

CBER DMPQ CMC BLA Review Memorandum

BLA STN 125741/0

**Vaxneuvance [Pneumococcal 15-valent Conjugate Vaccine [CRM197 Protein],
(b) (4)]**

Gregory Price/Biologist/DMPQ



U.S. FOOD & DRUG
ADMINISTRATION

1. BLA#: STN 125741/0

2. APPLICANT NAME AND LICENSE NUMBER

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc., License #0002

3. PRODUCT NAME/PRODUCT TYPE

Vaxneuvance/ Pneumococcal 15-valent Conjugate Vaccine [CRM197 Protein],

(b) (4)

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

a. Pharmacological category

Vaccine

b. Dosage form

Suspension for Injection

c. Strength/Potency

Vaxneuvance is a sterile opalescent liquid suspension for injection. The DP provides a total of (b) (4) of total Pneumococcal Polysaccharide (PnPs) Antigens conjugated to CRM197 (b) (4) 30 µg) as 15 serotype-specific (Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) Monovalent Bulk Conjugate (MBC) bulk drug substances (b) (4)

d. Route of administration

Intramuscular injection

e. Indication(s)

Prevention of Pneumococcal Disease (Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F)

5. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
10/21/2020	STN 125741/0	Original submission. Reviewed (Rolling Submission; Drug Substance and Appendices)
11/17/2020	STN 125741/0.1	Second half of rolling submission (Drug Product and Regional Information). Reviewed
1/25/2021	STN 125741/0.4 (response to IR # 1)	Clarification regarding equipment licensing status and equipment inquiries.
1/27/2021	STN 125741/0.6	Corrected QIA from amendment 0.4.
3/4/2021	STN 125741/0.17	Records Request (b) (4) documents

**CBER/DMPQ CMC BLA Review Memo BLA 125741/0-Pneumococcal 15-valent Conjugate Vaccine
[CRM197 Protein], (b) (4) / Vaxneuvance**

3/18/2021	STN 125741/0.20	Excel spread sheets of (b) (4) Deviations and Change Controls for Records Request
3/22/2021	STN 125741/0.21 (response to IR # 2)	(b) (4) deviation request, (b) (4) validation, shipping qualification
4/26/2021	STN 125741/0.30	Records Request #2 for (b) (4)
5/6/2021	STN 125741/0.33 (response to IR # 3)	Status of “ongoing” cleaning validations at (b) (4)
6/17/2021	STN 125741/0.41 (response to IR # 4)	(b) (4) method acceptance criteria justification and (b) (4) questions

6. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Vaxneuvance (V114) is a new pneumococcal conjugate vaccine that contains 15 distinct pneumococcal capsular polysaccharides individually conjugated to the CRM197 carrier protein originating from *Corynebacterium diphtheriae* C7. Pneumococcal polysaccharides of a given serotype and CRM197 carrier protein are conjugated to form the 15 unique serotype-specific drug substance monovalent bulk conjugates. Conjugation of polysaccharides to proteins changes the nature of the immune response to polysaccharide antigens from T cell-independent to T cell-dependent. The monovalent bulk conjugates are formulated with aluminum phosphate adjuvant and excipients to form the drug product that is filled into a syringe, stoppered, and assembled with a plunger rod. V114 contains the 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) included in the licensed vaccine Prevnar 13™ (pneumococcal 13-valent conjugate vaccine [diphtheria CRM197 protein], Wyeth Pharmaceuticals, a subsidiary of Pfizer, Inc., Philadelphia, PA), plus 2 additional serotypes (22F and 33F) that are not included in any currently licensed pneumococcal conjugate vaccine.

