



NDA 205508

COMPLETE RESPONSE

Heritage Pharmaceuticals Inc. d/b/a/ Avet Pharmaceuticals Inc.
U.S. Agent for Emcure Pharmaceuticals Limited, India
Attention: Bernadette Attinger
Vice President, Regulatory Affairs
One Tower Center Boulevard Suite 1700
East Brunswick, NJ 08816

Dear Ms. Attinger:

Please refer to your new drug application (b) (4)

for the following drug product:

- Atazanavir Sulfate and Ritonavir Tablets, (b) (4).

We acknowledge receipt of your amendment dated (b) (4), which constituted a complete response to our (b) (4), tentative approval action letter.

We also acknowledge receipt of your product quality amendment dated (b) (4), with supporting amendment dated (b) (4), which was not reviewed for this action. This amendment proposed withdrawal of the original drug product manufacturing facility, (b) (4)

and proposed a new drug product manufacturing facility, (b) (4)

you may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

Furthermore, we refer to our discipline review letter (DRL) dated (b) (4), informing you that the data (i.e., original exhibit batches and bio-batches) generated at the original drug product manufacturing facility, (b) (4) which were used to support the tentative approval decision for this application on (b) (4) may be potentially unreliable. Also, as stated in this DRL, we provided recommendations and expectations for you to address and mitigate our data reliability concerns.

We have received and reviewed your response dated and received (b) (4) to our DRL, where you informed the Agency of your plan to conduct a new bioequivalence (BE) study using batches manufactured at the new drug product manufacturing site, (b) (4) in order to address the Agency's data reliability concerns.

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

- (1) Following a CGMP inspection of the (b) (4) facility 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 Form 483 prior to your complete response submission to this application. 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 application. Therefore, you should coordinate with the facility for timely resolution. Your complete response submission to this application should include the date(s) of the facility's response(s) to the FDA Form 483 observations. 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 PAI of the facility. Satisfactory outcomes of both the PAI and the CGMP surveillance inspections will be needed prior to approval of the application.
- (2) To ensure the manufacturing process and controls proposed at the (b) (4) facility are adequately supported, submit the entire CMC data package for the new bio-batch to be used in the new BE study and any additional data generated at the new manufacturing facility for all applicable sections of Module 3, including 3.2.P.3 and 3.2.R, etc., in your resubmission. Prominently identify in your cover letter that the submission contains new CMC data. Additional information may be requested as needed in the next review cycle of this application.

BIOEQUIVALENCE/BIOAVAILABILITY

- (3) Due to the potential reliability concerns on the data generated at the original drug product manufacturing facility (b) (4) the results from the BE studies previously conducted are not able to provide sufficient evidence to support whether a newly manufactured batch within CGMP compliance will be bioequivalent to the reference drug(s).

PRODUCT QUALITY

(b) (4)



PRESCRIBING INFORMATION

(7) We reserve comment on the proposed labeling, which also includes your labeling amendments dated and received (b) (4), respectively, until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources¹ and Pregnancy and Lactation Labeling Final Rule² 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.

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

² <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

(b) (4)

CONTAINER LABELING

- (8) We reserve comment on the proposed labeling, which also includes your labeling amendment dated and received (b) (4), until the application is otherwise adequate.

ADDITIONAL COMMENTS

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

- (9) Provide further clarification in the cover letter and in Module 3 of your resubmission regarding whether you are withdrawing the (b) (4) facility, including all the data generated at this facility, or if you are delisting this facility as the commercial manufacturer and plan to retain the data in Module 3 to support a future regulatory decision by the Agency. Plan to provide this clarification in your resubmission to this complete response letter (CRL).

