CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761133Orig1s000

OTHER ACTION LETTERS

BLA 761133

COMPLETE RESPONSE

Takeda Pharmaceuticals, U.S.A., Inc.
Attention: Mayuresh Gadre
Senior Manager
Global Regulatory Affairs Development, GI
40 Landsdowne Street
Cambridge, MA 02139

Dear Mr. Gadre:

Please refer to your biologics license application (BLA) dated March 7, 2019, received March 7, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for MLN0002 SC.

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.

PRODUCT QUALITY

(b) (4)

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(b) (4)

HUMAN FACTORS

(5) The human factors (HF) validation study results for your Entyvio prefilled pen submitted on March 7, 2019 identified several use errors, close calls, and use difficulties with critical and non-critical tasks. However, you did not implement revisions to the product user interface to address these use-related issues. Upon review of the subjective feedback from study participants and your root cause analyses, we identified several recommendations to revise the user interface, including revisions to: device design, device label/labeling, (b) (4) (b) (4) and the Instructions for Use (IFU) to improve prominence, clarity, and understanding of important information.

The below recommendations (see Section below titled Product Design, Labels, and Labeling) are based on our review of the subjective feedback and root cause analysis of the use-related issues. We recommend that you implement these revisions along with additional mitigations that you determine to be necessary to address these use-related issues and conduct and submit results of another human factors validation study to demonstrate that the mitigations are effective and do not introduce new risks.

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(b) (4)

B. Prefilled Pen Instructions for Use (IFU)

1. Based on the HF study results and our heuristic analysis and expert review, we recommend labeling each figure (e.g., Figure A, B, C, etc.) and identifying which figure is related to the respective task/step, to improve the understanding and clarity of each task. For example:

(b) (4)

2. Based on the errors observed related to selecting the correct injection site, we recommend revising the figure depicting the back of the arm injection sites to better anatomically capture the appropriate injection sites. It is unclear from the current figure whether the shaded areas depict the front or the back of the arm (b) (4)
3. Based on the errors observed with participants recapping the pen, we recommend improving the emphasis of the “Do not” statements under “Pull the purple cap straight off and throw it away” in the IFU to minimize the risk of dose omission and disease reoccurrence.
4. Based on the errors observed related to administering a full dose, we recommend revising the IFU to further clarify the end of injection cues and better present this information to minimize the risk(s) of an underdose and disease reoccurrence. Additionally, consider revising the figures under (b) (4)” related to the injection sequence to add “clicks” placed near the needle end of the device and clarify to the user what each click signifies.

5. Based on the errors observed related to checking that the window is filled with purple, we recommend revising the IFU to improve emphasis and clarity around this task to minimize the risk of an underdose and disease reoccurrence. Additionally, consider including a fourth figure under (b) (4) ” after the confirmation figure that depicts lifting the prefilled pen from the injection site to complete the sequence. Based on the errors observed related to the knowledge task of having concerns with this product around children, we recommend revising the IFU to increase prominence of the Important Information section. You may also consider adding the statement under the storage section as well to minimize the risk of inadvertent pediatric exposure.
6. Based on the errors observed related to the knowledge task of what to do after removing the product from the refrigerator, consider revising the IFU to increase prominence and improve clarity to this preparation task to minimize the risk of pain at the injection site.
7. Based on the errors observed related to the knowledge task of knowing the device is safe to use, we recommend revising the IFU to emphasize this information to minimize the risk of an immune reaction, infection or reoccurrence of disease.

C. Prefilled Pen Device Labeling
   1. Based on the errors observed and subjective feedback related to removing the cap and placing the needle against the skin, we recommend labeling the needle end on the device body to minimize the risk of a needle stick injury and an underdose.

D. Prefilled Pen Device Design
   1. Based on the errors observed related to removing the cap and placing the needle against the skin along with the subjective feedback provided by the participants (e.g., the cap looked like a spring or button), consider revising the design of the cap to remove the ridges to minimize the risk of a needle stick injury and an underdose.

E. (b) (4)
(b) (4)

F. Prefilled Syringe IFU
   1. We recommend applying the following recommendations found under the Autoinjector IFU recommendations: C.1-2 and C.7-8 to the PFS IFU.

We acknowledge you submitted a HF study results report on December 9, 2019; however, we recommend you consider our recommendations for the user interface above, which may result in changes to your final intend-to-market user interface.

PRESCRIBING INFORMATION

(6) We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] 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 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.[3]

CARTON AND CONTAINER LABELING

(7) Submit draft carton and container labeling revised as follows:

A. General

1. Based on the incorrect responses related to the knowledge task comprehension question "Where would you store this product?" we recommend bolding the storage statement: "Store refrigerated at 2°C to 8°C (36°F to 46°F)" to increase prominence and minimize the risk of the storage information being overlooked.

