Health and Youth Care Inspectorate
Ministry of Health, Welfare and Sport

> Return address Postbus 2518 6401 DA Heerlen

AANGETEKEND VERSTUREN
Annora Pharma Private Limited
Att. Mr. Mohan Reddy
Sy. No. 261, Annaram Village,
Gummadidala Mandal, Sangareddy District.
Telangana State – 502313
INDIA
Mobile: 9100464449

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Information
M. van Berlo
GMPinspections@igj.nl

Our reference
2018-
2135944/V2003797/MvB/cs

Enclosure(s)
1

Date 25 June 2018
Subject Final inspection report and GMP certificate

Dear Mr. Mohan Reddy,

Referring to the European GMP inspection of the premises of your company Annora Pharma Private Limited located near Hyderabad in India on 13-15 March 2018, I herewith send to you the final report of the inspection. Your comments on factual errors as sent to us on 28 April 2018 have all been included in the final report.

As the observations did not include any deficiencies classified as "critical" or "major", you were not requested to send us a corrective action plan as response to the deficiencies. However, we expect you to address the deficiencies classified as "other" adequately as will be verified during the next inspection of your site.

The conclusion of this inspection is that the company Annora Pharma Private Limited located in Sy. No. 261, Annaram Village, Gummadidala Mandal, Sangareddy District, Telangana State – 502313, INDIA operates in accordance with the EU GMP requirements. A EU GMP Certificate is enclosed.

On behalf of the inspection team, I thank you and your colleagues again for the hospitality shown to us during our stay in India.

Yours sincerely,

Health and Youth Care Inspectorate
Mr. Mos van Berlo
Coordinating/specialised senior inspector IGZ[1]

[1] In our signature, we use the organisation name referred to in laws within the area of public health and youth care.

Report Reference no.:	2018-2135944/V2003797/MvB/cs
Name of product(s) and pharmaceutical form(s):	Darunavir 400 mg, 600 mg and 800 mg film-coated tablets
1. Inspected site(s):	Annora Pharma Private Limited Sy. No. 261, Annaram Village, Gummadidala Mandal, Sangareddy District. Telangana State – 502313 India Site location identifier (DUNS number/GPS coordinates): DUNS number: 65-098-0746 GPS: latitude 17°37'18.33"N, longitude 78°22'51.72"E

2. Activities carried out:

	Human	Veterinary	IMP
Manufacture of finished products			
Sterile	☐	☐	☐
Non-sterile	☒	☐	☐
Biologicals	☐	☐	☐
Sterilisation of excipient, active substance or medicinal product	☐	☐	☐
Primary packaging	☒	☐	☐
Secondary packaging	☒	☐	☐
Quality control testing	☒	☐	☐
Importing	☐	☐	☐
Batch certification	☐	☐	☐
Storage and distribution	☒	☐	☐
Manufacture of active substance	☐	☐	☐
Other:	☐	☐	☐

3. Inspection date(s):	13 -15 March 2018
4. Inspector(s):	Lead: Mr. M. van Berlo, Dutch Health and Youth Care Inspectorate (IGJ) Support: Mrs. A.E. Nicia, Dutch Health and Youth Care Inspectorate (IGJ)
Expert(s):	Name(s) of expert/assessor (if applicable): N/A Name(s) of the Competent Authority(ies): N/A
5. References:	
6. Date(s) of previous inspection:	N/A
Name(s) of inspector(s) involved in previous inspection:	N/A

7. Introduction:

Annora Pharma Private Limited (hereinafter Annora) is a green field project and the construction was commenced in Nov 2015. The local manufacturing license was issued Oct 2016 and the first local GMP certificate was issued Jan 2018. Annora is a subsidiary company of the Hetero group but operates independently i.e. the Quality Management System (QMS) of Annora is stand-alone.

