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Prequalification Unit Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**Zydus Lifesciences Limited** **(Formerly known as Cadila Healthcare Limited)**
Corporate address of manufacturer	Zydus Lifesciences Limited Zydus Corporate Park, Scheme No. 63, Survey No. 536 Khoraj (Gandhinagar), Near. Vaishnodevi Circle, Ahmedabad, Gujarat India – 382481
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Zydus Lifesciences Limited Kundaim Industrial Estate, Plot No.203-213, Kundaim, Goa- 403115, India. GPS location North latitude: 15.46143°N East longitude: 73.96989°E
Unit / block / workshop number	Oral solid dosage form block
Inspection details	
Dates of inspection	17-21 April 2023
Type of inspection	Routine GMP inspection
Introduction	
Brief description of the manufacturing activities	Zydus Lifesciences Limited manufacturing site located in Goa manufactures oral solid dosage (OSD) forms, hormone injections and rDNA anticancer injections in three separate blocks. The OSD block was under the scope of this inspection.
General information about the company and site	Zydus Lifesciences Limited manufacturing site located in Goa was started in the year 1989 as German Remedies and the same was acquired by Cadila Healthcare Limited in August 2003. In the year 2022 (24th February) the organization's name was changed to Zydus Lifesciences Ltd which is managed by the same management.
History	The manufacturing site named "Cadila Healthcare Limited" was inspected by the WHO PQ inspection in November 2018 for the same Daclatasvir tablets (HP017 and HP018). The site was declared non-compliant. The site was also inspected by the following authorities: 1. OGYEI, Hungary, April 2023 2. ANVISA, July 2021 3. NDA Uganda, TMDA Tanzania, PPB Kenya, MOH Yemen and

	MOH Libya
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	The following areas were inspected: - Pharmaceutical quality system - Personnel and training - Documentation - Hygiene and sanitization - Process and computerized system validation - Equipment and materials - Production and packaging - Quality control including microbiology laboratory - Utilities
Restrictions	None
Out of scope	The scope of the inspection was limited to the products submitted for the WHO Prequalification Program manufactured in the OSD II block. The rest of the products and their related areas were out of the scope of this inspection.
WHO products covered by the inspection	1. HP033 Daclatasvir (dihydrochloride) Tablet, Film-coated 30mg 2. HP034 Daclatasvir (dihydrochloride) Tablet, Film-coated 60mg 3. NT017 Miltefosine capsules, hard 50mg
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CFU	Colony-forming unit
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
GPT	Growth promotion test
HEPA	High-efficiency particulate air
HPLC	High-performance liquid chromatography (or high-performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification

LAF	Laminar airflow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MFT	Media fill Test
MR	Management review
NC	Non-conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

Part 2	**Summary of the findings and comments (where applicable)**

1. Pharmaceutical quality system

The site had a formal, documented quality system that met most of the requirements of the current WHO GMP Guidelines. The QA and production departments were independent of each other, and both QC and QA reported functionally and administratively to the Head of Technical Operations. The site policies and procedures that were reviewed and discussed during the inspection were generally satisfactory. Product and processes were monitored, and results were considered during batch release. The following electronic software were used at the site:

- SAP, ERP for inventory management
- TrackWise for quality management systems

- Documentum for SOPs
- Validator for product lifecycle management
- LIMS 3.4E for QC analysis
- Chromeleon 7.2 for HPLC/GC analysis
- ASRS, WMS for material management and a few other configured and custom build software

Annual Product Quality Review (APQR)

The APQR procedure was discussed and noted that a review was performed based on the date of commercialization of the product or the anniversary of the product. A minimum of 30 batches was required for assessment, if fewer than 30 batches were produced in a certain year, the review included batches manufactured in the previous two years. Minitab was used for the review. The CPPs and CQAs were extracted from the batch record of the respective product. The process capability index (CpK) was calculated. The APQR planner for 2023 was available which identified 237 products (covering OSD, injectables and anti-cancer products) to be reviewed in 2023. Similarly, the APQR planner for 2021 identified 228 products for the review period 2021. All the products identified for review were completed.