Manufacture of the V114 Pneumococcal 15-Valent Conjugate Vaccine consists of the following process steps:

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

The facilities that support V114 are the following:

**CBER/DMPQ CMC BLA Review Memo BLA 125741/0-Pneumococcal 15-valent Conjugate Vaccine
[CRM197 Protein], (b) (4) / Vaxneuvance**

- Merck (b) (4) of pneumococcal polysaccharides (PnPs).
- (b) (4); CRM197 (b) (4)
- Merck (b) (4) (Manufacture of the 15 Monovalent Bulk Conjugates [MBCs]).
- Merck (b) (4) (Formulation and filling of V114 drug product and APA manufacture)

All manufacturing sites that produce drug substance intermediates, drug substances and drug product are in existing licensed facilities. The manufacturing processes for both the drug substances and final drug product did not require any major facility or utility changes to accommodate the production of V114. All manufacturing steps to produce V114 have been validated and included in the current submission.

A. RECOMMENDATION

I. APPROVAL WITH AN INSPECTIONAL FOLLOW-UP

Based on the information provided in this application, approval is recommended with the following inspectional follow-up item requested for (b) (4). The CRM197 (b) (4) studies have yet to be completed to date. As a result, the (b) (4) validations have also yet to be completed until the (b) (4) have been established. Currently (b) (4) uses cleaning verification for the (b) (4). An inspectional follow-up is requested to demonstrate the (b) (4) are in a clean and sanitized state in lieu of completed cleaning validations.

II. COMPLETE RESPONSE (CR)

N/A

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Gregory Price, Biologist, DMPQ BI	Concur	
Lori Peters, Branch Chief, DMPQ BI	Concur	
John A. Eltermann, Jr, Director, DMPQ	Concur	

Review of CTD

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Module 3

3.2.S DRUG SUBSTANCE

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

We defer review of this section to the product office.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.P DRUG PRODUCT¹

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

V114 Drug Product (DP) is a sterile opalescent liquid suspension for injection. The DP provides a total of (b) (4) of total Pneumococcal Polysaccharide (PnPs) Antigens conjugated to CRM197 (b) (4) 30 µg) as Monovalent Bulk Conjugate (MBC) (b) (4)

The composition of the DP is provided in the table below.

The target formulated concentration and function of each of the components contained within the drug product is described below.

- Active Ingredients
 - MBC (b) (4) µg (Total PnPs)/dose (0.5mL)
- Inactive Ingredients
 - Aluminum Phosphate Adjuvant (APA) 125 µg (Al 3+ ions)
 - Polysorbate-20 1mg (surfactant)
 - L-Histidine (b) (4) (buffer)
 - Sodium chloride (b) (4) (isotonicity)

The DP is filled into a 1.5 mL glass syringe and stored at 2–8 °C.

The prefilled syringe components include:

- 1.5 mL (b) (4) glass syringe barrel with round flange and siliconized, and without graduation marks
- Plastic rigid tip cap with elastomer product-contact component
- Bromobutyl elastomer plunger stopper
- Polypropylene plunger rod

The combination product consists of V114 DP aseptically filled into the syringe barrel assembly and closed with a plunger stopper. Final device assembly includes the addition of the plunger rod to the filled and stoppered syringe container. The V114 combination product is defined as the syringe with plastic rigid tip cap, filled and stoppered, and with plunger rod inserted.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

V114 Drug Product (DP) contains 15 Monovalent Bulk Conjugates (MBC) for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F conjugated independently to the protein CRM197.

The buffer matrix is composed of the following:

- (b) (4)

Aluminum phosphate adjuvant (APA) is used to enhance the immunogenicity of V114. Results of preclinical and clinical studies for the V114 DP showed that formulations containing the Sponsor's aluminum-based adjuvant induced higher anti-PnPs responses than V114 vaccine formulations that did not include any adjuvant.

3.2.P.2.1.2 Excipients

Evaluation of excipients is deferred to the Product Office Reviewer.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

We defer review of this section to the PO.

3.2.P.2.2.2 Overages

We defer review of this section to the PO.

3.2.P.2.2.3 Physicochemical and Biological Properties

We defer review of this section to the PO.

3.2.P.2.3 Manufacturing Process Development

We defer review of this section to the PO.

