



DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA/CBER/OVRR/DVRPA

Memorandum

Date: July 7, 2021

From: Daphne D. Stewart, CSO
Regulatory Management Support Branch,
HFM-475, DVRPA/OVRR

Through: Tim D. Nelle, Ph.D., CAPT U.S. Public Health Service,
Branch Chief, RMSB

To: BLA STN 125741/0 File

Subject Review of Merck Sharp & Dohme Corp. – BLS 125741/0
Pneumococcal 15-valent Conjugate Vaccine [CRM197 Protein],
absorbed – VAXNEUVANCE®

Background

This Biologics License Application is for Pneumococcal 15-valent Conjugate Vaccine [CRM197 Protein], (b) (4) – VAXNEUVANCE®. It is indicated for the prevention of disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F in Adults 18 years of age and older. This submission contains the following labels that are the subject of this review:

- Single-Dose 0.5 mL Syringe Carton Label
- Single-Patient-Use 0.5 mL (10 doses) Syringe Carton Label
- Single-Dose 0.5 mL Syringe Carton Label

These labels were reviewed for compliance with the regulations 21 CFR 201.25 & 21 CFR 207.35, Subpart G – Labeling Standards 21 CFR 610.60 (a)(1) through (7) and 21 CFR 610.60 (7) (b) through (e), 21 CFR 610.62 (a) through (c), 21 CFR 610.63, 21 CFR 610.64, 21 CFR 610.67, the Drug Supply Chain Security Act (DSCSA) and CBER Job Aid 900.08: National Drug Code, Bar Code and Product Identifier. To ensure completeness, the CBER checklists were used during this review; however, only the checklists for the final draft labels are attached to this review (see Appendixes). In each checklist, an “x” next to each item denotes that the label was found to be compliant with the corresponding regulation.

Review of carton and container labels submitted November 17, 2020:

For all three labels (Single-Dose 0.5 mL Syringe Container Label (NDC 0006-4329-01), Single-Patient-Use 0.5 mL (10 doses) Syringe Carton Label (NDC 0006-4329-03), and Single-Dose 0.5 mL Syringe Carton Label (NDC 0006-4329-02)), the applicant will need to replace “Trademark” with “VAXNEUVANCE” as the tradename.

On June 11, 2021, CBER sent the applicant the following Informational Request:

1. Please update the tradename and non-proprietary name on the carton and syringe labels.
2. Except for identifying the adjuvant, the inclusion of the active ingredient and excipient information are not required on the carton. However, if you want to include this information, please remove it from the primary display panel, and include it on the back or side panel. In lieu of the ingredient information on the main panel, please include “For use in individuals 18 years of age and older”.
3. Please revise the back panel as follows:
 - a. Please modify the text related to the storage conditions from “2 - 8°C (36 - 46°F)” to “2°C to 8°C (36°F to 46°F)”. Please make this change to the syringe label as well.
 - b. Please remove “DOSAGE: See Prescribing Information.”
 - c. Please remove “Inject intramuscularly. Discard syringe after use.”
 - d. If space is limited, please delete “The tip cap and plunger stopper of the prefilled syringe are not made with natural rubber latex.”
 - e. Please add “See accompanying Prescribing Information for additional details.”

In response to this request, the sponsor submitted revised labels on June 17, 2021.

Review of carton and container labels submitted June 17, 2021:

The applicant agreed with all the recommendations posed in CBER’s June 11, 2021, information request except for the recommendation under item 2 concerning the indicated age range. The applicant stated that they prefer the indicated age range to be stated as “For indicated ages, see Prescribing Information”. The reason for this preference is that the applicant believes in the future, there will be a particular statement used for the indication of pediatric ages too.

On June 21, 2021, there was discussion concerning this issue between the Review Committee and OVR Management. It was decided that CBER would not agree with the applicant's proposal concerning the indicated age range, as CBER believes the carton labels need to be clear in consistency and present information critical to prevent administrative error. This will avoid accidentally administering this vaccine to individuals that would be younger than 18 years of age.