Quality risk management (QRM)

A site-specific procedure for quality risk assessment was discussed, and it was noted that FMEA was used to perform the risk assessment. No other tool was referred to when performing a risk assessment. The procedure was cross-referenced to the quality policy which was prepared by the corporate quality assurance department based in Ahmedabad. The QRM quality policy referenced various QRM-related guidelines. A risk register was maintained, stating various risks initiated by the site. Technology transfer from R&D/PTC to the manufacturing site procedure was discussed to understand the provision of risk assessment before the transfer of a new product.

Change control management

All quality system elements (change controls, deviations, CAPA, complaints, OOS, OOT, lab incidents) were handled through TrackWise (version 9.2) except for self-inspection and recall. The changes were handled through SOP. The personnel at the officer level have access rights to TrackWise and are thus responsible for raising any changes. The changes were classified into permanent and temporary and were further categorized into critical, major, and minor. At the time of the inspection, there were 25 change controls open, waiting for regulatory approvals.

Handling of deviation

The deviations were handled through the TrackWise system. Since personnel above the officer level were given access to TrackWise, the originator narrates the incident, and it is logged into the system by his/her supervisor. The investigation procedure has cited a reference to the Event First Investigation Report (EFIR), which required the operator to provide details of the incident or deviation in their vernacular language. The deviations were classified into critical, major and minor and required to be closed within 30 days. TrackWise was verified to note the number of deviations raised, their classification, and closure dates. A total of 13 deviations remained open (6 major and 7 minor) but were within the 30-day timeline. For tracking deviations, the dashboard was used.

Investigation
The investigation procedure was discussed which applied to various QMS elements such as complaints, deviations, failure investigation, OOS, recall, adverse events, audit findings etc. The procedure stated tools that should be used for the investigation e.g., fish-bone diagram, 5Why, FTA, brainstorming, etc.

In general, the concepts of pharmaceutical quality systems were in place.

The deficiencies noted from the pharmaceutical quality system section have been addressed satisfactorily and the same will be verified during future PQ inspections.

2. Good manufacturing practices for pharmaceutical products

Basic principles of good manufacturing practices were defined in standard operating procedures. Manufacturing and packaging steps were adequately defined in batch manufacturing records and batch packaging records. The storage and distribution of products ensured batch traceability from receiving to final product and testing. Required resources were available, including adequate premises, equipment, and utilities. Appropriately qualified personnel were employed, and in general, training was performed. Qualification and validation were performed following approved protocols. Access to the OSD-II manufacturing area was electronically controlled. Separate entries were available for men, women and visitors. Primary and secondary gowning was observed before entry into the manufacturing area and tertiary gowning to access dispensing areas.

Zydus Lifesciences Limited (OSD-II) is a multipurpose manufacturing facility that produces pharmaceutical products of different therapeutic areas. Following the PQ inspection, the company have taken appropriate actions to minimize the risk of contamination and cross-contamination in their existing shared facility.

The deficiencies have been addressed satisfactorily and the same will be verified during future PQ inspections.

3. Sanitation and hygiene

A considerable degree of sanitation and hygiene was in place from the changing room to the manufacturing floor and the packaging of the final product. The personnel were provided with appropriate gowning at each activity area commensurate with the level of cleanliness. Production equipment were in a clean state, and cleaning procedures for equipment were in place. Containers used for transporting raw dispensed and in-process materials were clean and covered. Production materials were appropriately stored to avoid contamination and cross-contamination. The facility was generally in an acceptable state of cleanliness at the time of inspection.

4. Qualification and validation

The validation master plan (VMP) provided a high-level overview of the validation and qualification activities carried out on-site. The scope included the OSD block and included process validation, packaging validation, computer system validation, cleaning validation, qualification, requalification etc.

