CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216962Orig1s000

OTHER ACTION LETTERS

NDA 216962

COMPLETE RESPONSE

AbbVie Inc.
Attention: Grace Chun, PharmD
Associate Director, Regulatory Affairs
5 Giralda Farms
Madison, NJ 07940

Dear Dr. Chun:

Please refer to your new drug application (NDA) dated May 19, 2022, received May 19, 2022, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Vyalev (foscarbidopa and foslevodopa) injection for subcutaneous use.

We acknowledge receipt of your amendment dated December 19, 2023, which constituted a complete response to our March 17, 2023, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

Following a CGMP inspection of (b) (4) (FEI (b) (4)), listed in this application, FDA conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to your complete response. The facility's satisfactory responses are dependent on FDA's determination that the facility has come into compliance with CGMP and may require re-inspection of the facility. The deficiencies identified during the inspection may not be specific to your pending application; therefore, you should coordinate with the facility for timely resolution. Your complete response should include the date(s) of the facility's response(s) to the FDA Form 483. Please refer to Compliance Program CP 7356.002 for guidance on post inspection activities. Following resolution of the CGMP inspection, FDA may need to conduct a pre-approval inspection (PAI) of the facility. Satisfactory outcomes of both the PAI and the CGMP surveillance inspections will be needed prior to an approval of the application.

PRESCRIBING INFORMATION

Submit draft labeling that is responsive to our electronic communication dated June 17, 2024, when you respond to the application deficiencies.

Prior to resubmitting the labeling, use the Selected Requirements of Prescribing Information (SRPI) checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[1]

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.
- Additional resources for the PI, patient labeling, and carton/container labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[3] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling revised, based on our recommendations noted below under Additional Comments, when you respond to the application deficiencies.

PROPRIETARY NAME

Please refer to correspondence dated, May 14, 2024, which addresses the proposed proprietary name, Vyalev. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have additional comments/recommendations that are not approvability issues.

We recommend the following be implemented for the carton labeling, container labels, and the Instructions for Use for Vyalev:

	Identified Issue	Rationale for Concern	Recommendation
Carton labeling			
	Based on our review of your response submitted on May 20, 2024, it appears that the front opening panel is the principal display panel (PDP). However, we note the Medication Guide (MG) statement is located on the (b) (4) instead of on the PDP.	Per 21 CFR 208.24(d), the label of each container or package, where the container label is too small, of drug product for which a MG is required under this part shall instruct the authorized dispenser to provide a MG to each patient to whom the drug product is dispensed, and shall state how the MG is provided. These statements shall appear on the label in a prominent and conspicuous manner.	Ensure the MG statement appears in accordance with 21 CFR 208.24(d). To ensure its prominence, we recommend relocating the MG statement to the PDP.
Container label			
	The container label does not include the container closure term (i.e., vial).	Omission of the container closure term after the package type term may lead to confusion.	Revise the statement “10 mL single-dose” to now read “10 mL single-dose vial”.

	Identified Issue	Rationale for Concern	Recommendation
Patient Instructions for Use (IFU) and Healthcare provider (HCP) IFU			
	You revised the patient IFU and HCP IFU to include the following statements to indicate patients should carry an alternative treatment option. • Patient IFU: (b) (4) [redacted] • HCP IFU: (b) (4) [redacted]	We acknowledge immediate release carbidopa-levodopa tablets are a reasonable alternative treatment option if Vyalev infusion is unavailable. However, there are additional alternative treatment options that can be considered (e.g., COMT inhibitors, etc.) if patients are unable to receive Vyalev infusion.	Revise the patient IFU statement (b) (4) [redacted] to now read "Talk with your healthcare provider about what to do in case you are unable to use VYALEV infusion. Keep a supply of backup oral Parkinson's Disease medicines with you at all times". Revise the HCP IFU statement (b) (4) [redacted] to now read "Instruct the patient to keep a supply of backup oral Parkinson's Disease medicines with them at all times in case they are unable to use VYALEV infusion".

