## Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer

### Part 1: General information

<table>
<thead>
<tr>
<th>Company information</th>
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<tbody>
<tr>
<td>Name of Manufacturer</td>
<td>Hetero Labs Limited (Unit 1)</td>
</tr>
</tbody>
</table>
| Corporate address of manufacturer | Hetero Labs Limited  
 Hetero Corporate,  
 7-2-A2 Industrial Estates  
 Sanath Nagar, Hyderabad  
 500 018 Telangana, India |

<table>
<thead>
<tr>
<th>Inspected site</th>
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</table>
| Name & address of manufacturing site | Hetero Labs Limited (Unit 1)  
 Survey No 10, I.D.A,  
 Gaddapotharam Village,  
 Jinnaram Mandal, Sangareddy Dist  
 502319  
 Telanagana, India |

### Desk assessment details

<table>
<thead>
<tr>
<th>Date of review</th>
<th></th>
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<tbody>
<tr>
<td>19 October 2022</td>
<td></td>
</tr>
<tr>
<td>APIs covered by this desk assessment</td>
<td>See full list of APIs under section c) below</td>
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</tbody>
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<table>
<thead>
<tr>
<th>List of documents submitted</th>
<th>The following documents were requested:</th>
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</thead>
<tbody>
<tr>
<td>a)</td>
<td>A list of all regulatory inspections performed in the last 5 years and their outcomes, including “non-compliant” inspections;</td>
</tr>
<tr>
<td>b)</td>
<td>Current full inspection report(s), 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;</td>
</tr>
<tr>
<td>c)</td>
<td>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);</td>
</tr>
<tr>
<td>d)</td>
<td>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;</td>
</tr>
<tr>
<td>e)</td>
<td>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;</td>
</tr>
</tbody>
</table>
f) The list of all the products and dosage forms manufactured on-site. The list should include proprietary names and International Nonproprietary Names (INN), including all types of chemicals and products (e.g., pesticides, herbal medicines, chemicals or veterinary products, etc.);
g) The most recent product quality review(s) (PQR(s)) of the concerned product(s); PQR(s) or equivalent documentation covering all required subsections and trend results, including statistical evaluation;
h) The completed batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant product(s);
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(s) has been performed and all matters dealt with;
k) Master batch manufacturing and packaging record(s) of the WHO product(s) 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.

### Part 2  
Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments

<table>
<thead>
<tr>
<th><strong>USA FDA</strong></th>
<th>Dates of inspection:</th>
<th>2 to 12 August 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of inspection:</strong></td>
<td>GMP for APIs</td>
<td></td>
</tr>
<tr>
<td><strong>Block/Unit/Workshop:</strong></td>
<td>Unit 1</td>
<td></td>
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<tr>
<td><strong>APIs covered:</strong></td>
<td>Various sartans</td>
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**Note**

The company submitted several rounds of corrective actions to USA FDA. The bulk of the CAPAs are related to “Sartans” and impurities including control of the process and validation of analytical procedures. The observations made by USFDA were more specifically relating to specific products that have not been submitted for WHO Prequalification and related impurities.

### Part 3  
Summary of the last WHO inspection

<table>
<thead>
<tr>
<th><strong>Date and conclusion of most recent WHO inspection</strong></th>
<th>October 2019 (Desk review) – GMP compliant</th>
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<tbody>
<tr>
<td><strong>20-24 February 2017 (Onsite) – GMP compliant</strong></td>
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**Brief summary of**

Production and control of APIs
| **General information about the company and manufacturing site** | According to the last WHO on-site inspection report, the site is located in Survey No.10, IDA, Gaddapotharam village, Jinnaram Mandal, Sangareddy district-502319, Telangana, India. There were 13 Production blocks (A, B, C, D, E, F, G, H, I, J, K, L, M) for pharma related production: Blocks E, G and M were for intermediates production. Blocks F, I, K and L were for oncology APIs. Penicillin, beta lactam antibiotics and hormonal APIs were not produced on this site. |
| **Focus of the last WHO inspection** | October 2019 Desk review, based on inspection reports for USA FDA, Health Canada, OGYEI Hungary, PMDA Japan. February 2017 Onsite inspection: |
| **Areas inspected** | Blocks A, B, C, D and H and ancillary areas were covered during the 2017 WHO Onsite inspection. |
| **Out of scope and restrictions (last WHO inspection)** | Manufacturing blocks that were not used for WHO APIs were not inspected. |
| **WHO APIs covered by the last WHO inspection** | Lopinavir  
Stavudine  
Tenofovir disoproxil fumarate  
Emtricitabine  
Lamivudine  
Abacavir sulfate  
Zidovudine  
Efavirenz  
Atazanavir monosulphate  
Abacavir sulfate  
Sofosbuvir  
Dolutegravir sodium  
Daclatasvir dihydrochloride  
Darunavir |
| **Additional products to be covered by this desk assessment:** | See section c |

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<tr>
<th><strong>Abbreviations</strong></th>
<th><strong>Meaning</strong></th>
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<tr>
<td>BMR</td>
<td>Batch manufacturing record</td>
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<tr>
<td>BPR</td>
<td>Batch production record</td>
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<tr>
<td>CAPA</td>
<td>Corrective and preventive action</td>
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<td>CC</td>
<td>Change control</td>
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<tr>
<td>GMP</td>
<td>Good manufacturing practices</td>
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<tr>
<td>NC</td>
<td>Non conformity</td>
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Hetero Labs Ltd, Unit I, Gaddapotharam, India-Desk Review-API

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<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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<td>QC</td>
<td>Quality control</td>
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<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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<td>QRM</td>
<td>Quality risk management</td>
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<tr>
<td>RA</td>
<td>Risk assessment</td>
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<tr>
<td>RCA</td>
<td>Root cause analysis</td>
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<tr>
<td>SOP</td>
<td>Standard operating procedure</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 manufacturing authorization issued by the local authority, was submitted.

b) Site master file (SMF):

A SMF (effective 22 July 2022) was submitted and was found acceptable.

