

**Prequalification Team  
WHO PUBLIC INSPECTION REPORT  
(WHOPIR)  
Active Pharmaceutical Ingredient (API) Manufacturer**

**PART 1: GENERAL INFORMATION**

Name of Manufacturer	Anhui Biochem United Pharmaceutical Co., Ltd
Buildings	No 3 and No 5
Physical address	Zone B, Innovation Avenue, Taihe Industrial Park, Anhui, People's Republic of China
Postal address	As above
Date of inspection	19 – 22 January 2016
Type of inspection	Routine GMP inspection (new site)
Active Pharmaceutical Ingredient(s) included in the inspection	<ul style="list-style-type: none"> <li>• APIMF264 zidovudine</li> <li>• APIMF265 lamivudine</li> </ul> used for HA656 lamivudine/zidovudine, tablet, film-coated 150mg/300mg
Production Lines	Chemical Synthesis
Summary of the activities performed by the manufacturer	Production and quality control of intermediates and finished non-sterile APIs. No toxic or hazardous substances were handled or manufactured

## **PART 2**

### ***General information about the company and site***

The Anhui Biochem United Pharmaceutical Co., Ltd manufacturing site is located at Zone B, Innovation Avenue, Taihe Industrial Park, Anhui, Peoples Republic of China.

There were the following facilities in the site.

- Warehouse Building for solid raw material, excipients, intermediates and API (Solid Warehouse);
- Liquid Warehouse;
- 5 Production Buildings in total, for producing the API products;
  - Lamivudine is manufactured in Building #3 for CME synthesis and
  - Building #5 for the other steps
  - Zidovudine is manufactured in Building #5 ( different production line with lamivudine)
- Comprehensive Building (General Office in 2nd floor, QC lab in 4th floor);
- Boiler Facility;
- Sewage station.

The number of persons working at Anhui Biochem United Pharmaceutical was about 492 of which 302 were involved in production, 42 in quality assurance (QA) and quality control (QC).

The following APIs and their intermediates for all APIs were manufactured at the site:

- Lamivudine
- Ritonavir
- Zidovudine
- Nevirapine
- Lopinavir
- Lafutidine
- Entecavir
- Tenofovir disoproxil fumarate
- Emtricitabine
- Efavirenz

### ***History of WHO and/or regulatory agency inspections***

The site was not previously inspected by a WHO Prequalification team.

The site has been inspected by the following authorities:

- China Food and Drug Administration (CFDA)
- Brazil National Health Surveillance Agency (ANVISA)

### ***Focus of the inspection***

The inspection focused on the production and quality control operations related to the zidovudine and lamivudine APIs.

### ***Inspected Areas***

- Quality Management
- Personnel
- Buildings and facilities
- Process equipment
- Documentation and records
- Materials management
- Production and in-process controls
- Storage and distribution
- Laboratory controls
- Validation
- Change control
- Rejection and reuse of materials
- Complaints and recalls
- Contract manufacturers (including laboratories)

## **PART 3: INSPECTION OUTCOME**

### **3.1 QUALITY MANAGEMENT (QM)**

#### Principles

The current organizational chart was reviewed. Quality manager was also the qualified person (QP), reporting directly to the president & general manager. Quality Unit was independent of Production Unit. QP, production manager and QA manager job responsibilities were reviewed. In general responsibilities were in line with GMP requirements. According to the QA manager job description he was deputizing QP in his absence.

#### Management review (MR)

The SOP “Management review (MR)” was discussed. This was the first version of the SOP, therefore till the date of the inspection management review was not carried out. According to the SOP MR should be carried out at least annually, quality department should report to the management at least every 3 months.

The company claimed that the first MR will be carried in March 2016.

#### Internal audits (self-inspection)

The SOP “Self inspection” and flow chart were discussed. According to the SOP self-inspection should be carried out at least once per year. According to the SOP the following topics should be covered:

- Organization and employees
- Facilities and utilities
- Equipment
- Materials and products
- Qualification, validation, calibration
- Documents management
- Record management

- Production and in-process control
- Quality management
- Contract production and testing
- Complaints
- Recalls
- Transportation

Self-inspection team consisted of the following team members of the following departments:

- QA
- QC
- Production department
- Supply department
- Warehouse
- Equipment
- Administrative department

Self-inspection team members were trained annually by the quality manager.

Self-inspections were carried out according to the form what was used also as a report. The report was approved by the team leader. CAPAs were proposed by the inspected department and approved by the quality manager. Implementation of CAPAs was monitored by team members. The last self-inspection was carried out in November 2016.

#### Product quality review (APQR)

The product quality reviews were compiled based on the SOP. The PQR's of lamivudine and zidovudine APIs were discussed.