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the

cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please contact Stacy Metz, PharmD, Senior Regulatory Project Manager, at stacy.metz@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Emily Freilich, MD
Director
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAURA A JAWIDZIK on behalf of EMILY R FREILICH
06/18/2024 03:28:48 PM

NDA 216962

COMPLETE RESPONSE

AbbVie Inc.
Attention: Grace Chun, PharmD
Associate Director, Regulatory Affairs
5 Giralda Farms
Madison, NJ 07940

Dear Dr. Chun:

Please refer to your new drug application (NDA) dated May 19, 2022, received May 19, 2022, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Vyalev (foscarbidopa and foslevodopa) Solution for Infusion.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

1. You have provided patient and healthcare provider Instructions for Use for the Foscarbidopa and Foslevodopa Delivery System (i.e., Vyafuser). The labeling provided does not include the recommended information outlined in the Agency's guidance *Infusion Pumps Total Product Life Cycle*.[1] As stated in the guidance, FDA recommends the labeling describe any factors that may affect flow accuracy such as ambient temperature, fluid temperature, pressure (e.g., head height, backpressure, atmospheric pressure), fluid viscosity, or changes in flow rate or bolus delivery (e.g., such as when titrating medications). Please note, some of the recommended factors may be included in the labeling and/or are inapplicable; however, the labeling for Vyafuser does not include information regarding head height or backpressure. Additionally, performance testing to support a claim of head height or backpressure not affecting the infusion system could not be located in the submission. The labeling should ensure sufficient information is included for safe use of the device by end users. To ensure users

[1] https://www.fda.gov/media/78369/download

are aware of this information, revise your patient Instructions for Use to include the information outlined above.

2. In the December 5, 2022, Information Request sent to Phillips-Medisize , we requested clarification on testing of Essential Performance Requirements (EPRs) as a feature test (b) (4) Your response states the feature testing wa (b) (4) While these may be attributable to the software component of the delivery system, a rationale was not provided for the type of testing EPRs have undergone to verify these requirements function as intended reliably and/or traceability to the software testing performed. Provide a rationale for the EPRs tested via feature testing, including the technical justification that there is no anticipated variability in the ability to meet the identified EPRs with traceability to software testing, if applicable. Additionally, it is important to note that EPRs are not product requirements as defined by device manufacturers. EPRs are essential design inputs and outputs critical to achieving the intended use of the device which, in this case, is successful delivery of the drug product as identified by AbbVie. EPRs should be verified to a 95% confidence and 95% reliability. If alternative verification methods are used, you should provide a justification for how the EPRs have been verified to function as intended reliably.

3. In response to our November 7, 2022, Information Request, you provided an overview of the infusion pump alarms and notifications; however, the information provided is incomplete. Alarms are safety mitigations for infusion pumps to ensure that infusions are delivered as intended and users are aware of any interruptions to therapy as described in IEC 60601-1-8:2020 Medical electrical equipment - Part 1-8: General requirements for basic safety and essential performance - Collateral Standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems. You will need to address the following:

    a. You have not provided sufficient details regarding the alarms implemented into the infusion pump. For example, the alarm triggers, thresholds, and time to alarm were not provided to determine if these are clinically reasonable. Further, the overview of the alarms provided does not align with the alarm descriptions provided in the patient and healthcare professional Instructions for Use. Provide a detailed description of each alarm and informational message available for both the end user and healthcare professional, including an overview of the triggers for each and remediation steps the user or healthcare professional must take.

b. In the overview of the alarms provided, you have identified each alarm as low priority, high priority, or notification. Low priority alarms may be missed by end users given their different audio/visual features, which has been reported in serious injury MDRs for other infusion pump problems. The low priority alarms identified include "Low battery", [redacted] (b) (4) "Priming error", and "Battery error". The notifications identified include "Battery is removed", "Pump has exceeded service life", "Malfunction", and "Syringe error". It is unclear how the risks associated with delay of therapy were considered when assigning low priority or notification status to the aforementioned alarms and notifications. For example, if the low battery alarm or notification is missed, there is a chance of delayed therapy for the patient, which presents of potential risk of harm to the patient. Provide a rationale for each alarm and notification included in the pump software that justifies the designation as a low priority alarm, high priority alarm, or notification. Your rationale should provide trace reference to the harm IDs associated with delay of therapy, as identified in your risk management documentation. Additionally, you should categorize the alarms indicating an immediate change in syringe, battery, pump error, etc. as a high priority alarms.