An impact assessment was done as part of the initial qualification to determine the direct or indirect impact of the quality before the requalification frequency was determined. In addition, a periodic review was performed once every year. The master validation schedule for cleaning validation, computer system and other activities was in place.

Process validation of Daclatasvir 30mg and 60mg

The SOP technology transfer from R&D/PTC to the manufacturing site was discussed. A chronology of process validation (3 exhibit batches in 2016, 1 engineering batch in 2018 and then one registration batch in 2022) was provided. Three (3) exhibit batches of each strength and one engineering batch had been destroyed. The registration batch produced in 2022 is under stability study and the remaining batch was lying in the store. The company confirmed that the manufacturing process would remain the same as per exhibit batches when Daclatasvir 30mg and 60mg batches would be commercialized.

Cleaning validation

The SOP was discussed. The cleaning validation was carried out based on the solubility, 10ppm, LD50 and PDE ppm. The procedure did not stipulate how the cleanability study and cleaning process capability should be performed. The worst case was calculated based on the solubility and quantity of insoluble components. Upon review of the cleaning validation data for the product (Trimethoprim and Sulfamethoxazole) identified as the worst case, it was noted that the solubility of the active substances was considered without considering other aspects such as permissible daily exposure (PDE). From the list of PDE values provided, Warfarin has the lowest PDE value of 0.2ug/day followed by Dexamethasone at 1.3ug/day.

Computer system validation master plan

GAMP-5 was referred to and classified into software and hardware, which were further categorized into Categories 1, 3, 4, and 5. Should there be a change in the software, it will be handled through change control, and an initial impact assessment will be performed. Software-based systems were requalified once every three years. A URS was prepared before the functional specification was developed for the new software. A list of centralized computerized systems dated 16 April 2023 was available. The list of software included SAP, Documentum, Zytims, TrackWise, Karomi (artwork), ZyUAMS (user access management system), Minitab, LIMS, BMS, Thermo client (warehouse), DAMS (NewTronics, incubators), Chromeleon, Caliber IPQC and validator. The SAP was validated on 01/05/2021 and is to be revalidated on 30/04/2024. For the rest of the centralized systems, it was stated that "revalidation shall be performed as and when software upgrades and modification are made as per QMS".

Qualification of the HVAC system

The qualification of HVAC systems was discussed. A validation planner for the year 2023 for AHUs was available. The OSD facility has a total of 45 AHUs. A total of 27 dust collectors were in place in the service area. The initial qualification on AHU 30024542 was performed in March 2021 (blending area number 2 and granulation area number 2 and MAL/PAL). The AHU was qualified for non-viable particle counts. Several critical alarms were generated. Trend analysis of critical alarms was performed. The initial qualification report related to AHUs was verified. As most of the qualification activities for HVACs were outsourced, the company should consider ensuring appropriate materials and standards were used e.g. smoke study was performed using water.

The procedure for handling gases (compressed air, oxygen, and nitrogen) was described in the SOP. A risk assessment for utilities was also provided as per Annexure. The qualification of the compressed air system included design, installation, operation, as well as performance. Acceptance and release procedures were set. Preventive maintenance, as well as requalification, were defined. Validation of air quality for OSD-II was as per protocol. The test included oil mist, carbon monoxide, carbon dioxide, nitro oxide, nitrogen dioxide, Sulphur dioxide, viable as well as non-viable particles as well pressure dew point. The frequency of testing was every 6 months for 34 user points. Test acceptance criteria were provided and the report of validation was in place. The microbiological test includes bacteria, fungi, and total aerobic count. The test was performed by Acme Room Service a contracted company with a quality agreement number

The deficiencies have been addressed satisfactorily and the same will be verified during future PQ inspections.

