HB™ at 2 and 6 months.

	Subjects in both groups received the same concomitant vaccines (RotaTeq™ and Prevnar 13™). Blood samples, for serologic evaluation, were collected at 4 time points (i.e. pre-dose 1, ~4 to 6 weeks post-dose 3, pre-toddler dose, and ~4 to 6 weeks post-toddler dose).	Subjects in both groups received the same concomitant vaccines (RotaTeq™ and Prevnar 13™). Blood samples, for serologic evaluation, were collected at 4 time points (i.e. pre-dose 1, ~4 to 6 weeks post-dose 3, pre-toddler dose, and ~4 to 6 weeks post-toddler dose).
Primary Objectives	1) To compare the immunogenicity of VAXELIS with the component vaccine control(s). (2) To compare the immunogenicity of pertussis antigens at one month after the Toddler dose of DAPTACEL after receiving an infant series of either 3 doses of VAXELIS or PENTACEL (3) To demonstrate that the IPV response rate is acceptable after receiving an infant series of 3 doses of VAXELIS.	To evaluate the consistency of the Post-dose 3 immune response to 3 manufactured lots of VAXELIS when given at 2, 4, and 6 months of age with respect to geometric mean titers.
Vaccination Groups and Numbers of Subjects Vaccinated	Randomized: 1473 VAXELIS: 986 Control: 487 Vaccinated: 1465 VAXELIS: 981 Control: 484	Randomized: 2808 VAXELIS: 2406 Control: 402 Vaccinated: 2800 VAXELIS: 2399 Control: 401
Subject Gender, Number of Subjects, Mean Age, and Age Range	Male: 780 Female: 693 Mean age (days): 65.4 Age range (days): 46 to 89	Male: 1470 Female: 1338 Mean age (days): 64.5 Age range (days): 46 to 89

Serology

The validation reports and other additional data submitted in the BLA and cross-referenced INDs were sufficient to support the adequate performance of the (b) (4) to quantitate antibody against the tetanus antigen and the (b) (4) to quantitate antibody against the diphtheria antigen. No aberrant or unusual data were noted in the clinical study reports that would indicate any performance issues with the assays.

The (b) (4) used to quantitate antibodies against Hib was originally validated by Merck in 1997 and transferred to the Wayne, PA facility in 2002. In 2008, Merck sold the (b) (4) thus the assay location has remained unchanged since 2002.This BLA, 125563/0, cross referenced IND 4011 for the validation, assay transfer and assay stability data. Assay stability data submitted to IND 4011 (control and reference data through 2013) and continued control of Hib disease in this country indicate no major issues with the assay. The assay is likely adequate for use to support the studies under this BLA. No aberrant or unusual data were noted in the clinical study reports that would indicate any performance issues with the assays.

Validation reports, SOPs and assay stability reports were cross referenced from IND 14668 in support of the data generated by these assays in the Phase 3 studies and support the

performance of the (b) (4) to quantitate antibody against the pertussis antigens (PT, FHA, PRN, FIM) in the vaccines. No aberrant or unusual data were noted in the clinical study reports that would indicate any performance issues with the assays.

Serum IgG antibody responses against pneumococcal vaccines were measured in protocols 004 and 006, where pneumococcal vaccines Prevnar® (protocol 004, non-U.S. study) or Prevnar13® (protocol 006) were administered concomitantly with VAXELIS. In protocol 004, (b) (4) were used to measure anti-PnPS antibody levels. In protocol 006, a newly developed pneumococcal antibody detection assay, (b) (4) was used to measure antibody responses against the concomitantly administered Prevnar13® vaccine. The (b) (4) assay SOPs, validation data and assay stability data from the testing period indicated that the assay performance was satisfactory.

The purpose of the hepatitis B (b) (4) assay is to detect total antibody to human plasma-derived hepatitis B surface antigen ([HBsAg] subtypes ad and ay before and after vaccination with HBsAg containing vaccines. The assay may also be used at study entry to determine if a subject or potential subject was previously infected with hepatitis B virus or had been vaccinated in the past with a HBsAg-containing vaccine. The Hep B (b) (4) assay is acceptable for testing anti-HBs levels in human serum samples from subjects immunized with VAXELIS.