c. You have not provided testing to demonstrate all alarms are triggered when their conditions are met. For example, you provided feature testing for general low priority and high priority alarms and verification testing for battery alarms, power loss alarms, depleted reservoir alarm, noise levels, lid open alarm, and occlusion alarm; however, you have not assessed battery removed alarms, incremental syringe empty alarms, or priming error alarms. Alarms cannot act as suitable risk mitigation if their performance is not demonstrated adequately. Provide results of testing to demonstrate all alarms are triggered when their conditions are met.

4. In the December 5, 2022, Information Request sent to Phillips-Medisize, we requested clarification on the number [redacted] (b) (4) utilized for durability testing. In their December 19, 2022, response, Phillips-Medisize provided a justification [redacted] (b) (4) as the worst-case scenario. However, the [redacted] (b) (4) durability testing performed did not assess the infusion system's EPRs [redacted] (b) (4) Testing of EPRs after undergoing worst case [redacted] (b) (4) is important to ensure your device functions adequately after being subjected to the worst-case [redacted] (b) (4) throughout its stated service life from baseline through aging (i.e., expiry). You need to provide reliability testing that captures all EPRs and include results for review after these [redacted] (b) (4) for unaged and aged infusion pumps.

5. The design verification testing provided in MAF (b) (4) contains a test case for Battery Operating Time and associated low priority alarms. However, the testing provided is inadequate to demonstrate that the battery operates as intended for the stated work time in worst-case conditions both at baseline and throughout the stated battery lifetime (i.e., with a new battery and with a battery that is nearing its end of life). This information is needed to assess the performance of the battery when operated in worst-case conditions throughout the intended lifetime. Therefore, you will need to provide the following information:

    a. Provide battery safety testing according to IEC 62133-2:2017 *Secondary cells and batteries containing alkaline or other non-acid electrolytes – Safety requirements for portable sealed secondary cells, and for batteries made from them, for use in portable applications – Part 2: Lithium systems*.

    b. Provide expected work time testing for the battery under worst-case conditions and average use conditions for a statistically significant sample size.

        i. It is recommended that you assess a sample size of at least 30 batteries + infusion pumps.
        ii. Testing should be conducted on new and aged batteries. For the aging process, you should describe how the batteries were aged (i.e., simulated charge/discharge cycles through stated battery lifetime).
        iii. The worst-case conditions should be included and justified as to how these constitute extreme cases the infusion pump may be exposed to during delivery. For example, the maximum flow rate, display, drug substance, largest loading dose and extra dose, and lock-out times should be used.

    c. The acceptance criteria for the Battery Operating Time and associated low priority alarms testing states (b) (4) This priority of alarms is not acceptable, as it does not ensure that users are aware and taking actions to address the issue in a timely manner and are not determined per Table 1 in IEC 60601-1-8. In addition, the threshold for the alarms (b) (4) (b) (4) are not adequate as they are inaccurate and allow for assumptions and user errors. Battery alarm thresholds need to be clear, stating the exact time after which the battery will deplete under the current conditions of use. Finally, this test does not demonstrate the infusion pump will run for at least the allotted amount of time to ensure that it does not deplete unexpectedly and lead to patient

harm. Additionally, it is reasonable to expect that batteries may be used for longer than the intended lifetime as there is no battery degradation alarm. You will need to address the following:

i. Revise the low battery and very low battery alarms to be latching and have a medium and high priority, respectively. This is to ensure that users are aware and taking actions to address the issue in a timely manner.

ii. Revise the low battery and battery empty alarm thresholds to be 30 minutes for low battery and 5 minutes for battery empty alarms. These thresholds should account for the conditions under which the pump operate at the time and take into account the capacity fade. Provide the equation you use to assess the remaining capacity and the time left, such that the expected time of operation does not change based on conditions of use or age of battery.