3.2.P.2.4 Container Closure System

The prefilled syringe components include the syringe barrel, plastic rigid tip cap, and plunger stopper. Syringe barrels are assembled with tip caps and sterilized by the vendor using (b) (4) prior to delivery as ready-to-use. Stoppers are sterilized by (b) (4) and are ready to use. The polypropylene plunger rod does not have

direct contact with the DP suspension and therefore is not considered a primary packaging component. The compendial testing and ISO standards of the syringe materials are presented below.

- Syringe Barrel and Tip Cap
 - Glass (b) (4) glass; (b) (4) Containers – Glass (b) (4) Containers for Pharmaceutical Use
 - (b) (4))
 - Sterility
 - (b) (4)
 - (b) (4) blend (tip cap, elastomer part)
 - Formulation meets ID tests according to ISO (b) (4)
 - (b) (4) Elastomeric Closures for Injections,
 - (b) (4) Rubber Closures for Containers for (b) (4)
 - (b) (4)
 - Tested per ISO (b) (4)
 - Polypropylene (tip cap, plastic part)
 - Tested per ISO (b) (4)
- Plunger Stopper
 - Bromobutyl elastomer
 - Formulation meets ID tests according to ISO (b) (4)
 - (b) (4) Elastomeric Closures for Injections
 - (b) (4) Rubber Closures for Containers for (b) (4)
 - (b) (4) and for (b) (4)
 - Tested per ISO (b) (4)
- (b) (4)
 - Sterility
 - ISO (b) (4)
 - (b) (4)
- Plunger Rod (Note: the plunger rod does not have direct contact with the DP)
 - Polypropylene (plastic part); Tested per ISO (b) (4)

We defer review of the extractable/leachables and toxicology assessments to the PO.

3.2.P.2.5 Microbiological Attributes

The Drug Substances (DS) formulated to the (b) (4)

Regular process simulations (media fills) are conducted to verify the aseptic process in steps of the DP formulation and filling.

For release, V114 DP is tested for sterility in accordance with (b) (4) and tested for bacterial endotoxins according to (b) (4).

A bacteriostatic and fungistatic examination of the drug product formulation is performed to verify non-interference of that formulation and filled DP on the compendial methods, and verification testing for endotoxin is also performed to demonstrate that the material does not inhibit or enhance the endotoxin test at the (b) (4) used.

Additional assurance of the microbiological quality of the DP is provided by the container closure integrity validation, release, and stability testing. Selection of the container closure system and its components focused on their ability to protect the quality of the DP over its shelf life.

Overall Reviewer's Assessment of Section 3.2.P.2:

- The data provided here is adequate. There are no problems associated with microbiological control of bulk or final DP. No additional inquiries required here.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The following DP manufacturing facilities along with their manufacturing responsibilities is presented below.

- (b) (4)
 - Drug Product formulation fill and inspection
 - APA manufacturing, testing and release (Microbiological)
 - Drug Product release and stability testing (Microbiological)
 - Drug Product Release
- (b) (4)
 - APA testing and release (Chemical)
 - Drug Product release and stability testing (Chemical)
- Merck Sharp & Dohme Corp (b) (4)
 - Drug Product release and stability testing
 - Secondary packaging syringe, pre-filled syringe device assembly and Labelling
 - Finished goods release

- (b) (4)
 - Drug Product stability testing (Container Closure Integrity)
- (b) (4)
 - Drug Product stability testing (Combination Product)

3.2.P.3.2 Batch Formula

Target quantities of the drug substances and other components used in the formulation of the drug product is presented below.

- Batch Formula for a typical batch of V114 DP
 - Each MBC (15 serotypes) (b) (4) batch
 - APA (b) (4) target batch
 - Sodium chloride (b) (4) target batch
 - Polysorbate-20 (b) (4) target batch
 - L-Histidine (b) (4) target batch

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:

- The information provided here is adequate. No further information required.

3.2.P.3.3 Description of Manufacturing Process

(b) (4)

(b) (4)

[REDACTED]

Overall Reviewer's Assessment of Section 3.2.P.3.3:

- ☐ The information provided in this section is acceptable. No further inquiries required.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Formulation

The V114 Drug Product (DP) formulation process has been validated. The critical steps and associated process parameters that are monitored for commercial-scale manufacturing are provided below.