5. Complaints

The procedure for complaint was as per SOP titled 'Handling of Market Complaints TrackWise'. Complaints were categorized into critical, major, and minor based on the effect on patient safety. Specific timelines were provided per complaint category. A flow chart for complaint management was available as per the annexure. When complaints are received from various channels including emails, they are acknowledged by Zydus Lifesciences. An investigation team was constituted. The affected product's details are then acquired. Investigations for complaints were initiated and preliminary evaluations were conducted; the investigation was properly carried out and an investigation report was provided.

6. Product recalls

The procedure for the management of recall was described in the SOP. Recalls were classified into 3 categories: class I, class II and class III based on their effect on patient safety. The timelines to effect the recall of each class were provided. Class I was within 24 hours, 10 days for class II and about a month for class III. The types of recalls provided were voluntary and statutory. The SOP was supported by other documents, such as the product recall annexure. The effectiveness of the arrangement of recall was tested by the conduct of a mock recall. Mails of communication to wholesalers and distribution records of the product were available. A summary and conclusion report were provided in which reconciliation of distributed products and recalled products was done and found satisfactory.

The deficiencies noted from the product recall section have been addressed satisfactorily and the same will be verified during future PQ inspections.

7. Contract production, analysis and other activities

The handling of service providers and contract laboratories was described in the SOP. The list of 20 approved contract laboratories was provided in the annexure. The documents provided included the name of the contract laboratory, its location address, its approval date and the range or category of tests the lab can provide. The contract agreements, validity periods, and the date the companies were audited by Zydus Lifesciences were also provided. The audit reports were generated, and findings were sent to the

companies. CAPAs were implemented by the companies and were reviewed by Zydus and closed. Documentation for three of the approved laboratories was reviewed. The contract test requirements of Zydus were within the scope of the test or analysis for which these companies were accredited.

The deficiencies have been addressed satisfactorily and the same will be verified during future PQ inspections.

8. Self-inspection, quality audits and suppliers' audits and approval

The procedure for self-inspection was conducted in accordance with the respective SOP. The procedure clearly stated that lead auditors/team members in a specific inspection would not be allowed to audit their own department. The auditors were qualified, and the list of eight (8) qualified auditors was provided in Annexure 0303-SOP-QA-00065-3, as per the criteria for qualification. The training records of 3 lead auditors and some self-inspections they conducted were reviewed. Every auditor was trained on the SOP for self-inspection. Self-inspection scheduled for 2022 and 2023 were available. The observations made and the CAPAs implemented with root cause analysis (RCA) were reviewed. Self-inspection compliance reports were also available. Unscheduled self-inspections could be carried out based on critical market complaints, deviations or non-compliance. Written instructions in the form of a checklist (questionnaire) for the conduct of self-inspection were available for all items earmarked for self-inspection.

The deficiencies have been addressed satisfactorily and the same will be verified during future PQ inspections.

9. Personnel

There were organograms available for the site and other functional departments such as QC, production, and warehouse to ensure that reporting lines between various levels of management, head of the various departments, supervisors, and operatives were clear. For the organogram of the OSD, the operators reported to their supervisors in charge of granulation, compression, and coating, who in turn reported to the managers in charge of granulation, compression and coating. The manager in charge of QMS along with managers in charge of granulation, compression and coating reported to the Senior Manager. The Senior Manager reported to the Production Manager, and the Production Manager reported to the Site Manager. The personnel of the company had their job description outlined to ensure that personnel knew their responsibilities and to avoid duplication and conflict**.** The job descriptions of the Sr. General manager, production head OSD and one of the authorized persons were reviewed. All their job descriptions had been signed indicating that they were aware and had accepted the assigned responsibilities. These documents were duly approved by the Head of Quality Assurance. The roles and separation between production and QA were adequately depicted on the site organogram. It was however noted that the site QA Head reported functionally to the Head of technical operations instead of the corporate QA. Such an arrangement may pose a potential conflict of interest.

The deficiencies have been addressed satisfactorily and the same will be verified during future PQ inspections.