#### Quality Risk Management (QRM)

The SOP "Quality Risk Management" was discussed. The SOP was applicable to validation, deviations, change controls and other topics related to the quality management. According to the SOP the following tools could be used for QRM:

- Flow charts
- Check lists
- Failure mode effect analysis – FMEA
- Hazard analysis and critical control points - HACCP
- Ishikawa diagram

Risk was classified as:

- High
- Middle
- Low

Lamivudine and zidovudine production process RAs using FMEA were carried out in 2013.

### **3.2 PERSONNEL**

#### Personnel qualifications

There were an adequate number of personnel qualified to perform and supervise the manufacture of intermediates and APIs. The responsibilities of personnel engaged in the manufacture of intermediates and APIs were specified in writing.

#### Personnel hygiene

The SOP “Management of personnel health” was discussed. According to the SOP all staff should pass medical examination yearly.

The SOP “Hygiene management procedure in synthesis area” and the “Hygiene management procedure in clean area” were discussed. Eating, drinking, smoking and personal medicines were not allowed in production areas.

#### Training

The SOP “Training management” was discussed. The SOP listed the following training topics.

- Induction training:
- On job training:
- On-going training – carried out yearly according to the approved training plan.

Training files were kept by the administrative department.

The training file for the operator working at the lamivudine workshop was review. The training effectiveness was evaluated by written open questions.

The training file for the analyst was reviewed. The new analyst and group leader performed tests on the same samples and results were compared. Reviewed training file contained tests of impurities.

#### Consultants

One consultant was used for consultation of the manufacturing process, process optimisation and GMP. Consultant CV was available and reviewed.

### **3.3 BUILDINGS AND FACILITIES**

#### Design and construction

There were general and product specific SOPs in place containing facility layouts:

- SOP “Company layout”
- SOP “Company surrounding layout”
- SOP “Equipment layout of Lamivudine”
- SOP “Equipment layout of Zidovudine”.

#### Purified Water System

Purified water (PW) was produced from bore well water using double reverse osmosis. PW system was commissioned in 2012. PW was supplied to the lamivudine and zidovudine workshops. PW system qualification was carried out using 3 phase approach.

Storage tank and pipelines were made from SS 316 L. Welding and welder's certificates were provided for the inspection. Boroscopic photos were available.

The PW system storage tank and loop was sanitized once per month using hot water above 80 °C for 2 hours. Action and alert limits were established.

From 20 November, 2015 the R2A media was used for PW analysis. PW trends for 2014 and 2015 were discussed.

### HVAC

The powder processing areas of building 5 were qualified as Class “D” and supplied by 2 independent air handling units (AHUs). The qualification and monitoring protocols and records of Workshop 7 were discussed.

The HVAC system was installed in year 2012. Re-qualification was performed in 2015 following to the change of HEPA filters, test results for velocity, pressure differentials, temperature, humidity, partial count; settle plate and airborne particle monitoring were available.

There were different SOPs in place for the periodic (quarterly) monitoring.

## **3.4 PROCESS EQUIPMENT**

### Design and construction

The process equipment was made of SS, identified and status labelled. The flow direction and any other relevant information were indicated on the fixed pipelines.

The process equipment had instrument logbooks, where the batch numbers and the time of the activities were recorded. The year 2016 logbooks of reactors XXX and YYY were available and reviewed.

The test devices e.g. temperature probes were listed in “Measurement Instrument Periodic Schedule” issued annually, referring to the corresponding production equipment.

### Equipment qualification, maintenance and cleaning

The general requirements for equipment qualification were summarized in SOP “Validation management” and SOP “Validation of equipment and facility”.

The qualification protocols and records of the crystallizer XXX were available and discussed.

The equipment maintenance program consisted on monthly and annual activities.

The temperature probe XXX connected to the crystallizer YYY was calibrated according to the protocol and the next calibration was due after 12 months.

There were written cleaning instructions available. At product changeover, a thorough cleaning was done followed by a cleaning check. The following records were discussed: “Cleaning inspection report for product changeover (zidovudine – lopinavir) in workshop 8”.

Cleaning effectiveness check test was carried out in case change over from lopinavir to zidovudine. Sampling methods were different for different equipment. HPLC method was used to analyse the samples.

SOP “SOP for vacuum dryer cleaning” was discussed. The vacuum dryer (non-dedicated) was used for drying finished API

#### Computerized systems

The documentation system, the material management was paper based. The only computerized systems considered as critical therefore to be validated were the instrument operation, data acquisition and processing software’s of the QC laboratory.

### **3.5 DOCUMENTATION AND RECORDS**

#### Documentation system and specifications

The SOP “SOP for document management” was discussed. According to the SOP all company documents should be approved by the Quality manager (QP). After approval documents were valid for 3 years. There were three levels of the documents:

- Level I – Quality manual
- Level II – management SOPs
- Level III – operational SOPs

All documents were distributed by the QA documentation section and distribution was recorded. Expired documents Master copies were kept in QA documentation archive without time limit.

The identification of the SOPs referred to the concerned department/area, e.g.: SOP-QA for Quality Assurance, SOP-PD for Production, SOP-EM for Engineering, SOP-MM for Material management, SOP-QC for Quality Control, SOP-GEN for General.