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

The site listed 121 APIs being manufactured on site by chemical synthesis, from many different classes. There are no penicillins or beta-lactam antibiotics or steroidal hormones manufactured on site.

The list of APIs for the WHO is the following:
- Sofosbuvir
- Lopinavir
- Tenofovir Disoproxil fumarate
- Emtricitabine,
- Abacavir (sulfate)
- Dolutegravir (sodium)
- Daclatasvir (dihydrochloride)
- Darunavir (ethanolate)
- Dolutegravir (sodium)
- Velpatasvir
- Nevirapine Anhydrous,
- Efavirenz
d) List of all regulatory inspections performed in the last 3 years and their outcomes:

- AIFA, Italy. 28 January 2019 to 2 February 2019. Acceptable
- AEMPS, Spain. 28 January 2019 to 2 February 2019. Acceptable
- OGYEI, Hungary. 18 March 2019 to 22 March 2019. Acceptable
- WHO. PQT, Geneva. 2 September 2019 to 1 October 2019. Acceptable
- NDA, Uganda. 12 September 2019 to 13 September 2019. Acceptable
- CDSCO, India. 17 September 2019 to 19 September 2019. Acceptable
- CDSCO, India. 4 November 2019 to 6 November 2019. Acceptable
- DCA, India. 4 November 2019 to 6 November 2019. Acceptable
- CDSCO, India. 23 June 2021 to 25 June 2021. Acceptable
- DCA, India. 23 June 2021 to 25 June 2021. Acceptable
- FDA, USA. 2 August 2021 to 12 August 2021. OAI
- DCA, India. 17 August 2022 to 18 August 2022. Await report
- CDSCO, India. 17 August 2022 to 18 August 2022. Await report
- PMDA, Japan. 23 August 2022 to 25 August 2022. Await report

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

The company submitted several product quality review reports for the period of January to December 2021. A few were randomly selected for review.

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

The company submitted batch manufacturing records (and certificates for analysis) for several products. A few were randomly selected for review. See comments below.

- Daclatasvir dihydrochloride
- Dolutegravir sodium
- Abacavir sodium
- Lopinavir
- Emtricitabine
- Sofosbuvir
- Darunavir ethanolate
- Abacavir sulfate

Batch production records were generally found acceptable.

Copies of analytical reports for various products, (as above) were submitted. Spot checks were done. The reports were generally found acceptable and no significant observations were made.
Declaration:
The company provided a declaration stating that the following products had not been manufactured during the previous 3 years:
- Velpatasvir
- Tenofovir disoproxil fumarate
- Lamivudine
- Efavirenz

g) Master batch manufacturing and packaging record(s) of the API(s) of interest:
The following master records were submitted. These were spot checked and found acceptable in general.
- Daclatasvir dihydrochloride
- Dolutegravir sodium
- Abacavir sulfate
- Lopinavir
- Emtricitabine
- Emtricitabine
- Sofosbuvir
- Darunavir ethanolate
- Abacavir sulfate
- Velpatasvir
- Tenofovir disoproxil fumarate
- Lamivudine
- Efavirenz
- Nevirapine

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

Losartan Potassium. 99 Batches were recalled on 30 October 2021 due to the presence of Azido impurity. The recall is completed.

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 provided a declaration that a self-inspection is conducted every six months.

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 provided a declaration stating that there no warning letter (or equivalent had been issued to the company.
k) Out-of-stock situations:

The company issued a declaration that no out of stock situation had been experienced, or was foreseen.

l) Additional documents submitted:

The following inspections were anticipated:
ANVISA, Brazil. September 2022
COFEPRIS, Mexico. October 2022
Health Canada, Canada. October 2022

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<tr>
<th>Part 5</th>
<th>Conclusion – Desk assessment outcome</th>
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<tbody>
<tr>
<td>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 Limited Unit 1, located at Survey No 10, I.D.A, Gaddapotharam, Jinnaram Mandal, Sangareddy Dist. 502319, Telanagana, India is considered to be operating at an acceptable level of compliance with WHO GMP guidelines for APIs.</td>
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<tr>
<td>This WHOPIIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.</td>
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<tr>
<th>Part 6</th>
<th>List of guidelines referenced in this inspection report</th>
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</thead>
</table>

   Short name: WHO TRS No. 1033, Annex 3 
   9789240020900-eng.pdf (who.int)


   Short name: WHO TRS No. 929, Annex 4 


   Short name: WHO TRS No. 1010, Annex 8 


   Short name: WHO TRS No. 937, Annex 4 


   Short name: WHO TRS No. 961, 957), Annex 1


   Short name: WHO TRS No. 957, Annex 3


    Short name: WHO TRS No. 961, Annex 6

   **Short name:** WHO TRS No. 961, Annex 7
   


   [https://digicollections.net/medicinedocs/#d/s21438en](https://digicollections.net/medicinedocs/#d/s21438en)


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