10. Training

The procedure for training was as per SOP for personnel training and employee certification. Annual training planners for 2022 and 2023 were available and reviewed. Two training scheduled in the year 2023 annual training planner.

The deficiencies have been addressed satisfactorily and the same will be verified during future PQ inspections.

11. Personal hygiene

The procedure for personnel hygiene was as per SOP for "entry procedure involving primary garment change and personnel hygiene for OSD". It included areas designated as general, protected, and controlled. The primary changing procedure was outlined and uniform codes for the various departments were provided. Also available was the SOP for "employee's medical health check-up". This provided medical checks that are conducted on workers annually and every six months for personnel working in the hormones section. Additional tests were also conducted for workers in the anticancer area. The procedure for reporting contagious diseases was in place.

An Excel sheet was provided for tracking the health records of personnel, this Excel sheet was password-protected, but it was not validated.

The deficiencies have been addressed satisfactorily and the same will be verified during future PQ inspections.

12. Premises

The manufacturing site located in Goa was comprised of three separate blocks/plants:

- OSD II block (under the scope of WHO PQ inspection) consists of a separate water system, compressed air, quality control laboratory
- Hormone injection block, separate warehouse, utilities, quality control lab
- Anti-cancer block (r-DNA), separate warehouse, and utilities

The microbiology laboratory was common for all three blocks.

The OSD II block was separated from the rest of the plants in terms of separate entry, exit, utilities, personnel, etc. The company has made several changes since the last WHO PQ inspection held in 2018. The old OSD block was used for the manufacturing of Daclatasvir tablets and Miltefosine capsules exhibit batches. The company confirmed during the inspection that the old OSD facility would not be used for the commercialization of the above products for the WHO PQ program.

The OSD II manufacturing block had an HVAC system located on the top floor, with quality assurance and control on the second floor, whilst the ground floor housed the manufacturing floor and warehouse. The first floor housed the laundry service area, male and female toilets, and primary changing areas. The

design and construction of the premises allowed for effective cleaning and accumulation of dirt. The floor was smooth and the wall to the floor was epoxy-covered. The rooms were spacious and clean. Dust extractors were provided to reduce dust in dispensing areas and most production areas.

The deficiencies noted from the premises section have been addressed satisfactorily and the same will be verified during future PQ inspections.

13. Equipment

Calibration of equipment was as per SOP titled 'calibration of the instrument". A schedule on the SAP system provides the name of equipment, ID of equipment, location of equipment, frequency of calibration, date last calibrated, and next due date for calibration.

Maintenance of equipment was conducted by procedure titled "equipment preventive maintenance using the SAP module". Other documents to support the process were the SOP for the breakdown maintenance program, SOP number, preventive maintenance process flow, preventive maintenance checklist, preventive maintenance labels, and breakdown maintenance requisition cum report form. The preventive maintenance planner available provided information on equipment name, location, ID number, last date of maintenance, and next due date. Maintenance records of the compression machine and RMG were reviewed in the SAP system and found satisfactory.

The deficiencies noted from the equipment section have been addressed satisfactorily and the same will be verified during future PQ inspections.

14. Materials

A receiving bay as well as dispatch bays were provided at the warehouse. Baits for rats were provided outside the premises whilst baits for crawling insects were provided inside the warehouse. The standard operating procedure for handling and storage of raw materials and packaging materials was as per document. Materials are received in a waiting area and passed through the dedusting tunnel into the pre-sample staging area. They were sampled as per SOP for sampling and quality control purposes. The sampling plans for raw materials as well as packaging materials were in place. Two dynamic sampling booths were provided for raw materials and one static booth for packaging materials. A sampling room equipped with two (2) dynamic pass boxes serving the two raw material sampling booths available was equipped with an oven, washing area, disinfectant, 70% IPA, and a supply of purified water. A recall room was provided.