The assays used to evaluate the immune response to anti-rotavirus vaccines when administered concomitantly with the VAXELIS vaccine were previously used to evaluate the response to RotaTeq vaccine in clinical trials. Validation documents for both assays were previously submitted in the BLA for RotaTeq (BLA #125122). Both serum anti-rotavirus IgA (b) (4)) and rotavirus serum neutralizing antibody (SNA) (b) (4) ((b) (4) are adequate to evaluate the immunogenicity of rotavirus vaccines when administered concomitantly with VAXELIS.

Anti-poliovirus types 1, 2, and 3 titers were measured by the (b) (4) Assay. Assays were conducted at the Sanofi Pasteur Inc. GCI platform in Swiftwater, PA. Validation reports, SOP and assay stability reports for this (b) (4) assay were previously reviewed under INDs 14668 (Quadracel vaccine) and 14496 (PR5I vaccine) in support of the data generated by this assay in the Phase 3 studies for both vaccines. The data supporting the performance of the (b) (4) serologic assay used to quantitate antibodies against polioviruses types 1, 2, and 3 during the Phase 3 clinical studies are sufficient and indicate that the assay performs adequately for its intended use.

Bioresearch Monitoring Review

Bioresearch Monitoring (BIMO) inspections were conducted at six clinical sites that participated in the conduct of Study V419-005 or V419-006. The inspections did not reveal any issues that impact the data submitted in this application.

Pharmacovigilance Review

When the initial BLA was submitted on August 13, 2014, VAXELIS was not licensed in the U.S. or any other country. Therefore, no epidemiological safety study data for VAXELIS were available. In February 2016, VAXELIS was licensed in EU and is currently registered and approved in 31 countries. After MCM responded on June 29, 2018 to the CR letter, dated November 01, 2015, an Information Request was issued to MCM on October 12, 2018, to submit the most recent Periodic Benefit-Risk Evaluation Report (PBRER) to the BLA. In response, MCM submitted the latest Periodic Safety Update Reports (PSUR) to the BLA on October 19, 2018, for Reporting Interval February 16, 2018, to August 15, 2018. During the indicated period, VAXELIS was marketed in Germany, France, the Netherlands and in multiple regions of Spain and Italy. Post-marketing patient exposure was calculated from internal distribution data for the period from February 01, 2018, to July 31, 2018. During the reporting interval of this PSUR, the estimated number of marketed VAXELIS doses distributed between 16-Feb-2018 to 15-Aug-2018 was approximately (b) (4) . Approximately 198,919 to (b) (4) individuals are estimated to have been vaccinated, based on the assumption that each individual received 1, 2 or 3 dose(s).

Cumulatively, since non-U.S. market introduction (February 15, 2016) to August 15, 2018, the estimated number of marketed VAXELIS doses distributed worldwide was (b) (4) . Approximately 319,518 to (b) (4) individuals are estimated to have been vaccinated, based on the assumptions that each received 1 to 4 doses and that all distributed doses were administered. There are no records of any registration being revoked or withdrawn for safety reasons. During the reporting period of this PSUR, no regulatory or manufacturer actions, changes to the Company Core Safety Information (CCSI) or update to the Investigator's Brochure (IB) related to VAXELIS due to safety reasons have been reported.