The activities envisaged at the site are the production and packaging of (film-coated) tablets, capsules, pellets, liquid orals, powders and suppositories for export only. At the time of the inspection, the construction of three production modules was completed and only exhibit batches had been manufactured for filing purposes in the US and the EU. No commercial production has taken place as of yet. Construction is ongoing and the site is expected to grow from the current approximately 300 employers to 800 employers within the next two to three years.

The site was inspected for a site clearance in connection with the DCP application for the marketing authorisation for Darunavir 400 mg, 600 mg and 800 mg film-coated tablets.

Major changes since the previous inspection:

N/A. This is the first inspection of the site.

International cooperation:

☒ The Competent Authority of the country where the inspection took place *was not* informed and *did not take* part in the inspection.

☐ Not applicable

8. Brief report of the inspection activities undertaken:

☒ GMP ☐ GDP ☐ GcLP

☐ Defect Notification ☒ Requested by: Dutch Medicines Evaluation Board (CBG-MEB)

☐ Routine ☐ Product specific:

Legal references:

☐ Geneesmiddelenwet (8 februari 2007, Stb. 93), Regeling Geneesmiddelenwet (25 juni 2007, nr. GMT/MVG 2780607, Stcrt. 123).

☐ Wet Dieren (19 mei 2011), Besluit Diergeneesmiddelen (2 november 2012), Regeling diergeneesmiddelen (12 december 2012).

☒ EU Guidelines to Good Manufacturing Practice for medicinal products for human and veterinary use (EUDRALEX Volume 4).

☐ EU Guidelines on Good Distribution Practice of medicinal products for human use (5 November 2013 - 2013/C 343/01)

☐ Other:

9. Inspected area(s) and main steps/history of the inspection:

Quality systems, warehouses, production areas, laboratories, utilities and equipment used in the production, packaging and storage of Darunavir film-coated tablets.

Activities not inspected:

Areas and activities not concerning the manufacture of Darunavir film-coated tablets.

10. Personnel met during the inspection:

Dr. G. Palleswara Rao, Director - Formulation Operations

H.S. Jagadeesha, General Manager – Operations

N. Rama Mohan Reddy, Senior General Manager - Quality Assurance

S. Bhagavan, Senior General Manager - Quality Control

D. Chiranjeevi, Deputy General Manager - Quality Assurance

Vishal Dengre, Senior Manager - Engineering

G.S. Gurumuthy, Senior Manager - Stores

11. Inspectors findings and observations relevant to the inspection; and deficiencies:

11.0 Deficiencies during last inspection

Not applicable.

11.1 Pharmaceutical Quality System

Management review

The following documents were reviewed:

- SOP OA/QA034-01 dated 8 Feb 2018 Quality Management Review
- Report of Q4 2017 dated 10 Jan 2018

No remarks were made.

Product Quality Review (PQR)

The following document was reviewed:

- SOP OA/QA057-00 dated 3 May 2017 Annual Product Quality Review

In the procedure for Annual Product Quality Review (OA/QA057-00), the maximum period between the reported period and the PQR report was not defined.

Deviations and CAPAs

The following documents were reviewed:

- SOP OA/QA 019-02: Handling of deviations (20-2-2018). "Deviations" are planned deviations.
- SOP OA/QA 018-02: Reporting, investigation and disposition of incidents (20-2-2018). "Incidents" are unplanned deviations.
- SOP OA/QC 006-01: Handling of laboratory incidents (18-8-2017).
- SOP OA/QA 021-01: CAPA (8-2-2018)
- Deviation log 2017 (30 deviations)
- Incident log 2017 (70 incidents)
- Incident OA/INR/17/PD0013: Lower coating bed temperature out of range for Efavirenz tablets USP 600mg (3-6-2017). No actions were defined because of incorrect interpretation of process validation scope, refer to 11.5 and 15.3.7.
- Incident OA/INR/18/EN0062: Data EMS not recorded for 8 hours (13-11-2017)
- Deviation OA/DVR/18/QC006: Change the dedication of HPLC column HC 079 from Darunavir to Bromocryptine (10-1-2018)
- Incident OA/INR/18/PD009: Multiple alarms during drying stage of batch OA180007 (22-1-2018)
- CAPA log 2017 (91 CAPA's)
- CAPA OA/CAPA/17/080: Issue with average fill weight and net fill weight: impacted batches recalculation pending and training to the concerned personnel pending (11-12-2017)
- Deviation OA/DVR/18/QC006: Change the dedication of HPLC column HC 079 from Darunavir to Bromocryptine (10-1-2018)