- (b) (4)

- (b) (4)

(b) (4)

(b) (4)

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.3.4:

- ☐ The information provided in this section is adequate and explains the CPPs and IPCs. No further inquiries.

3.2.P.3.5 Process Validation and/or Evaluation

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.P.4 Control of Excipients

We defer review of the entire 3.2.P.4 section to the PO.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Analytical test methods together used in release and stability testing for V114 Drug Product (DP) are listed below.

- Appearance (Opalescence)
- Identity by (b) (4)
- Saccharide Content by (b) (4)
- Conjugated Saccharide Content by (b) (4)
- Aluminum Content (b) (4)
- Polysorbate-20 (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- Container Closure Integrity
- Endotoxin (EU/mL)
- Sterility

The release and stability tests germane to this review are the microbial attributes and device functionality. These will be discussed below.

- **Sterility**

The method for sterility is performed in alignment with (b) (4)

Release:

Throughout the clinical history of the program, Sterility has been a release expectation for final container release. Sterility of (b) (4) was added as a release requirement prior to Phase 3.

- **Endotoxin**

The Endotoxin method for drug product is performed in alignment with (b) (4)

The acceptance criterion for release of DP has consistently been (b) (4) through the product development history. The main source of endotoxin in DP derives from the (b) (4). The current Endotoxin limit is (b) (4) than the (b) (4) which represents the approximate threshold dose for humans. The Endotoxin data generated on all batches manufactured to date has met the established specification.

Device Functionality


- (b) (4)

- **Container Closure Integrity Testing**

Container Closure Integrity (CCI) is performed on stability in order to meet (b) (4) requirements per (b) (4). Due to the presence of the vaccine adjuvant in DP, (b) (4) was selected as the CCI method in favor of alternate methods such as dye ingress. CCI by (b) (4) has been used to support DP Clinical, FSS, and PPQ testing. A review of available stability data confirms the ability to routinely meet the established CCI limit of "No leaks detected".

- (b) (4)

(b) (4)







Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:

- The specifications and justifications provided by the Firm and reviewed in this memo are adequate to ensure a safe product. No further inquiries required.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

We defer review of method validations for sterility and endotoxin to DBSQC.

(b) (4)



(b) (4)

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

- The methods provided here are adequate for measuring, CCIT & and syringe function. All validations passed acceptance criteria. No further inquiries.

3.2.P.5.4 Batch Analyses

Batch analysis for the PPQ batches was presented above in Section 3.2.P.3.5-Process Validation and/or Evaluation and will not be repeated here.

3.2.P.5.5 Characterization of Impurities

Endotoxin results were presented above in Section 3.2.P.3.5 Process-Validation and/or Evaluation and will not be repeated here.

3.2.P.6 Reference Standards or Materials

There are none for the drug product.

3.2.P.7 Container Closure System

The components of the V114 combination product is presented above in Section 3.2.P.2.4. For secondary packaging, the assembled syringes are affixed with labels then packaged in a tray and placed into cartons of 1 or 10 along with a package circular. The batch number and expiry date will be applied to both the labels and cartons.

Overall Reviewer's Assessment of Section 3.2.P.7:

- The container closure is pre-sterilized and compliant with the appropriate compendia. The information provided here is adequate, no further inquiries.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

Several stability studies were conducted over the course of the stability program in support of the recommended and accelerated storage conditions, each with the same core testing strategy. The V114 stability protocols are presented below.

- (b) (4)

(b) (4)

(b) (4)

All the above stability batches have passed acceptance criteria for sterility, endotoxin, CCIT, (b) (4) functionality (where applicable). For the remainder of the tests we defer review to the PO.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

(b) (4) commits to continuing the ongoing stability studies to support DP shelf-life at the long-term storage conditions.

