### Part 1: General information

#### Company information

<table>
<thead>
<tr>
<th>Name of Manufacturer</th>
<th>Hetero Labs Ltd. Unit 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corporate address of manufacturer</td>
<td>Hetero Corporate 7-2-A2 Industrial Estates Sanath Nagar, Telangana Hyderabad, 500 018 India</td>
</tr>
</tbody>
</table>

#### Inspected site

<table>
<thead>
<tr>
<th>Name &amp; address of manufacturing site</th>
<th>Hetero Labs Ltd. Unit 3, Survey No.120, 128, 150 (PART), 150/1, 151/2 &amp;158/1, N. Narasapuram, Nakkapally (M), Visakhapatnam, Andhra Pradesh, 531 081, India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic Unit/Block/Workshop</td>
<td>Production blocks E, I, P, J Intermediate Drying section - I</td>
</tr>
</tbody>
</table>

#### Desk assessment details

<table>
<thead>
<tr>
<th>Date of review</th>
<th>5 October 2022</th>
</tr>
</thead>
<tbody>
<tr>
<td>APIs covered by this desk assessment</td>
<td>1. Lamivudine API intermediate used in Dolutegravir (sodium)/Lamivudine/Tenofovir Disoproxil fumarate tablet, film-coated 50mg/300 mg/300 mg 2. Emtricitabine intermediate 3. Dolutegravir intermediate</td>
</tr>
</tbody>
</table>

#### List of documents submitted

- A list of all regulatory inspections performed in the last 5 years and their outcomes;
- The full inspection reports, including deficiency letters, for inspections performed by a competent stringent regulatory authority in the past three years with a certified translated copy where this is not in English;
- Proof of CAPA implementation and final decision by the competent stringent regulatory authority related to observations or deficiencies noted in the latest inspection report or to any warning letter or equivalent regulatory action (production-line specific);
- A copy of the manufacturing authorization and GMP certificate granted by the local national authority together with a certified translation, where this is not in English;
e. A site master file whose approval date was not more than one year ago, and any forecast modifications, together with legible colour printouts of water treatment and air-handling systems, including pipeline and instrumentation drawings in A3 or A2 format;

f. The list of all the products including APIs manufactured on-site;

g. The most recent product quality review (PQR) of the concerned API covering all required subsections and trend results, including statistical evaluation;

h. The completed batch manufacturing and packaging records, including the analytical part, for the most recently validated/released batch of relevant product;

i. The list of any recalls in the past three years related to any product manufactured on site with quality defects;

j. A confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the product has been performed and all matters dealt with;

k. Master batch manufacturing and packaging records of the WHO product of interest;

l. Copy of any warning letter, or equivalent regulatory action, issued by any authority to which the site provides or has applied to provide the product;

m. Description of any recent or foreseen out-of-stock situations;

n. A list of notifications of upcoming inspections by competent national regulatory authorities in the next 6 months.

Any documents missing?  N/A

### Part 2

**Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments**

**USA FDA**

- Dates of inspection: 19 to 23 November 2018
- Type of inspection: Pre-approval for intermediate
- Block/Unit/Workshop: Not mentioned
- APIs covered: Imatinib Mesylate API intermediate by chemical synthesis

### Part 3

**Summary of the last WHO inspection**

- Date and conclusion of most recent WHO inspection: 18 October 2017
  - Compliant with GMP for APIs

**Brief summary of manufacturing activities**

Unit III had several production blocks for the production of intermediates. Block E was dedicated to Lamivudine anhydrous. Activities in various blocks included hydrogenation, and other steps and stages in the production, drying and control of intermediates and APIs.
<table>
<thead>
<tr>
<th>General information about the company and manufacturing site</th>
<th>Production, packaging, labelling and control of intermediates and APIs. The company Hetero Drugs Ltd has several manufacturing sites. Unit III was established in 2008 and produces and controls key starting materials, intermediates and APIs. A full description was provided in the 80 page (plus annexes) Site Master File dated effective September 2022.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focus of the last WHO inspection</td>
<td>Pharmaceutical Quality system Documentation system Production system Facilities and equipment system Laboratory control system</td>
</tr>
<tr>
<td>Areas inspected</td>
<td>Generally, all areas of WHO GMP were covered during the inspection. This included, but was not limited to quality system, reprocessing, reworking, complaints, premises, equipment, materials, production system, computerized systems and others. The report was available and the WHOPIR was already archived.</td>
</tr>
<tr>
<td>Out of scope and restrictions (last WHO inspection)</td>
<td>N/A</td>
</tr>
<tr>
<td>WHO APIs covered by the last WHO inspection</td>
<td>Sofosbuvir API intermediate Lamivudine API intermediate Atazanavir API intermediate</td>
</tr>
<tr>
<td>Additional products to be covered by this desk assessment</td>
<td>General GMP for APIs, see also above Emtricitabine API intermediate Dolutegravir API intermediate</td>
</tr>
<tr>
<td>Abbreviations</td>
<td>Meaning</td>
</tr>
<tr>
<td>BMR</td>
<td>Batch manufacturing record</td>
</tr>
<tr>
<td>BPR</td>
<td>Batch production record</td>
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<tr>
<td>CAPA</td>
<td>Corrective and preventive action</td>
</tr>
<tr>
<td>CC</td>
<td>Change control</td>
</tr>
<tr>
<td>GMP</td>
<td>Good manufacturing practices</td>
</tr>
<tr>
<td>NC</td>
<td>Non conformity</td>
</tr>
<tr>
<td>NRA</td>
<td>National regulatory agency</td>
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<tr>
<td>PQR</td>
<td>Product quality review</td>
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<td>PQS</td>
<td>Pharmaceutical quality system</td>
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<tr>
<td>QA</td>
<td>Quality assurance</td>
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<tr>
<td>QC</td>
<td>Quality control</td>
</tr>
<tr>
<td>QCL</td>
<td>Quality control laboratory</td>
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<tr>
<td>QMS</td>
<td>Quality management system</td>
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<tr>
<td>QRM</td>
<td>Quality risk management</td>
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Part 4  Summary of the assessment of supporting documentation