2. As currently presented, the format for the expiration date is defined as MM/YYYY. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. We recommend revising the proposed expiration date format to improve clarity.

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

3. Revise the “Manufactured by” statement to be consistent with the name of the applicant Takeda Pharmaceuticals, U.S.A ., Inc. on the Form FDA 356h.

B. Container Label (prefilled syringe label)

1. Please provide a label with a linear bar code per 21 CFR 201.25 and 21 CFR 610.67. The bar code requirement does not apply to prescription drug samples.

C. Container Label (prefilled pen label)

1. Please include the handling statement “Do not shake”.

2. Please provide a label with a linear bar code per 21 CFR 201.25 and 21 CFR 610.67. The bar code requirement does not apply to prescription drug samples.

D. Tray Lid Labeling

1. Please revise the wording from (b) (4) to read “No Preservative” per 21 CFR 610.61(e).

2. Please include the handling statement “Do not shake”.

3. Please provide a label with a linear bar code per 21 CFR 201.25 and 21 CFR 610.67. The bar code requirement does not apply to prescription drug samples.

E. Carton Labeling

1. Please revise the wording from (b) (4) to read “No Preservative” per 21 CFR 610.61(e).

2. Please include the handling statement “Do not shake”.

3. Consider revising the inactive ingredient “Sodium citrate dihydrate” to appear in lower case lettering to be consistent with the format of the other inactive ingredients.

4. Consider revising your dosage statement to read “Dosage: See Prescribing Information”. The term prescribing information is more consistent with labeling following the Physician Labeling Rule format.

MEDICATION GUIDE

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

PROPRIETARY NAME

The review of your proposed proprietary name has been terminated due to the deficiencies with the application as described in this letter. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

NON-PROPRIETARY NAME

We acknowledge that the Agency previously notified you that your proposed BLA is within the scope of the naming guidance[4] and that FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA. However, we have determined that a suffix will not be designated for this proposed product. Therefore, vedolizumab will be the proper name designated in the license should your 351(a) BLA be approved in a future resubmission.

FACILITY INSPECTIONS

(9) During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved in a future resubmission.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies/trials of the product 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:

[4] Available at https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf

- 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 patient 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 product. Include an updated estimate of use for product 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:

Product Quality

1. Reference is made to the deficiencies related to product quality (i.e., for device design, control and performance) and the recommended resolution to these deficiencies as conveyed above. While the deficiencies are related to the manufacture and control of device-constituents of the proposed combination products, changes that could significantly impact the manufacture and control of vedolizumab and final combination products (b) (4) (b) (4) are recommended to address

these deficiencies. Therefore, the Chemistry, Manufacturing and Control (CMC) information and data provided are considered inadequate to support the intended performance of the proposed combination products from a biologic product quality perspective. You should perform a risk assessment to determine the type and amount of additional CMC information and data (e.g., process development, process validation, comparability, compatibility, stability data, etc.) that need to be provided in the BLA resubmission, and update the appropriate Module 3 sections to reflect any CMC changes made to fully address these deficiencies. For ease of review, include a detailed summary table of the location and justification for updates made to each Module 3 section. If you intend to leverage information and data currently provided in the BLA to support the introduction of CMC changes and/or the manufacture of vedolizumab, device, and final combination product(s) in the resubmission, provide appropriate justification to support the relevance of the information and data. The updated CMC information and data provided in the resubmission will be evaluated to support the licensure of the proposed combination product(s).

2. (b) (4)

3. 

Microbiology

4. (b) (4)

5. The response to question 5 of sequence 0022 indicates that the rabbit pyrogen test (RPT) will be implemented as an interim release test for the drug product until a suitable in vitro endotoxin method is developed. The release RPT may not be necessary if you can demonstrate that endotoxin spiked drug product samples are not pyrogenic in rabbits. Refer to PDA Technical Report 82 for additional information on endotoxin dosing in rabbits. In addition, the Bacterial Endotoxin Test specification should remain in 3.2.P.5.1 until a suitable endotoxin method is developed.

Clinical Pharmacology

6. If major changes in formulation or device are made in order to address the identified major deficiencies, additional clinical pharmacology studies may be necessary to bridge between the to-be-marketed and clinical trial formulations/presentations. We encourage you to request a meeting to discuss the potential need for additional PK studies prior to resubmission.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b)). 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 601.3(c). 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.

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, contact Kelly Richards, Senior Regulatory Health Project Manager, at (240) 402-4276 or kelly.richards@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

Joyce Korvick, MD, MPH
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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/

JOYCE A KORVICK
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