Changes

The following documents were reviewed:

- SOP OA/QA 004-00: Change control programme (17-6-2016)
- Change log 2017
- Change log 2018
- Documentation on change OA/CRN/17/QA0063 change of batch size of Levetiracetam oral solution 100 mg/ml from 1000 L to 900 L

- SOP OA/QA 023-01 Technology transfer of pharmaceutical product. This procedures prescribes the activities for introduction of new products
- OA/TTP/0004-00 Technology transfer protocol – Darunavir tablets 400mg, 600mg & 800mg (22-4-2017)

No remarks were made.

Agreement with Hetero Europe.

There is a Regulatory Service Agreement in place between Annora and Hetero Europe S.L. (Barcelona, Spain) for advise on regulatory activities but not yet a Quality Agreement concerning all activities for the medicinal products, refer to 11.12 and 15.5.1.

11.2 Personnel

The assessment of training was based on the following:

a. SOP OA/QA003-03 dated 6 Mar 2018 Training Programme
b. SOP OA/QC020-00 dated 20 Jul 2016 Training and Qualification for QC Personnel
c. Training file QC analyst K.C.
d. Training file operator L.V.
e. Demonstration of Nichelon 5 used for planning and tracking of training of the quality management system and general GMP training

No remarks were made.

11.3 Premises and Equipment

Facilities

During the tour, the following areas were visited: storage area for raw materials and packaging materials, sampling room, dispensing room, manufacturing area Module I regarding Darunavir film-coated tablet production, primary and secondary packaging for blister pack, manufacturing area Module II regarding Darunavir film-coated tablet primary and secondary packaging for bottle pack, storage of exhibit batches, technical area for Purified Water (PW) system and HVAC system, the QC laboratory (physicochemical and microbiological areas) and stability chambers.

The storage area for raw materials and packaging materials visited during the tour was temporary. Additional storage space was under construction including a finished product warehouse.

The following processes regarding the warehouse were discussed: receipt of materials, quarantine, sampling, status control and pest control. The manufacturing process is discussed in section 11.5

In addition the following documentation was reviewed:

- SOP OA/HR005-01 dated 7 Mar 2018 Pest and Rodent Control
- Insecticutors cleaning records (flying insects)
- Records of weekly checks for rodents, lizards and spiders

Quantitative data of pests other than flying insects were not collected nor evaluated.

Utilities

Temperature control, mapping, monitoring and handling of excursions of the temperature storage areas were discussed. For the temperature mapping of the main storage area in 2017, a three season mapping approach was applied, namely summer (May), monsoon (August) and winter (December). Mapping report OA/MSR/QA0008-01 (1-2-2018) was reviewed and found acceptable. Based on the mapping results, each room was fitted with a probe for temperature and relative humidity.

The pressure cascade, monitoring, handling of alarms and the preventive maintenance programme of the HVAC were discussed. When no sampling or dispensing is taking place, the HVAC of the sampling and dispensing areas is turned off. Prior to sampling or dispensing, the HVAC is turned on. This procedure was assessed based on SOP OA/QC013-02 Sampling, testing and release of raw materials (8-3-2018) and Annexure OA/QC013/A02 Line clearance of sampling room.

The arrangements in place in case of power failures were discussed. In addition the Service agreement with Macro Power Solutions signed 10 Jul 2017 was reviewed. An employee of the service

provider is always on site at Annora.