a) Manufacturing authorization and GMP certificate granted by the local authority:

A copy of the license and GMP certificate were provided.

b) Site master file (SMF):

A detailed, 80 page SMF, with annexes (meeting the guideline for SMFs) were submitted. The document was dated September 2022 and found acceptable.

c) List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:

A list consisting of 8 pages, was provided – listing the chemical intermediates / substances produced on site.

d) List of all regulatory inspections performed in the last 3 years and their outcomes:

Drug Control Administration (DCA), Andhra Pradesh, India. June 2022

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO API(s):

Product quality review reports were submitted for Dolutegravir, Lamivudine and Emtracitabine intermediates. (Note: No batches of Emtracitabine were manufactured during the period January to December 2021). The PQR reports were acceptable and represented the required sections for review including complaints, trending of data, hold time, recalls etc. In general, results were tabulated and graphically presented including control limits or calculation of process capability index.

f) Batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant API(s):

Batch records and parts of an analytical report were submitted for Dolutegravir and Lamivudine intermediate. These were generally acceptable and no comments were made.

g) Master batch manufacturing and packaging record(s) of the API(s) of interest:

Declared that the company has ceased manufacturing Emtracitabine intermediate. Parts of the master documents were submitted for dolutegravir (process I), lamivudine and (dolutegravir process II)

h) Recalls in the past three years related to APIs with quality defects:

Hetero Labs Ltd., Unit 3, Visakhapatnam, India-Desk Review-API 5 October 2022
This inspection report is the property of the WHO
Contact: prequalinspection@who.int
The company declared that there were no recalls in the last 3 years

i) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the API(s) has been performed and all matters dealt with:

The company declared that a self-inspection programme was followed.

j) copy of any warning letter, or equivalent regulatory action, issued by any authority for their market, to which the site provides or has applied to provide the API(s):

The company declared that no warning letter (or similar) had been received to date.

k) Out-of-stock situations:

The company had no recent out-of-stock product and did not foresee any out-of-stock situation in the near future.

l) Additional documents submitted:

N/A

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<tr>
<th>Part 5</th>
<th>Conclusion – Desk assessment outcome</th>
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<tr>
<td>N/A</td>
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</table>

Based on the previous WHO inspections and on the GMP evidence received and reviewed, it is considered that a desk assessment is acceptable in lieu of a WHO onsite inspection. The site Hetero Labs Ltd., Unit 3, located at Survey No.120, 128, 150 (PART), 150/1, 151/2 &158/1, N. Narasapuram, Nakkapally (M), Visakhapatnam, Andhra Pradesh, 531 081, India is considered to be operating at an acceptable level of compliance with WHO GMP guidelines for APIs.

This WHOPIIR will remain valid for 3 years provided that the outcome of any inspection conducted during this period is positive.

<table>
<thead>
<tr>
<th>Part 6</th>
<th>List of guidelines referenced in this inspection report</th>
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9789240020900-eng.pdf (who.int)


  Short name: WHO TRS No. 961, Annex 7

  Short name: WHO TRS No. 961, Annex 9

  Short name: WHO TRS No. 943, Annex 3
  https://digicollections.net/medicinedocs/#d/s21438en

  Short name: WHO TRS No. 961, Annex 2

  Short name: WHO TRS No. 981, Annex 2
  https://digicollections.net/medicinedocs/#d/s20177en/

  Short name: WHO TRS No. 981, Annex 3
  https://digicollections.net/medicinedocs/#d/s20175en/
**Short name: WHO TRS No. 961, Annex 14**
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1


Essential Medicines and Health Products Information Portal (digicollections.net)

9789240020900-eng.pdf (who.int)

**Short name: WHO TRS No. 996, Annex 10**


9789240020900-eng.pdf (who.int)

9789240001824-eng.pdf (who.int)