Flow charts for the movement of raw materials as well as packaging materials were displayed at the receiving bay. The checklist for the receipt of raw materials provided details for the verification of vendor, purchase order, batch number, etc. The weighing scales provided were duly calibrated, and calibration stickers were attached. Weights used for the calibration of scales were calibrated by an external agency, and records were available. Racks were provided for storage. And the removal of raw materials was robotically automated. The temperature qualification of the warehouse was conducted with seasonal changes considered. The protocol and qualification were reviewed. Hot spots were provided without cold spots. The qualification was per protocol. Mapping reports for winter, as well as the rainy season, were provided as per reports respectively.

Semi-finished goods were kept in cleaned and labelled containers with tags. The storage conditions were monitored. A finished goods warehouse was available as well as a finished goods staging area.

The deficiencies noted from the materials section have been addressed satisfactorily and the same will be verified during future PQ inspections.

15. Documentation

There were various levels of documents, including the site master file, protocols, policies, and standard operating procedures. These documents were designed, prepared, reviewed, approved, authorized, dated, and duly signed. Changes were made through approval. Though documentation handled by electronic data processing systems was passworded to restrict access, some privileges accorded to some users were not appropriate to ensure that data integrity breaches were prevented. A system was in place to ensure the retention and backup of data.

The batch manufacturing records of 3 exhibit batches of Daclatasvir tablets were reviewed. Similarly, three exhibit batches of Daclatasvir tablets were also reviewed. The raw materials specifications were as per IP, JP, Eur Ph, and NF, except for water which was BP. Batch manufacturing records for the Miltefosine capsule were also reviewed. Line clearance records were provided, and previous product processes were indicated. The equipment used had their identification numbers indicated and their locations provided.

Manufacturing equipment, testing equipment and instruments, processing areas, and transfer tubes were appropriately labelled. Batch processing records and specifications records were provided with unique identification numbers. Contract documents with external agencies were provided with unique identification numbers. In general, the system available did not permit the use of obsolete documents.

The deficiencies noted from the documentation section have been addressed satisfactorily and the same will be verified during future PQ inspections.

16. Good practices in production

The inspectors visited the OSD-II plant. The area was adequately maintained at the time of the inspection in terms of adequate light, space, and cleanliness. The OSD area was classified as Grade D (Class 100,000) and separate material airlocks and personnel airlocks were provided before entering the core processing areas. Lighting, temperature, humidity and ventilation were appropriate. Thermohygrometers were provided to monitor the temperature and humidity conditions. Temperature and humidity conditions were controlled and monitored. Magnehelic gauges were provided to monitor the pressure differential between corridors, changing rooms and other areas. The core processing areas were maintained at negative pressure concerning the surroundings i.e., airlocks.

During the tour of the manufacturing areas, some manufacturing activities were ongoing. At the dispensing area room-1, a product was being dispensed under a reverse laminar air flow unit, of equipment ID number. A scale provided in the area was under maintenance and appropriately tagged. The cabinet provided for the storage of used hand gloves had lint-free material and foil stored in it. In

dispensing room-2, another product was being dispensed. It was observed that the differential pressure limit was kept between 10–50 Pascal. At the blending room-2, activities were ongoing and the personnel in charge were appropriately gowned. The Fluidized bed dryers' bags which were molecules dedicated were stored in a dedicated room with cabinets provided for their storage. At the IPQC, the available instruments and equipment such as friability, hardness tester, and dissolution apparatus were calibrated and stickers of calibration were provided. The testing conducted was documented in the E-Calibre software. At the coating area, room -2, used for coating Daclatasvir tablets, Glatt GCS equipment was in use. At the tablet staging area, products were in cleaned containers, tightly covered with barcode detectors attached. Racks were available for storage. A logbook provided details on the name of the product, batch number and the number of containers in store, with inward as well as outward dates indicated. At the primary packing area, room-3 processing was ongoing. The coating of exhibit batches was conducted with ACG auto-coater (640mm/750mm). At the time of the inspection line 1 and line 2 were shut down.