Post-approval, a minimum of (b) (4) of DP will be enrolled in the commercial stability program and tested at the long-term storage condition of 5 ± 3 °C each year, if the site has manufactured V114 DP. The same primary packaging and fill per the marketed product will be used for the stability samples.

Overall Reviewer's Assessment of Section 3.2.P.8:

- Stability studies are ongoing for the V114 PPQ batches with no failures in terms of sterility, endotoxin, CCIT, (b) (4) and functionality. (b) (4) commits to placing (b) (4) a (b) (4) on stability. The information provided here is adequate. No further inquiries.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Pneumococcal Polysaccharide (PnP)-Merck (b) (4)

V114 purified PnP (b) (4) are manufactured in the multi-product Building (b) (4) (abbreviated as (b) (4)). Each of the 15 serotypes is manufactured independently utilizing a common manufacturing platform with variations in the parameters to accommodate differences in strain, PnPs and process stream properties. (b) (4) facility currently manufactures the licensed products; (b) (4)

(b) (4)

The (b) (4) facility has (b) (4) floors and is operated in conformance with current good manufacturing practices (CGMPs). Environmentally classified process suites are located on the (b) (4) floor and mechanical support systems are located on the (b) (4) floor.

Reviewer Comments (b) (4)

Merck (b) (4) is an FDA-approved facility which manufactures PnPs used in the currently licensed (b) (4). Fourteen of the 15 PnP serotypes in the manufacture of V114 are legacy serotypes also used for (b) (4). Serotype 6A is a new serotype used in the current submission, however there are no process changes or new equipment being introduced for the manufacture of 6A or any of the legacy PnPs for this submission. In addition, 6A is not considered a worst-case soil for any of the manufacturing equipment, so all equipment cleaning validations were reviewed here and have been validated. The (b) (4) facility has an acceptable compliance history with no outstanding issues identified and will therefore not be reviewed here further.


(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)



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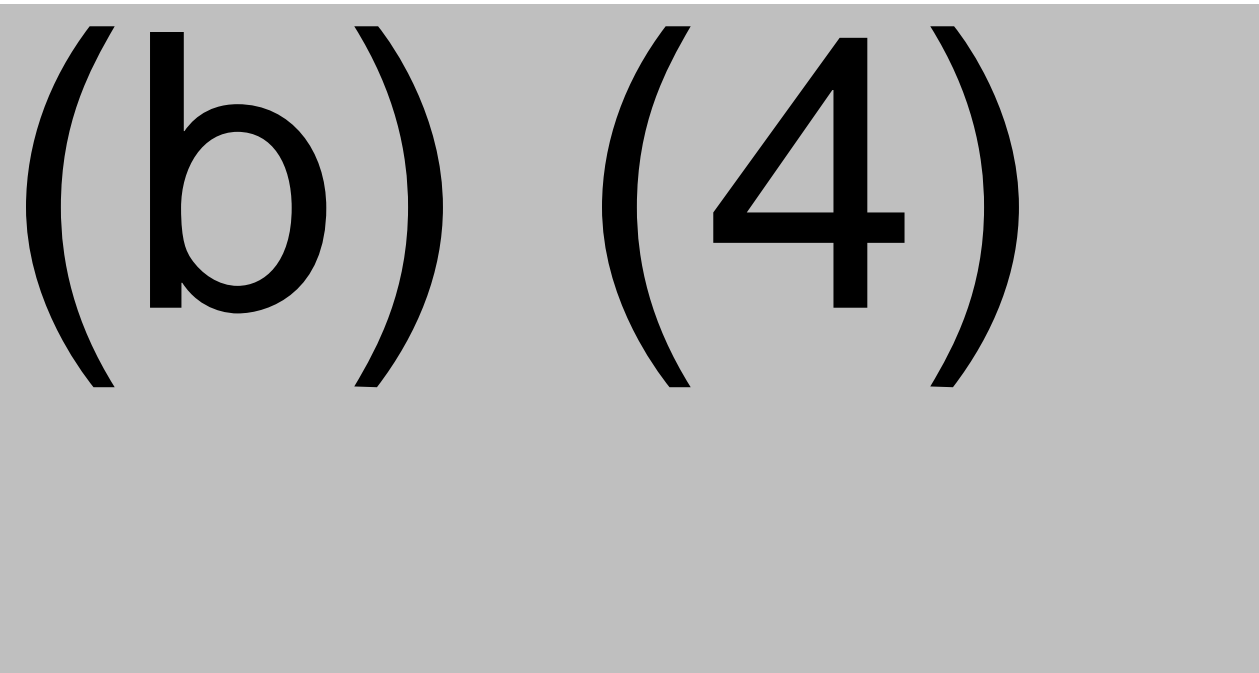