b) Pediatrics

Determinations regarding VAXELIS with respect to the Pediatric Research Equity Act considered the availability of currently licensed vaccines which provide protection against diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b and hepatitis B. VAXELIS, as a vaccine that contains antigens already licensed in the U.S., if approved, could reduce the number of injections required at some infant visits, which may increase compliance. Safety was evaluated following vaccinations at 2, 4, and 6 months of age in the pivotal studies, with additional supportive safety data from two other studies where VAXELIS vaccine was administered at 15 months of age. Safety and immunogenicity data would be extrapolated for infants and toddlers >15 months through 4 years of age. The Applicant requested, for this pediatric vaccine, partial waivers for the age groups of infants less than 6 weeks of age and children and adolescents 5 to 17 years of age. The request was reviewed by CBER under IND 14496 as a proposed initial Pediatric Study Plan. The request for partial waivers was granted under the BLA per Section 505B(a)(4)(B)(iii). The Pediatric Review Committee concurred with CBER's evaluation of the pediatric issues.

c) Other Special Populations

VAXELIS vaccine has not been studied in any special population other than the pediatric populations as mentioned above.

7. SAFETY

The safety evaluation for VAXELIS was based upon the two Phase 3 studies conducted in the U.S. under Protocols V419-005 and V419-006, as described above in Table 7, with supplementary safety data from two additional Phase 2 studies, V419-003 and V419-004, conducted in Canada, for the evaluation of Serious Adverse Events (SAEs). V419-005 and V419-006 studies enrolled a total of 4265 subjects (3380 received VAXELIS and 885 received control vaccines). Studies V419-003 and V419-004 enrolled a total of 495 subjects who received the vaccine and 339 subjects who received control vaccines. In the phase 3 studies, V419-005 and V419-006, no clinically important imbalances for local solicited adverse events (AEs) (i.e., pain/tenderness, erythema, and swelling) or systemic AEs (i.e., crying, decreased appetite, irritability, pyrexia, somnolence and vomiting) were identified between groups for days 1-5 after each vaccination. However, in the combined Phase 3 studies, rates of fever (defined as ≥38◦C) were increased for VAXELIS (47.2%) as compared to the Control vaccines (33.6%); [difference 13.6% (95%CI: 9.7, 17.3)].

The most frequent SAE reported in both studies in the 30 days following any vaccination was respiratory syncytial virus-mediated bronchiolitis. The majority of SAEs that occurred during this time period in both studies were due to conditions commonly found in this age group, including gastroenteritis/dehydration, GERD, respiratory tract and other infections. AEs leading to study vaccine discontinuation were reported by 8 subjects (0.2%) in the VAXELIS group and 1 subject (0.1%) in the control group. Death, was reported for 6 subjects (0.2%) in the VAXELIS group and 1 subject (0.1%) in the control group, all of which were considered unrelated to study vaccination.

8. ADVISORY COMMITTEE MEETING

An Advisory Committee Meeting for VAXELIS vaccine was not held, because there were no issues pertaining to this BLA that required input from the Vaccines and Related Biological Products Advisory Committee.

9. OTHER RELEVANT REGULATORY ISSUES

None

10. LABELING

The Agency found the applicant's changed proprietary name, VAXELIS (formerly (b) (4) acceptable. This change harmonized the product's name in both US and the European Union. Appropriate sections of the revised PI and package/container labels were reviewed for accuracy by clinical, statistical, product, and pharmacovigilance reviewers. Recommendations for revisions were collectively provided to the applicant.

The APLB found the prescribing information and package/container labels to be acceptable from a promotional and comprehension perspective. All issues with the PI were acceptably resolved after exchange of information and discussions with the applicant. Issues identified with the package and container labeling were acceptably resolved.

The applicant submitted revised versions of all reviewed labeling in agreement with CBER recommendations.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

Based on the review of the clinical, pre-clinical, and product-related data submitted in the BLA, the Review Committee recommends approval of the VAXELIS vaccine for the proposed indication and usage.

b) Risk/ Benefit Assessment

Considering the data submitted to support the safety and efficacy of the VAXELIS vaccine that have been presented and discussed in this document, the Review Committee is in agreement that the risk/benefit profile for VAXELIS is favorable and supports approval in infants and children 6 week through 4 years of age (before 5th birthday).

c) Recommendation for Post-Marketing Activities

The review committee recommends routine pharmacovigilance with enhanced pharmacovigilance for any newly identified or potential safety issues, as proposed by the sponsor.