The deficiencies noted from the production section have been addressed satisfactorily and the same will be verified during future PQ inspections.

17. Good practices in quality control

The QC lab was separated from the production areas. The area was spacious for its activities. Storage areas were adequately provided for materials. Instrumentation rooms were provided. A changing room equipped with a cross-over bench, a steel locker for clean and unclean garments, a dustbin, and a hand sanitizing station. The SOP for change, as well as pictograms, were posted. Sample receipt into the QC laboratory for analysis was via a pass box into the sample receipt and storage area, where racks were adequately provided for storage. The temperature and humidity conditions were monitored. Temperature mapping for the area where incoming samples were stored, was conducted and the hot spot was located, labelled, and connected via temp/humidity sensor to the software for temperature monitoring. Access to this area was controlled via the electronic pass. Goods receipts were raw materials, semi-finished goods, finished goods and stability samples. Goods receipt slip provided for the name of the product, batch number, manufacturing date, expiry date as well as the site of manufacture for raw materials. The test to be conducted on samples was also provided. The Calibre LIMS was used for the allocation and monitoring of the analysis to be conducted. The privileges/rights matrix of document number was in place to control access to the system by analysts, administrators, LIMS coordinators and other users.

Personnel competency was assessed as two personnel were made to demonstrate the calibration of the dissolution test apparatus and the other calibration of an analytical balance. Daily, weekly, monthly, yearly, and infinite backups were conducted for electronic records. Rooms were available for GC instruments, glassware, ICP and servers. A dedicated washroom equipped with potable water, a decantation area, a 1% Teepol area, and two (2) lab ovens were in place, and an emergency shower was provided. A cabinet was provided for the storage of pharmacopoeias.

Stability studies

The stability area had a well-equipped change room with a change-over bench and cabinet for storage of dirty and clean garments. The area was epoxy-coated and floor-to-wall joints coved. Eight Walk-in stability chambers were in place and the access to chambers was restricted by the use of passwords. Spot check was made on WHO products.

Out-of-specification (OOS)
The procedure for OOS was handled through TrackWise and the procedure guided how to handle the OOS for finished products, APIs, excipients, stability samples, validation samples and other samples including the exception of dissolution and content uniformity (usually followed through general notices of the pharmacopoeia).

Out-of-trend results
The SOP guided the identification and investigation of OOT results using the TrackWise application, observed during stability and QC release testing. A minimum of 30 batches are required to establish a trend for out-of-trend analysis. Where a trend is not established, follow the pharmacopeial methods (e.g., dissolution using Stages 1, 2 and 3). Minitab was used for performing OOT analysis. Prediction analysis. 3-Sigma was used for setting limits based on 30 batches before the release of a batch.

Handling of laboratory incidents procedure was discussed. The lab incidents were further classified as non-quality impacted and quality impacted lab incidents. The SOP was supported with examples of lab incidents e.g., communication error, network failure, system suitability, spikes, baseline drifts etc. It is handled through TrackWise.

Trend analysis and data evaluation were discussed. The trend analysis was performed quarterly and yearly for OOS, OOT and lab incidents. Data from TrackWise was imported to the spreadsheet and graphs were prepared. Q1 2023 lab incident trend data were trended and compared against the previous quarter and year data. It was noted that most of the incidents were classified under "others and oversights".
The deficiencies noted from the good practice in the quality control section have been addressed satisfactorily and the same will be verified during future PQ inspections.