iii. Include a degraded battery alarm and include this as a POST test to ensure pumps are not used with a degraded battery. Include the alarm text to clarify that the pump should not be used.

d. The Patient Instructions for Use instructs users on how to replace the battery during use of the infusion pump. Page 111 of these instructions states that the patient should (b) (4) The instructions do not provide a definitive timeframe the patient has before the pump restarts. Additionally, there are no warnings within the instructions of any changes to flow rate or whether there is a chance of a bolus after changing the battery. You will need to address the following:

i. Revise the instructions to state a definitive timeframe the patient has to change the battery to avoid a reset.

ii. Revise the instructions to warn patients of any potential changes to flow rate or possible boluses that may occur after the battery change and provide performance verification of flow rate and bolus volume (if any) following battery change and restart.

iii. Establish a “time to change battery” system/software requirement and provide traceability to associated verification and validation of the requirement.

This information is necessary to demonstrate that your combination product has been adequately demonstrated to be safe and effective under realistic

environmental and use conditions and therefore the device design is adequately verified per 21 CFR §820.30(f).

6. The design verification testing provided in MAF (b) (4) contains an assessment of the design inputs and outputs established for the infusion pump. However, the testing provided does not adequately demonstrate that the infusion system functions as intended throughout the anticipated delivery time and when exposed to factors that impact flow accuracy as per the Agency's guidance *Infusion Pumps Total Product Life Cycle*.[1] The infusion system has not been exposed to factors such as head height and backpressure of which impact the flow accuracies of an infusion system. Additionally, the infusion pump has not been assessed throughout its intended delivery time. This testing is needed to demonstrate the infusion system maintains its accuracy and functionality for continuous delivery and when exposed to environmental factors.

    a. The healthcare professional Instructions for Use states "Continuous dose delivery accuracy testing was performed based upon IEC 60601-2-24:2012". We were unable to locate this testing within the MAF. Additionally, we note that IEC 60601-2-24, under its current iteration, is not fully recognized by the FDA. You should consider the following with regards to infusion pump performance testing:

        i. The IEC 60601-2-24:2012 standard recommends assessing the accuracy of the system after a 24-hour initiation period, and this may not be representative of actual use of the pump system. We recommend you assess the accuracy incorporating the first 24 hours of use.

        ii. The IEC 60601-2-24:2012 standard does not recommend that the ability of the pump to meet its accuracy specifications despite changes in ambient temperature, fluid temperature, pressure (e.g., head-height, backpressure, atmospheric pressure), or fluid viscosity is demonstrated at representative flow rates. The ability of the pump to meet its accuracy specifications under these conditions needs to be demonstrated at the minimum, intermediate, and maximum flow rates, and needs to include combinatorial considerations (e.g., backpressure at maximum specified ambient temperature). Additionally, because the pump is to be worn, the delivery accuracy of the pump needs to be verified when exposed to cyclic and vibrational shock.

        iii. When developing and verifying the flow accuracy specifications, you should consider the flow rates and duration of time over which the accuracy specification is defined. Your current flow accuracy specification does not provide a time over which the accuracy is specified (e.g., mL to be delivered/24 hours).

b. Provide testing of the Basal Delivery, Loading Dose, and Extra Dose accuracies when exposed to applicable factors such as head height and backpressure. The results should be included within the patient labeling to ensure users are aware of these factors.

c. Provide testing of the Basal Delivery over the indicated maximum duration of infusion (i.e., 24 hours).

We refer you to AAMI TIR101:2021 *Fluid delivery performance testing for infusion pumps* for additional information on performing this testing. This information is necessary to demonstrate that your combination product has been adequately demonstrated to be safe and effective under realistic environmental and use conditions and, therefore, that the device design is adequately verified per 21 CFR §820.30(f)).