During the tour the schematics of the PW system were explained. The qualification and monitoring of the PW system was assessed based on the following documents:

- Performance qualification report water phase III OA/QR/EN-E0009-03-01
- SOP OA/QC012-03 dated 12 Feb 2018 Sampling, Testing and Release of Water
- OA/QC012/F01-01 version 00 Sampling schedule
- Monthly trend report Jan 2018 dated 15 Feb 2018
- Annual report, reporting period 31 Oct 2016 – 30 Oct 2017, dated 30 Nov 2017

Annora has defined a strategy to determine the house flora. Due to the life cycle of the facility, determination of the house flora is in a start up phase.

No remarks were made on utilities.

Equipment

The following documentation was reviewed:

- Validation Master Plan for Facility OA/VMP/001-00 dated 1 Jul 2016, including Annexure IX re-qualification schedule for production equipment.
- Master list of assets OA/QA012/F04-01 dated 15 Feb 2018
- SOP OA/QA015-01 dated 30 Jan 2018 Qualification and Re-qualification, including Annexure 14 Periodic review of equipments and facilities
- Documentation of the qualification of the rapid mixer granulator used in the production of Darunavir film-coated tablets; risk analysis report OA/RA/PD001-00, IOQ report OA/QR/PD-E0001-01-00 and PQ report OA/QR/PD-E0001-02-00.
- Documentation of the qualification of the fluid bed dryer used in the production of Darunavir film-coated tablets; IOQ report OA/QR/PD-E0003-01-00 and PQ report OA/QR/PD-E0003-02-00.
- Documentation of the qualification of the compression machine used in the production of Darunavir film-coated tablets; IOQ report OA/QR/PD-E0010-01-00 en PQ report OA/QR/PD-E0010-02-00.
- PQ report Tablet counter OA/QR/PD-E0046-02-00.
- SOP OA/EN001-3 Maintenance (12-2-2018).
- PM schedule 2018.
- PM checklist for rapid mixer granulator #PD-E0001 OA/PMP010-02 (executed 5-1-2018).
- SOP OA/QA007-03 Calibration (3-1-2018).
- Calibration schedule of measuring instruments for the year 2018.
- Calibration raw data record and certificate for pressure difference transmitter #PD-E0003/MI08 of the fluid bed dryer (executed 3-3-2018).

No remarks were made on equipment.

11.4 Documentation

Data integrity

The SOP on Data Integrity OA/QA029-01 dated 30 Nov 2017 and the SOP on Good Documentation Practice OA/QA005-01 dated 14 Sept 2017 were reviewed. Furthermore, the controls implemented to ensure the integrity of electronic QC data were discussed during the tour in the physicochemical lab and the assessment of the review of the analytical data. See also section 11.6.

An overall risk analysis concerning data integrity covering all types of data was not performed.

Batch documentation

The batch documentation for submission batch OA180007 was reviewed and discussed. It concerned the BMR and BPR for a batch of Darunavir tablets 800mg, approx. 135,000 tablets, mfd 01/2018. The specification for the addition times of purified water were not met. Additionally, limits for reconciliation of product and packaging materials were not yet set (also refer to section 11.5 Process validation). Furthermore, the following recommendation was made:

It is recommended to consider implementing a 100% weight control for bottles filled with tablets or

perform a more elaborated performance qualification of the counting device.

11.5 Production

The manufacturing process of Darunavir film-coated tablets consists of the following steps: dry mixing, wet granulation, drying, dry mixing, lubrication, compression, film-coating, primary packaging (blister and bottles) and secondary packaging. All steps were assessed, including set up and line clearance procedures, management of machine parts, in-process controls, transfer of materials, intermediate storage and cleaning.

At the time of the inspection, only exhibit batches of Darunavir film-coated tablets were manufactured. No printed materials were available yet and secondary packaging was performed manually where this will be (semi) automated for commercial batches.