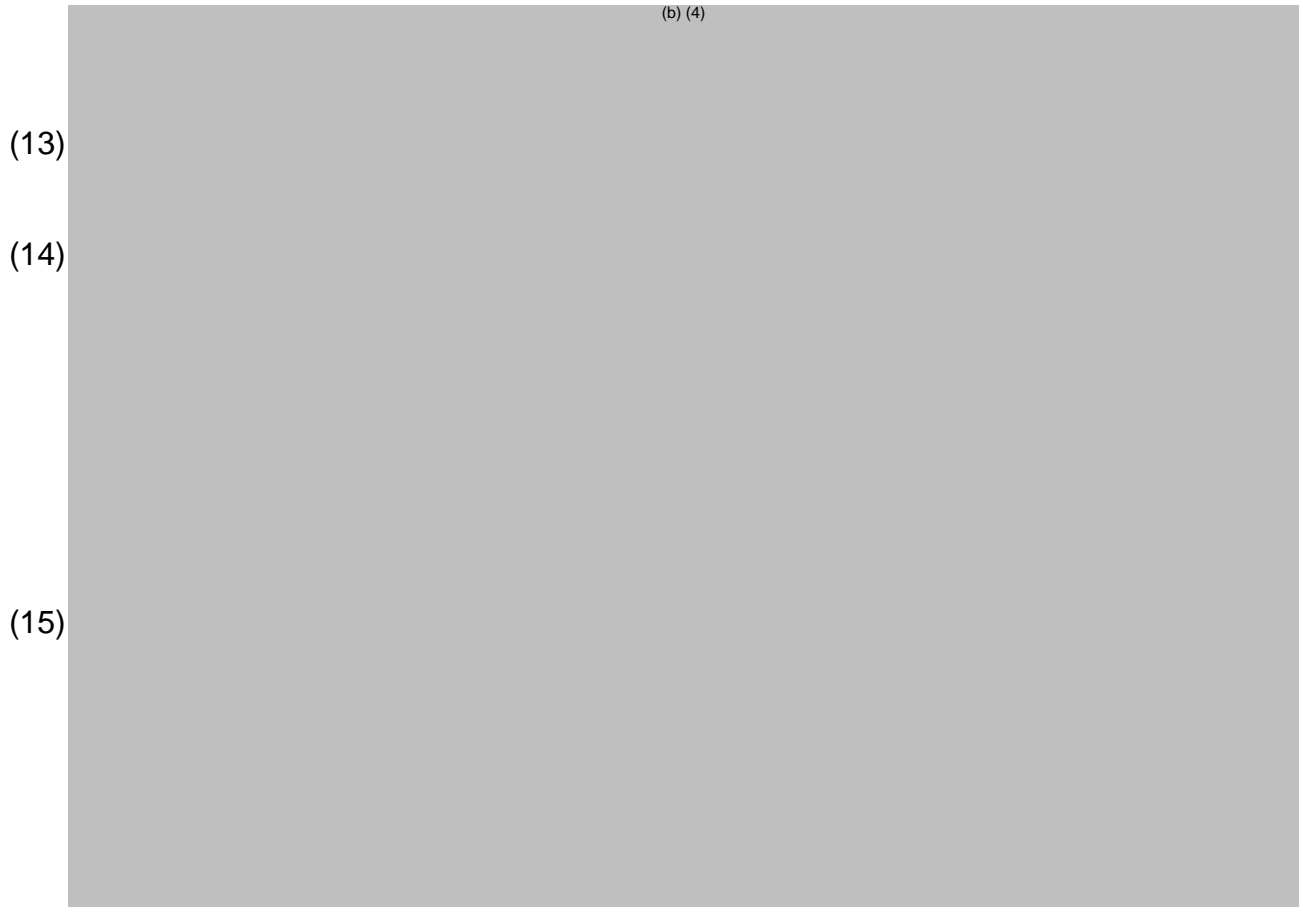
(10)

(b) (4)

(11)

(12)

(b) (4)



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 product is not approved and may not be legally marketed in the United States until you have been notified in writing that this application is approved. Moreover, as described in 21 CFR 314.105(d), FDA's tentative approval of a drug product is based on information available to FDA at the time of the tentative approval letter (i.e., information in the NDA and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to FDA's attention. The status of your application in FDA's PEPFAR database will be reflected accordingly.

If you have any questions, please contact

(b) (4)

Sincerely yours,

{See appended electronic signature page}

(b) (4)

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/

(b) (4)

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