7. As part of the reliability (i.e., durability) testing performed for the infusion pump, the original submission of the MAF contains testing performed on aged infusion pumps within VOL_009_Design Verification Testing. However, the acceptance criteria utilized to assess whether the infusion pumps functioned after aging to shelf-life and service life were not the EPRs as established by AbbVie. The essential performance of the infusion pump should be assessed after aging to demonstrate that the pump functions as intended throughout expiry. Provide testing of the EPRs after the infusion pump has been aged to its intended shelf-life and service life.

8. As part of the reliability (i.e., durability) testing performed for the infusion pump, the original submission of the MAF contains testing performed on infusion pumps after dropping (i.e., free-fall testing) within VOL_009_Design Verification Testing. This was performed with an open and closed lid. The test did not evaluate EPRs after dropping and did not contain device observations (e.g., cracks, etc.) which may impact the functionality of the pump. Provide testing of the EPRs after the infusion pump has been dropped and include any device observations after dropping. This information is necessary to demonstrate that your combination product has been adequately demonstrated to be safe and effective under realistic environmental and use conditions and, therefore, that the device design is adequately verified per 21 CFR §820.30(f).

9. As part of assessing the performance and reliability (i.e., durability) of the infusion pump, the original submission of the MAF contains unintended bolus testing within VOL_009_Design Verification Testing as part of verification testing as well as thermal cycling, performance, and packaging reliability testing. These tests were performed (b) (4) It is unclear how the tests performed, outlined above, were conducted using worst-case conditions. When assessing unintended boluses, it is important to conduct testing under the worst-case conditions as this is an important operational hazard associated with

infusion pumps per the Agency's guidance *Infusion Pumps Total Product Life Cycle*.[1] You will need to provide a rationale for the parameters tested including how they demonstrate worst-case conditions. Alternatively, you could provide repeat testing of unintended bolus under the worst-case conditions which should include a rationale for the parameters, as well. This information is necessary to demonstrate that your combination product has been adequately demonstrated to be safe and effective under realistic environmental and use conditions and, therefore, that the device design is adequately verified per 21 CFR §820.30(f).

10. Within VOL_006_Software Information of the original submission of the MAF, the document titled "(b) (4) _Software_Risk_Control_Analysis" contains the software risk analysis. However, the software risk analysis has not identified all applicable risks associated with the infusion pump. For example, the risk analysis identifies the technical cause of (b) (4) were not included in the risk analysis. A comprehensive software risk analysis is needed to ensure that all failure modes have been assessed and demonstrate acceptable mitigations have been implemented and verified. Provide a revised software risk analysis that includes all applicable risks associated with the software component of the infusion pump.

11. In the December 5, 2022, Information Request sent to Phillips-Medisize, we requested additional software verification and validation test reports, including system, regression analysis, static analysis, code coverage, integration testing, unit testing, and runtime. We also requested this to include an overview of the user stories and continuous software testing. In response, Phillips-Medisize stated (b) (4) and provided a tabular view of the software testing performed. However, the full reports could not be located within the response. As stated in the Information Request, this testing is needed to demonstrate that the software has been verified and validated within acceptable parameters. Provide the full test reports for all testing conducted on the final software version including, but not limited to, system testing, integration testing, unit testing, regression analysis, and code coverage.

12. In the December 5, 2022, Information Request sent to Phillips-Medisize, we stated that multiple unresolved anomalies had to be resolved prior to release, because they impact basic safety or cause an unnecessary delay to therapy. In response, Phillips-Medisize provided a detailed document titled "4000401660_Software_Unresolved_Anomaly_List_01" with a description of each unresolved anomaly to facilitate review. Based on your cross-functional team review, these anomalies were deemed acceptable for release. While a majority of these anomalies are claimed to be able to be resolved within an hour of occurrence, these anomalies remain an unnecessary delay of therapy and

patient inconvenience. You will need to resolve the identified unresolved anomalies communicated in deficiency #20 in our December 5, 2022, Information Request.