Process validation

The following process validation reports were reviewed and discussed:

- OA/PVR/3100082-01-00 Darunavir tablets 400mg and 600mg (common blend) (13-3-2018).
- OA/PVR/3100083-01-00 Darunavir tablets 400mg (13-3-2018) - compression and coating.
- OA/PVR/3100081-01-00 Darunavir tablets 600mg (13-3-2018) - compression and coating.
- OA/PVR/3100079-01-00 Darunavir tablets 800mg (13-3-2018) – full process.

The acceptance criteria for a number of process parameters were not met during the validation such as fluid addition time and wet mixing time.

Before starting process validation, the process is insufficiently defined. Diversion of stated specifications for process parameters should not be standard practice. Furthermore, during current process validation exercises, these excursions were not addressed. Additionally, limits for reconciliation of product and packaging materials were not yet set.

Hold time studies

The following documents regarding intermediate hold time studies were reviewed and found acceptable:

- SOP OA/QA043-02 Procedure for hold time study (10-3-2018).
- Hold time study OA/HSP/0033-00 Darunavir tablets 400mg and 600mg (blend) (8-12-2017).
- Hold time study OA/HSP/0034-00 Darunavir tablets 400mg (tablets) (8-12-2017).
- Hold time study OA/HSP/0036-00 Darunavir tablets 800mg (blend + tablets) (8-12-2017).

Cleaning validation

The following documents were reviewed:

- Cleaning validation OA/QA030-01 dated 8 Mar 2018
- Cleaning validation protocol OA/CVP/0014-01
- Cleaning verification observation OA/CVR/0014-00
- Analytical method validation report OA/MVR/0021-00
- Cleaned equipments hold time study OA/MSR/QA0005-00
- Dirty equipment hold time study OA/MSR/QA0004-00

No remarks were made on cleaning validation.

11.6 Quality Control

Physicochemical laboratory

This part of the QC laboratory, including the stability chambers, was visited. The physicochemical laboratory is equipped for a wide range of tests like HPLC, GC, FTIR, UV, IC, particle size analysis, titration and pH.

The quality control of printed packaging materials was assessed based on SOP OA/GTP/113-00 dated 14 Mar 2018 Text matter and colour scheme. At the time of the inspection, no printed materials were available on site. Therefore, a procedure for version control of printed packaging materials was not

yet in place.

The processes for sampling plans, sample receipt, sample handling, testing in general and HPLC in more detail, review of test results and issuing of the certificate of analysis has been assessed based on discussions during the tour and the following documentation:

- Demonstration of LIMS
- Worksheet of sample OA01FP18000123 Darunavir film-coated tablets
- SOP OA/QA060-00 dated 12 Jan 2018 Review Audit Trails
- Review audit trail of assay by HPLC of sample OA01FP18000106 Darunavir film-coated tablets
- SOP OA/QC031-01 dated 10 Jul 2017 Review and Approval of Analytical Document in the QC Laboratory
- Register OAR0164/18 for monthly review of system audit trails in Empower 3.

The management of reference standards and the management of test materials was discussed during the tour. In addition SOP OA/QC028-00 dated 6 Sept 2016 Preparation of Mobile Phase for HPLC/UPLC Analysis was reviewed.

It is recommended to add to the Quality Agreement with Hetero Labs that Annora will be informed by Hetero Labs of changes to the reference standard.

The logbook of the leak tester QC-I0020 and the calibration report of micrometer QC-MMT-001 dated 17 Nov 2017 were reviewed.