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(b) (4)



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3.2.A.2 Adventitious Agents Safety Evaluation

We defer review of this section to the PO.

3.2.A.3 Novel Excipients

None

3.2.R Regional Information (USA)

❑ Executed Batch Records

Executed batch records were not included with the original submission but were provided in amendment STN 125741/0.19 (eCTD # 0020) upon request by the PO.

❑ **Method Validation Package**

Method validation documents were presented with this submission.

❑ **Combination Products**

As described above the V114 combination product consists of a single dose syringe with the end user being a licensed health care provider.

The following steps were executed in series to establish the final design controls for the V114 combination product:

1. Design inputs
2. Design outputs
3. Design verification
4. Design validation
5. Design reviews
6. Design transfer
7. Design changes

1. Design Inputs

The design requirements for the V114 combination product took into account the following categories:

- Functional requirements
- User requirements
- Performance and design requirements
- Biocompatibility requirements
- Safety
- Durability requirements
- Final assembly and packaging requirements
- Storage and transportation requirements
- Regulatory inputs and considerations

The User Requirements Specification and Design Requirements Specifications are filed within the Design History File (DHF).

2. Design Outputs

Final Design Outputs consist of the results of the design effort, and consist of the following specifications:

- Components and their constituent parts, including materials;
- Combination product;
- Combination product labeling; together with
- Packaging specifications

The design outputs are documented in the Device Master Record (DMR) and Design History File (DHF).

3. Design Verification

The design verification functional performance testing conducted on the V114 syringe are listed below.

- Biocompatibility
- Functional testing of syringe components and filled presentation which include:
 - Design verification functional testing for syringe barrel, plunger stopper, and plunger rod.
 - Dose delivery
 - Functional stability
- Additional performance testing included the following:
 - Prefilled syringe DP formal stability study
 - CCIT
 - Extractable/leachable
 - Compatibility
 - Shipping

4. Design Validation and Human Factors

Design validation was performed through reviewing the results from clinical trials as well as the outcomes from the V114 formative human factors (HF) study. No adverse events or device failures were noted.

5. Design Changes

Design change is any modification conducted to the product form, fit, and/or function. Design changes can occur at any stage in the product lifecycle and will be handled in accordance to the Merck's design controls procedure. Design changes are controlled during development and post regulatory filing. Design changes post design transfer or regulatory filing (whichever comes first) will follow the Sponsor's Global Change Management procedures established for commercial products. Appropriate functional areas will perform technical evaluation of proposed changes, including risk analysis.

6. Design Review

The purpose for holding design reviews during the product design and development process includes, but is not limited to the following:

- Provide a systematic assessment of the design results relating to either the design phase under review or the subject of the review.
- Assure the device design and the associated requirements for production and support processes meet the design requirements.
- Assure applicable manufacturing processes, tests, methods, specifications are properly in place, and assure applicable processes are properly validated.
- Ensure the combination product design has been correctly translated into production specifications.
- Prove that the combination product, as currently manufactured and tested, fulfills user needs and claims as expressed in the design requirements.

Design reviews were documented in the DHF.