Part 3	**Conclusion – Inspection outcome**

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, ***Zydus Lifesciences Limited***, located at ***Kundaim Industrial Estate, Plot No.203-213, Kundaim, Goa, 403115, India*** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR

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

Part 4	**List of WHO Guidelines referenced in the inspection report**

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   Short name: WHO TRS No. 986, Annex 2
   https://www.who.int/publications/m/item/trs986-annex2

2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
   Short name: WHO TRS No. 957, Annex 2
   https://www.who.int/publications/m/item/annex-2-trs-957

3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3.
   Short name: WHO TRS No. 1033, Annex 3
   https://www.who.int/publications/m/item/annex-3-trs-1033

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4.
   Short name: WHO TRS No. 929, Annex 4
   https://www.who.int/publications/m/item/annex-4-trs-929

5. WHO good practices for pharmaceutical quality control laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1.
   Short name: WHO TRS No. 957, Annex 1
   https://www.who.int/publications/m/item/trs957-annex1

6. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 3.
   Short name: WHO TRS No. 957, Annex 3
   https://www.who.int/publications/m/item/trs957-annex3

7. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8.
   Short name: WHO TRS No. 1010, Annex 8
   https://www.who.int/publications/m/item/Annex-8-trs-1010

8. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditioning systems

for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Third Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1019), Annex 2.
Short name: WHO TRS No. 1019, Annex 2
https://www.who.int/publications/m/item/trs1019-annex2

9. WHO guidelines on technology transfer in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 4.
Short name: WHO TRS No. 1044, Annex 4
TRS 1044 - 56th report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations
TRS 1044 - Annex 4: WHO guidelines on technology transfer in pharmaceutical manufacturing

10. WHO Good Manufacturing Practices for Sterile Pharmaceutical Products, WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 2.
Short name: WHO TRS No. 1044, Annex 2
TRS 1044 - 56th report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations
TRS 1044 - Annex 2: WHO good manufacturing practices for sterile pharmaceutical products

11. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3. ***Short name: WHO TRS No. 943, Annex 3***
https://www.who.int/publications/m/item/trs943-annex3

12. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2.
Short name: WHO TRS No. 961, Annex 2
https://www.who.int/publications/m/item/trs961-annex2

13. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2.
Short name: WHO TRS No. 981, Annex 2
https://www.who.int/publications/m/item/trs981-annex2

14. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3.
Short name: WHO TRS No. 981, Annex 3
https://www.who.int/publications/m/item/annex-3-trs-981

15. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14.
Short name: WHO TRS No. 961, Annex 14
https://www.who.int/publications/m/item/tr961-annex14

16. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3.
Short name: WHO TRS No. 1019, Annex 3
https://www.who.int/publications/m/item/trs1019-annex3

17. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4.
Short name: WHO TRS No. 992, Annex 4
https://www.who.int/publications/m/item/trs992-annex4

18. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9.
Short name: WHO TRS No. 961, Annex 9
https://www.who.int/publications/m/item/trs961-annex9-modelguidanceforstoragetransport

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5.
Short name: WHO TRS No. 992, Annex 5
https://www.who.int/publications/m/item/trs992-annex5

20. WHO Recommendations for quality requirements when plant – derived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6.
Short name: WHO TRS No. 992, Annex 6
https://www.who.int/publications/m/item/trs-992-annex-6

21. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4.
Short name: WHO TRS No. 1033, Annex 4
https://www.who.int/publications/m/item/annex-4-trs-1033

22. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10.
Short name: WHO TRS No. 996, Annex 10
https://www.who.int/publications/m/item/trs966-annex10

23. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10. ***Short name: WHO TRS No. 1010, Annex 10***
https://www.who.int/publications/m/item/trs1010-annex10

24. Points to consider when including Health-Based Exposure Limits in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2.
Short name: WHO TRS No. 1033, Annex 2
https://www.who.int/publications/m/item/annex-2-trs-1033

25. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6.
Short name: WHO TRS No. 1025, Annex 6
https://www.who.int/publications/m/item/trs-1025-annex-6

26. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3.
Short name: WHO TRS No. 1025, Annex 3
https://www.who.int/publications/m/item/trs-1025-annex-3-water-for-injection

27. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS No. 1025, Annex 4
https://www.who.int/publications/m/item/trs1025-annex4