Qualification, monitoring and handling of excursions of storage conditions in the stability chambers were discussed. In addition, the following documents regarding this topic were reviewed:

- Qualification documents for the stability chamber QC-I0048 (25°C, 60% RH), namely OQ protocol OA/QP/QC-I0048-02-00 and PQ protocol OA/QP/QC-I0048-03-00.
- SOP OA/QC017-00 dated 8 Jul 2016 Handling of Instrument/equipment Breakdown and Follow up Action
- SOP OA/QC087-01 dated 27 Dec 2017 Operation and Calibration of Walk-in Stability Chamber
- SOP OA/QC127-00 dated 2 Mar 2018 Operation Procedure for Remote Alarm System of Stability Chambers

The procedure and application for Out of Specification results (OOS) were reviewed and discussed including the following documentation:

- SOP OA/QC007-00 Investigation of OOS (8-9-2016)
- OOS log 2017 (50 records) and 2018 (6 records)
- OOS 17047 (23-12-2017): Assay too low for stability sample Levetiracetam solution due to analyst error in sample preparation
- OOS 17032 (22-9-2017): Assay OOS for Darunavir amorphous API due to incorrect information regarding the reference standard supplied by the API manufacturer Hetero Labs

The instruction in the OOS procedure for enabling automatic invalidation of the initial OOS result in case the root cause cannot be found and the following four retest results are within specification, is not a correct practice. Such an invalidation should be supported by robust data.

Microbiological laboratory

This part of the QC laboratory was visited. The process of sample receipt, sample handling, testing, media preparation and testing (growth promotion test) and review of the test results was discussed.

All results are reviewed by a second analyst.

The alarm for temperature excursions of incubators was only local. Therefore, when no personnel is present, immediate response to alarms is impossible.

11.7 Outsourced activities

The following documents were reviewed and discussed regarding the qualification and requalification of material vendors:

- SOP OA/QA009-01 Vendor qualification: vendors for API's, excipients and packaging materials.
- Vendor quality questionnaire for Darunavir amorphous API (21-1-2017). The vendor is Hetero Labs Limited (Unit IX) (Visakhapatnam, Andhra Pradesh, India).
- Vendor site audit report and follow-up for Hetero Labs Limited (Unit IX) (Visakhapatnam, Andhra Pradesh, India), dated 6-8-2016. The scope of the audit was Lamivudine API. Darunavir API will be added to the scope of the next audit as prescibed by the SOP. The last audit included the

manufacturing block for Darunavir API.
- Technical Agreement with Hetero Labs Limited (Unit IX) (Visakhapatnam, Andhra Pradesh, India) dated 8-5-2017.
- Approved vendor list (2-2-2018) – raw materials.
- Vendor requalification schedule. Hetero Labs Limited (Unit IX) (Visakhapatnam, Andhra Pradesh, India) is scheduled for Q2-2020.
- List of qualified auditors (9-2-2018): 6 auditors.
- (Re)qualification documentation for Bilcare Limited (Rajgurunagar, Pune, India). Bilcare is vendor for foils for blister packaging.

The following observation was made regarding vendor qualification:

In the procedure for vendor qualification, no maximum time was defined for periodic audits of (critical) vendors and audit visits are not mandatory for all critical suppliers.

The following documents were reviewed and discussed regarding the qualification and requalification of service providers:

- SOP OA/QC009-00 Analysis of materials/products/water samples by outside analytical laboratories (7-7-2016). Biannual audits and quality agreements are mandatory.
- (Re)qualification documentation for Analys Lab Private Ltd (India) including quality agreement (18-11-2016), audit checklist (18-11-2016) and audit report (22-11-2016). Darunavir API was not yet part of the agreement and audit scope, but will be added shortly.

11.8 Complaints and Product Recall

The following documents were reviewed:

- SOP OA/QA040-00 dated 20 Jan 2017 Handling of Market Complaints
- SOP OA/QA041-00 dated 8 Nov 2016 Product Recall

No remarks were made.

11.9 Self Inspection

The following documents were reviewed:

- SOP OA/QA032-00 dated 23 Nov 2016 Self Inspection Programme
- Self inspection schedule 2018 OA/QA032/F01-00 dated 5 Jan 2018
- Self inspection schedule and execution 2017 OA/QA032/F01-00 dated 2 Jan 2017
- Checklist and report of self inspection of Production dated 11 Dec 2017.

No remarks were made.

11.10 Distribution and shipment

Transportation to Europe was not yet arranged and could therefore not be reviewed.