On June 28, 2021, CBER sent the applicant the following Informational Request:

CBER sent the following comment regarding the applicants June 17, 2021 response to CBER container and carton label comments:

1. The Carton labeling should be clear and present information critical to prevent administration errors. Given that there will be three PCV vaccines on the market as well as a polysaccharide vaccine we consider that it is important to minimize the possibility that the PCV-15 vaccine will be inadvertently administered to individuals younger than 18 year of age. Of note ISMP in 2016 published a report which noted that one in three vaccine errors were associated with age-related factors (<https://www.ismp.org/resources/ism-p-national-vaccine-errors-reporting-program-one-three-vaccine-errors-associated-age>). The reasons for these vaccination administration errors were varied but included confusion between "numerous age-dependent vaccines that target the same diseases." Thus, FDA continues to request the inclusion of the proposed age on the carton.

In response to this communication, the sponsor submitted new labels on July 2, 2021.

Review of carton and container labels submitted July 2, 2021:

As detailed in both the June 11, 2021 and June 28, 2021, Informational Request communications from CBER, the applicant was requested to revised their labels to include on their carton labels the statement "For use in individuals 18 years of age and older". The applicant included this statement on their carton labels for all both of their labels for the Single-Patient-Use 0.5 mL (10 doses) Syringe Carton Label (NDC 0006-4329-03) and the Single-Dose 0.5 mL Syringe Carton Label_(NDC 0006-4329-02).

Single-Dose 0.5 mL Syringe Carton Label (NDC 0006-4329-02):

As detailed in Appendix 1, this label is acceptable for approval.

Single-Patient-Use 0.5 mL (10 doses) Syringe Carton Label

(NDC 0006-4329-03):

As detailed in Appendix 2, this label is acceptable for approval.

Single-Dose 0.5 mL Syringe Container Label (NDC 0006-4329-02):

As detailed in Appendix 3, this label is acceptable for approval.

Recommendations

These labels are currently in compliance with 21 CFR 201.25, 21 CFR 207.35 and 21 CFR 610.60 through 21 CFR 610.67, Drug Supply Chain Security Act (DSCSA), the Guidance for Industry, "Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use", and CBER Job Aid 900.08: National Drug Code, Bar Code and Product Identifier. Therefore, these labels are recommended for approval.

Appendix 1: Review Checklist for Single-Dose 0.5 mL Syringe Carton Label
(NDC 0006-4329-02): submitted on July 2, 2021

21 CFR 610.61 (a) through (s)	Checked items “x” indicate compliance
a. The proper name of the product;	X
b. The name, address, and license number of manufacturer;	X
c. The lot number or other lot identification;	X
d. The expiration date;	X
e. The preservative used and its concentration, or if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative”;	X
f. The number of containers, if more than one;	X
g. The amount of product in the container expressed as (1) the number of doses, (2) volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable;	X
h. The recommended storage temperature;	X
i. The words “Shake Well”, “Do not Freeze” or the equivalent, as well as other instructions, when indicated by the character of the product;	X
j. The recommended individual dose, for multiple dose containers.	0.5 mL
k. The route of administration recommended, or reference to such directions in an enclosed circular	X
l. Known sensitizing substances, or reference to an enclosed circular containing appropriate information;	X
m. The type and calculated amount of antibiotics added during manufacture;	X
n. The inactive ingredients when a safety factor, or reference to an enclosed circular containing appropriate information;	X
o. The adjuvant, if present;	N/A
p. The source of the product when a factor in safe administration;	X
q. The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information	X
r. Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words “No U.S. standard of potency.”	X
s. The statement: “Rx only” for prescription biologicals.	X