13. Within VOL_006_Software Information of the original submission of the MAF, you provided the document titled "(b) (4) – Software SOUP Components" which includes an overview of the seven (7) software of unknown provenance (SOUP) items included in the software to support the pump's functionality. However, you have not provided the required documentation per FDA's guidance document *Guidance for Off-the-Shelf Software Use in Medical Devices*.[2] The SOUP documentation should include a description of the software, system specifications, traceability to testing completed to verify and validate, control measures, and a comprehensive hazard analysis demonstrating the Level of Concern for the SOUP components are appropriate. This information is needed to assess the functionality of the SOUP components within the infusion pump and whether you have mitigated relevant hazards. Provide the relevant documentation per the guidance for review.

14. We requested revised batch release testing which included all identified Essential Performance Requirements (EPRs) for the infusion pump in our December 5, 2022 Information Request sent to Phillips-Medisize. In the December 19, 2022, response, the specifications provided included Priming of Infusion Set, Initiation & Completion of Loading Dose Delivery, Basal Flow Rate, Initiation & Completion of Extra Dose Delivery, Generation of High Priority Alarm for Power Loss, Generation of High Priority Alarm for Syringe Depleted, and Occlusion Detection & Generation of High Priority Alarm. These tests do not include all identified EPRs as established by AbbVie for the proposed infusion system. You may choose to assess EPRs through acceptance activities and/or in-process controls; however, a rationale for exclusion of any EPRs from release testing needs to be provided. Therefore, you will need to provide a table of all EPRs identified for the infusion system and include whether each individual EPR is assessed through acceptance activities, in-process controls, and/or release testing. For each, provide an overview of how these are assessed through the identified process.

CLINICAL

15. We request a tabulation of reports of malfunction of the device component of this combination product and identification of what types of events occurred (e.g., pump shut-off, kinking of tubing, separation of tubing from infusion pump, leakage from infusion pump).

[2] https://www.fda.gov/media/71794/download

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[5]

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

MEDICATION GUIDE

Add the following bolded statement or appropriate alternative to the carton and container labeling per 21 CFR 208.24(d): "**ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide**."

PROPRIETARY NAME

Please refer to correspondence dated, August 16, 2022, which addresses the proposed proprietary name, Vyalev. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical

[3] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[4] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
[5] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

Human Factors

The comments in this section are not intended to convey human factors (HF) approvability issues with your proposed product; however, it will be necessary for you to consider how any revisions to your proposed product to address the deficiencies outlined above will impact your user interface.

- If your user interface is revised in response to the CR, you should update your use-related risk analysis (URRA) to determine whether any new risks, including new critical tasks or failure modes are introduced by the changes. You will need to provide this information to the Agency to determine whether the changes to your user interface will require submission of additional HF data to validate the revised user interface.

  If you determine that an additional HF study does not need to be submitted, submit your justification, updated URRA, comparative analyses such as a labeling comparison, a comparative task analysis, and a physical comparison between your revised user interface and the user interface that is the subject of the complete response. We strongly recommend you submit this information to the Agency for review prior to resubmitting NDA 216962 to ensure the Agency agrees with your determination regarding the HF data need to support your revised user interface. If you determine that you do need to submit the results of an additional HF validation study for your revised user interface, we recommend you submit your study protocol for feedback from the Agency before commencing your study and prior to resubmitting NDA 216962. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible, but this is a decision for your company.

- Results from the HF validation study reported use errors with responding to alarms, which may result in loss of mobility. After you consider the deficiencies above, we recommend you consider adding an alarm troubleshooting guide regarding the alarms and corrective actions to resolve the alarms that is attached to the pump to minimize the risk of users failing to respond to alarms adequately. We recommend you ensure the information in the alarm troubleshooting guide is consistent with the Instructions for Use. Additionally, consider adding the helpline phone number and hours the helpline is available to the pump so users can contact the helpline to assist with resolving alarms or other issues if needed. We acknowledge the Instructions for Use provides information on corrective actions to take to respond to alarms; however, this information may not be always readily available to users.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please contact Stacy Metz, PharmD, Senior Regulatory Project Manager, at stacy.metz@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Teresa Buracchio, MD
Director
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TERESA J BURACCHIO
03/17/2023 04:17:00 PM