11.11 Questions raised relating to the assessment of a marketing application

Not applicable.

11.12 Other specific issues identified

Not all prerequisites were in place for starting commercial manufacturing of Darunavir film-coated tablets and transport to Europe. Examples are:

a. *Management of printed packaging materials*
b. *Finished product warehouse*
c. *Quality Agreement with Hetero Europe*
d. *Transport and transport validation*
e. *Audit of Hetero Labs and Analys Lab Private with Darunavir API included in the scope.*

The site is planning to manufacture Levetiracetam oral solution 100mg/mL for the EU market via a transfer from another site. The transfer process will contain a regulatory variation to an existing marketing authorization.

11.13 Site Master File

☐ A Site Master File was not available.

☒ A Site Master File, number OA/SMF/001-01, dated 22 February 2018 was available. The inspectors find this SMF acceptable.

12. Miscellaneous:

☒ Not applicable
☐ Samples taken
☐ Legal issues

13. Distribution of report:

☒ IGJ
☒ CBG-MEB
☒ Company
☐ European Medicines Agency
☐

14. Annexes attached:

Annex 1: Definition of Significant Deficiencies

15. List of deficiencies classified into critical, major and others:

15.1 Critical deficiencies

None

15.2 Major deficiencies

None

15.3 Other deficiencies

15.3.1	The alarm for temperature excursions of incubators was only local. Therefore, when no personnel is present, immediate response to alarms is impossible. EU GMP 3.3
15.3.2	In the procedure for Annual Product Quality Review (OA/QA057-00), the maximum period between the reported period and the PQR report was not defined. EU GMP 1.4 (viii) and 1.10
15.3.3	Quantitative data of pests other than flying insects were not collected nor evaluated. EU GMP 3.4
15.3.4	An overall risk analysis concerning data integrity covering all types of data was not performed. EU GMP Chapter 4 principle and 4.1
15.3.5	In the procedure for vendor qualification, no maximum time was defined for periodic audits of (critical) vendors and audit visits are not mandatory for all critical suppliers. EU GMP 5.27, 5.29 and 5.45

15.3.6	The instruction in the OOS procedure for enabling automatic invalidation of the initial OOS result in case the root cause cannot be found and the following four retest results are within specification, is not a correct practice. Such an invalidation should be supported by robust data. EU GMP 1.4 (xiv) and 1.7.13, 1.7.16, 3.1
15.3.7	Before starting process validation, the process is insufficiently defined. Diversion of stated specifications for process parameters should not be standard practice. Furthermore, during current process validation exercises, these excursions were not addressed. Additionally, limits for reconciliation of product and packaging materials were not yet set. EU GMP Annex 15: 5.7, 5.21

15.4 Legal issues

None

15.5 Comments / recommendations

15.5.1	Not all prerequisites were in place for starting commercial manufacture of Darunavir film-coated tablets and transport to Europe. Examples are: a. Management of printed packaging materials b. Finished product warehouse c. Quality Agreement with Hetero Europe d. Transport and transport validation e. Audit of Hetero Labs and Analys Lab Private with Darunavir API included in the scope
15.5.2	It is recommended to add to the Quality Agreement with Hetero Labs that Annora will be informed by Hetero Labs of changes to the reference standard.
15.5.3	It is recommended to consider implementing a 100% weight control for bottles filled with tablets or perform a more elaborated performance qualification of the counting device.

16. Inspectors' comments on the manufacturer's response to the inspection findings:

Not applicable.

Inspectors' comments on the questions/issues raised in the assessment report:

Not applicable.

Recommendations for further actions:

Not applicable.

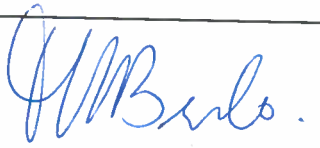
17. Summary and conclusions:

Based on the findings of this inspection the company Annora Pharma Private Limited, Sy. No. 261, Annaram Village, Gummadidala Mandal, Sangareddy District. Telangana State – 502313, India:

☒ is in general compliance with the requirements of Directive(s) 2003/94/EC and/or 91/412/EEC. The company is acceptable for the products in question.