JA 900.08: NDC, Bar Code, & Product Identifiers/21 CFR 201.25 & 21 CFR 207.35 (3)(i)	Checked items “x” indicate compliance
<p>9. Barcode & Linear or One-Dimensional (1D) (Parallel Lines)</p> <p>NDC</p> <p>a. Using the website https://www.fda.gov/industry/structured-product-labeling-resources/ndcnhrac-labeler-codes (to check the sponsor’s NDC)</p> <p>b. Click “Open”</p> <p>c. Click “ndc_hrac_labeler_codes”</p> <p>d. Click “Yes”</p> <p>e. Locate the Firm Name and the NDC Labeler Code will be to the right</p>	<p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p>
<p>10. Detachable Portion</p> <p>If the detachable label has a 2D Barcode, then you need to follow steps #8 & steps #9</p> <p>(Barcode & NDC/2D Barcode)</p> <p>The actual detach label needs to include:</p> <p>a. Proprietary Name</p> <p>b. NDC #</p> <p>c. Lot # & Expiry Date</p>	<p>N/A</p>
<p>If the detachable label cannot contain all the above information, then it should have:</p> <p>a. Proprietary Name</p> <p>b. NDC #</p> <p>c. Lot #</p> <p>For 2D Barcodes on the carton label to meet the regulations for the Drug Supply Chain Security Act (DSCSA).</p> <p>Product Identifier - 2D Barcode</p> <p>a. Locate the symbol and the datamatrix codes will consist of:</p> <p style="padding-left: 100px;">NDC (01):</p> <p style="padding-left: 100px;">EXPIRY (17):</p> <p style="padding-left: 100px;">BATCH/LOT (10):</p> <p style="padding-left: 100px;">SERIAL (21):</p>	<p>N/A</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p>

Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use Guidance for Industry	Checked items “x” indicate compliance
a. Multiple-Dose b. Single-Dose c. Single-Patient-Use	x
11. <u>If there is an age range associated with the label it should be included on the label. The placement should not be on the detachable portion.</u>	In Adults 18 years of age and older.
Comments: This label is acceptable for approval.	

Appendix 2: Review Checklist for Single-Patient-Use 0.5 mL (10 dose) Syringe Carton
(Package) Label (NDC 0006-4329-03) submitted on July 2, 2021

21 CFR 610.61 (a) through (s)	Checked items “x” indicate compliance
a. The proper name of the product;	X
b. The name, address, and license number of manufacturer;	X
c. The lot number or other lot identification;	X
d. The expiration date;	X
e. The preservative used and its concentration, or if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative”;	X
f. The number of containers, if more than one;	X
g. The amount of product in the container expressed as (1) the number of doses, (2) volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable;	X
h. The recommended storage temperature;	X
i. The words “Shake Well”, “Do not Freeze” or the equivalent, as well as other instructions, when indicated by the character of the product;	X
j. The recommended individual dose, for multiple dose containers.	0.5 mL = 10 dose
k. The route of administration recommended, or reference to such directions in an enclosed circular	X
l. Known sensitizing substances, or reference to an enclosed circular containing appropriate information;	X
m. The type and calculated amount of antibiotics added during manufacture;	X
n. The inactive ingredients when a safety factor, or reference to an enclosed circular containing appropriate information;	X
o. The adjuvant, if present;	N/A
p. The source of the product when a factor in safe administration;	X
q. The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information	X
r. Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words “No U.S. standard of potency.”	X
s. The statement: “Rx only” for prescription biologicals.	X

JA 900.08: NDC, Bar Code, & Product Identifiers/21 CFR 201.25 & 21 CFR 207.35 (3)(i)	Checked items “x” indicate compliance
<p>9. Barcode & Linear or One-Dimensional (1D) (Parallel Lines)</p> <p>NDC</p> <p>b. Using the website https://www.fda.gov/industry/structured-product-labeling-resources/ndcnhric-labeler-codes (to check the sponsor’s NDC)</p> <p>b. Click “Open”</p> <p>c. Click “ndc_hric_labeler_codes”</p> <p>d. Click “Yes”</p> <p>e. Locate the Firm Name and the NDC Labeler Code will be to the right</p>	<p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p>
<p>10. Detachable Portion</p> <p>If the detachable label has a 2D Barcode, then you need to follow steps #8 & steps #9</p> <p>(Barcode & NDC/2D Barcode)</p> <p>The actual detach label needs to include:</p> <p>a. Proprietary Name</p> <p>b. NDC #</p> <p>c. Lot # & Expiry Date</p>	<p>N/A</p>
<p>If the detachable label cannot contain all the above information, then it should have:</p> <p>a. Proprietary Name</p> <p>b. NDC #</p> <p>c. Lot #</p> <p>For 2D Barcodes on the carton label to meet the regulations for the Drug Supply Chain Security Act (DSCSA).</p> <p>Product Identifier - 2D Barcode</p> <p>b. Locate the symbol and the datamatrix codes will consist of:</p> <p style="padding-left: 100px;">NDC (01):</p> <p style="padding-left: 100px;">EXPIRY (17):</p> <p style="padding-left: 100px;">BATCH/LOT (10):</p> <p style="padding-left: 100px;">SERIAL (21):</p>	<p>N/A</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p>

Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use Guidance for Industry	Checked items “x” indicate compliance
d. Multiple-Dose e. Single-Dose f. Single-Patient-Use	x
11. <u>If there is an age range associated with the label it should be included on the label. The placement should not be on the detachable portion.</u>	In Adults 18 years of age and older.
Comments: This label is acceptable for approval.	

Appendix 3: Review Checklist for Single-Dose 0.5 mL Syringe Container Label
(NDC 0006-4329-01) submitted June 17, 2021

21 CFR 610.60(a)(1) through (7)	Checked items “x” indicate compliance
a. <i>Full label.</i> The following items shall appear on the label affixed to each container of a product capable of bearing a full label:	X
* 1. The proper name of the product;	X
* 2. The name, address, and license number of manufacturer;	X
* 3. The lot number or other lot identification;	X
* 4. The expiration date;	X
* 5. The recommended individual dose, for multiple dose containers.	0.5 mL
* 6. The statement: “Rx only” for prescription biologicals.	X
7. If a Medication Guide is required under part 208 of this chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label.	N/A

21 CFR 610.62 (7) (b) through (e)	Checked items “x” indicate compliance
b. <i>Package label information.</i> If the container is not enclosed in a package, all the items required for a package label shall appear on the container label.	N/A
c. <i>Partial label.</i> If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label.	X
d. <i>No container label.</i> If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label.	N/A
e. <i>Visual inspection.</i> When the label has been affixed to the container a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents.	X

JA 900.08: NDC, Bar Code, & Product Identifiers/21 CFR 201.25 & 21 CFR 207.35 (3)(i)	
<p>*8. Barcode</p> <p>Linear or One-Dimensional (1D) (Parallel Lines)</p> <p>NDC</p> <p>a. Using the website https://www.fda.gov/industry/structured-product-labeling-resources/ndcnhric-labeler-codes (to check the sponsor's NDC)</p> <p>b. Click "Open"</p> <p>c. Click "ndc_nhric_labeler_codes"</p> <p>d. Click "Yes"</p> <p>e. Locate the Firm Name and the NDC Labeler Code will be to the right</p>	<p>N/A</p> <p>N/A</p>
<p>*9. Product Identifier - 2D Barcode</p> <p>a. Locate the symbol and the datamatrix code information will consist of:</p> <p>NDC (01): EXPIRY (17): BATCH/LOT (10): SERIAL (21):</p>	<p>N/A</p>
<p>10. Detachable Portion</p> <p>If the detachable label has a 2D Barcode, then you need to follow steps #8 & steps #9 (Barcode & NDC/2D Barcode)</p> <p>The actual detach label needs to include:</p> <p>a. Proprietary Name b. NDC # c. Lot # & Expiry Date</p> <p>If the detachable label cannot contain all the above information, then it should have:</p> <p>a. Proprietary Name b. NDC # c. Lot #</p>	<p>N/A</p> <p>N/A</p>

Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use Guidance for Industry	Checked items “x” indicate compliance
<ul style="list-style-type: none"> a. Multiple-Dose b. Single-Dose c. Single-Patient-Use 	x
<p>11. <u>If there is an age range associated with the label is should be included on the label. The placement should not be on the detachable portion.</u></p>	In Adults 18 years of age and older.
<p>Comments:</p> <ul style="list-style-type: none"> • This label is acceptable for approval. 	

*** Minimum requirement for partial labels**