7. Design Transfer

In accordance with the Merck's QMS, design transfer plans were established for (i) the transfer of approved design outputs to Sponsor's manufacturing locations and (ii) for their translation into manufacturing specifications at these locations. To demonstrate the effectiveness of the approved manufacturing specifications, process qualification activities were conducted, which showed that the manufacturing processes met the product's quality attributes. The final design transfer report is intended to document the results and findings from qualification activities.

Design History File

The DHF is maintained to include or reference the records necessary to demonstrate that the design was developed in accordance with the approved design and development plan and the requirements described in 21 CFR 820.30. The Index of DHF documentation resides with the Sponsor. Handling and maintenance of DHF documents follow the processes detailed in company guidelines.

Essential Performance Requirements

(b) (4) constitute the Essential Performance Requirements (EPRs) for V114 combination product. These EPRs were selected based on the clinical performance of the device at the point of use. Clinical performance is defined as the ability of the intended user to deliver a complete dose using the syringe.

Risk Management

Risk management activities were performed according to the requirements of Merck's QMS for risk management and appropriately documented within device risk management files. Risk analyses were performed to identify risks associated with user tasks, design, and assembly of the combination product.

Risk management activities were performed in accordance with the device risk management plan and are documented in the DHF.

Combination Product Reviewer Assessment

The information provided here appear adequate. Merck fills other products in syringes, so they have a history with the device and controls. No further inquiries required.

□ Comparability Protocols

One Post-Approval Change Management Protocol (PACMP) was submitted by Merck to support the introduction of new products (NPI) into the CRM197 manufacturing facility (b) (4), an approved multi-product manufacturing facility.

In accordance with FDA's July 1997 Guidance for Industry - Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products, the manufacture of an additional product in a previously approved multiple product manufacturing area using the same equipment and/or personnel, if there have been no changes to the approved and validated cleaning and changeover procedures, and there are no additional containment requirements, requires the submission of a CBE-30 supplement before commercial lots filled after the introduction can be released for distribution. This PACMP proposes to submit NPIs into the previously approved multi-product manufacturing area at (b) (4) as an annual reportable change when it has been confirmed that the prerequisites have been met to ensure no additional level of risk on product quality as a result of an NPI. The prerequisites are listed below.

- The facility to which the new product is being introduced is an approved multiple product manufacturing facility.
- The existing validated cleaning procedures are sufficient, and there is no need for any changes to the existing procedures for change-over between products as a result of the NPI(s).
- There are no additional containment requirements, and the products do not represent an additional level of risk.
- Robust documentation systems exist to prevent misidentification of products manufactured in the same manufacturing area.
- Procedural controls exist to minimize the risk of cross-contamination between CRM197 and the to-be-introduced product.

If these prerequisites cannot be confirmed the NPI will be submitted as a CBE-30 or PAS pending assessment of potential impact to product quality.

Reporting of NPIs in the V114 Annual Report will include the following information:

- A list of all new products introduced into the same manufacturing area since the last registration update; product reference and description (e.g., (b) (4) /company reference or name', and 'biologic'); product type (e.g., commercial, investigational); date of first introduction; and host strain type.
- Manufacturing areas affected by the NPI.
- A statement that the effects of the NPI have been assessed, and that the NPI does not represent an additional level of risk to the facility, personnel, or other products manufactured in the facility. The assessment of the NPI will include within its scope: (b) (4)
- A letter or authorization to reference the applicable DMF, with reference to the relevant version number, which addresses the introduction of the new products

into the manufacturing area and which includes a listing of other products manufactured at the facility.

This PACMP is applicable to NPIs affecting the CRM197 manufacturing area at (b) (4) and will be used (upon Agency approval) for NPIs over the life cycle of the product. CRM197 manufactured in the affected manufacturing area following the NPI will not be considered approved for either clinical or commercial use until the site's quality unit has confirmed that the criteria specified in this protocol have been met and have approved the implementation of the change. This protocol will be considered implemented upon Agency approval of this new product submission.

Merck commits to withdrawing this protocol in the event that it becomes no longer applicable.

Reviewer Comments

This approach appears reasonable. No further inquiries.

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

Evaluation deferred to CMC product office reviewer.