☐ will only be in general compliance with the requirements of Directive(s) 2003/94/EC and/or 91/412/EEC after a satisfactory action plan is received for the correction of the Major deficiencies. Until then the company is not acceptable for the products in question.

☐ is not in general compliance with the requirements of Directive(s) 2003/94/EC and/or 91/412/EEC. The company is not acceptable for the products in question.

Signature: 

Date: 25 june 2018

Name: Mr. M. van Berlo, lead inspector

Organisation: Dutch Health and Youth Care Inspectorate (IGZ[1])

Signature: 

Date: 25 juni 2018

Name: Mrs. A.E. Nicia, supporting inspector

Organisation: Dutch Health and Youth Care Inspectorate (IGZ[2])

[1] In our signature, we use the organisation name referred to in laws within the area of public health and youth care.
[2] In our signature, we use the organisation name referred to in laws within the area of public health and youth care.

Annex 1: Definition of Significant Deficiencies

1 Critical Deficiency:

A deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

2 Major Deficiency:

A non-critical deficiency:

which has produced or may produce a product, which does not comply with its marketing authorisation;

or

which indicates a major deviation from EU Good Manufacturing Practice;

or

(within EU) which indicates a major deviation from the terms of the manufacturing authorisation;

or

which indicates a failure to carry out satisfactory procedures for release of batches or (within EU) a failure of the Qualified Person to fulfil his legal duties;

or

a combination of several "other" deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such;

3. Other Deficiency:

A deficiency, which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice.

(A deficiency may be "other" either because it is judged as minor, or because there is insufficient information to classify it as a major or critical).

Health and Youth Care Inspectorate – Pharmaceutical Affairs

CERTIFICATE NUMBER: *NL/H 18/2003797*

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER [1, 2]

Part 1

Issued following an inspection in accordance with :
Art. 111(5) of Directive 2001/83/EC as amended

The competent authority of Netherlands confirms the following:
The manufacturer: ***Annora Pharma Private Limited***
Site address: ***Sy. No. 261, Annaram Village, Gummadidala Mandal, Sangareddy District, Telangana, 502313, India***
DUNS Number: ***65-098-0746***

Has been inspected in connection with marketing authorisation(s) listing manufacturers located outside of the European Economic Area in accordance with Art. 111(4) of Directive 2001/83/EC transposed in the following national legislation:
Art. 100 of the Medicines Act

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2018-03-15*** , it is considered that it complies with :

- The principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/EC [3]

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field. This certificate is valid only when presented with all pages and both Parts 1 and 2. The authenticity of this certificate may be verified in EudraGMDP. If it does not appear, please contact the issuing authority.

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[1] *The certificate referred to in paragraph 111(5) of Directive 2001/83/EC and 80(5) of Directive 2001/82/EC, shall also be required for imports coming from third countries into a Member State.*

[2] *Guidance on the interpretation of this template can be found in the Help menu of EudraGMDP database.*

[3] *These requirements fulfil the GMP recommendations of WHO.*

Part 2

Human Medicinal Products

1 MANUFACTURING OPERATIONS	
1.2	**Non-sterile products**
	1.2.1 Non-sterile products (processing operations for the following dosage forms) 1.2.1.13 Tablets
1.5	**Packaging**
	1.5.1 Primary Packing 1.5.1.13 Tablets
	1.5.2 Secondary packing
1.6	**Quality control testing**
	1.6.2 Microbiological: non-sterility *1.6.3 Chemical/Physical*

2018-06-15

Name and signature of the authorised person of the Competent Authority of Netherlands

Ing. Mos van Berlo
Health and Youth Care Inspectorate – Pharmaceutical Affairs
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Fax *+31 88 1205001*