The list of valid SOPs was available and presented to the inspectors.

#### Master production instructions (MPI)

MPI were available for manufacture of all APIs and intermediates. MPI were drafted by the production department and approved by the QA department. Distribution of MPI was controlled by the QA department.

#### Batch production records and packaging records (BMR/BPR)

BMR/BPRs were available for manufacture of all API. MPI were drafted by the production department and approved by the QA department. Distribution of MPI was controlled by the QA department.

#### Laboratory control records

Laboratory note books and analytical work sheets were numbered and controlled by the QA department.

#### Out of specification (OOS) and out of trends (OOT)

The SOP “Investigation procedure of OOS/OOT” was discussed. The SOP was applicable for finished APIs, raw materials, intermediates, environmental monitoring results and stability studies. OOS/OOT register for 2015 was discussed.

### **3.6 MATERIALS MANAGEMENT**

#### General controls

Only materials received from approved suppliers, sampled, tested and approved for manufacturing was used.

The material management at the warehouses was paper based. In parallel an electronic system (ERP) was used, but not validated and for accounting purposes only.

#### Qualification of the suppliers

The suppliers of the raw materials (such as: “general materials”, “key materials”, “solvents”, “catalysts”) were qualified according to SOP. The qualification was based on amongst supplier questionnaire and site audits. The suppliers were approved by the QP.

The list of approved suppliers, together with the evaluations due in 2016 was available.

The approved suppliers and the supplier evaluation records of cytosine and the sodium azide were discussed.

#### Receipt and quarantine

The incoming materials were de-dusted in the newly constructed de-dusting area, and then placed in the warehouse area. The status change of the materials was managed by status labelling. Therefore there was no area assigned for the materials of different status e.g. quarantine.

The inventory of the incoming materials was paper based: Stock Material Notation Lodger, and Raw Material Incoming Inspection Record. The records of Cytosine raw material were available in the solid warehouse containing the relevant information of the materials (e.g. date of receipt, supplier, amount, number of packages, stock, issue to the production, batch number of the manufacturer, internal ID, etc.).

#### Sampling and testing of incoming production materials

The SOP “Sampling of raw materials, excipients and packaging materials” was discussed.

### **3.7 PRODUCTION AND IN-PROCESS CONTROLS**

#### Production operations

The general information regarding manufacturing, the detailed manufacturing instructions and the corresponding batch manufacturing record masters were discussed.

The list of product codes serving as a base of batch numbering was available. The issued batch manufacturing records/batch numbers were recorded in product specific logbooks.

The manufacturing records of the specific batches were discussed.

#### In-process sampling and controls

Some Thin layer chromatography (TLC) tests were carried out by the production operators and some by the QC laboratory analysts. Other in-process tests were carried out in the QC laboratory.



### Blending batches of intermediates or APIs

The SOP “Blending and packaging procedure for intermediates and API” was discussed. The expiry date of the blended batch was based on the manufacturing date of the oldest tailings or batch in the blend. Blending operations were recorded in the blending BMR. After blending the full tests according with the specifications were carried out. As an example BMR for blended batches XXX was checked. The BMR of the blending process allowed traceability back to the individual batches that make up the blend.

### Contamination control

The environmental monitoring (EM) in clean rooms was carried out every 3 months by settle plate method and active air sampling. The settle plates were exposed for 4 hours. The SOPs on EM were discussed. Alarm limits were set up for total aerobic microbial counts (TAMC). Total yeasts & moulds counts (TYMC) were expected to be 0. EM results were checked for 2015 – all results for TAMC were well within alert limit, TYMC counts were 0.

### Deviations

The SOP “Investigation of Deviations” was discussed. Deviations were classified as:

- Major
- Minor

Deviations were recorded and approved by the Quality manager. Production process deviations were also recorded in the respective BMR. Quality department should investigate the root cause of the deviation and CAPAs should be proposed by the production department. CAPAs should be reviewed by the QA manager and approved by Quality manager. The SOP “Management of planned deviations” was discussed. QA department should be informed about the planned deviation. Planned deviation should be evaluated by the R&D, QC and production department and approved by the QA manager.

### Corrective Actions and Preventive Actions (CAPA)

The SOP “Corrective and preventive actions” was discussed. The SOP was applicable to the:

- Deviations
- OOS
- Recall’s
- Complaints
- Rejection of materials
- Self-inspection
- External inspection
- PQR
- Management review
- QRM

CAPAs should be approved by the quality manager and implementation monitored by the QA. QA should organize also evaluation of the effectiveness of CAPAs.

### **3.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES**

#### General

The majority of the manufacturing steps were continuous processes performed in the same or adjacent rooms; therefore the packaging/labelling/transfer/storage of the materials did not apply.

The materials in the final processing area (after centrifuge-before drying, after drying-before milling and packing) were stored in single/double PE bags in an SS container labelled.

The final (milling) step was always performed together with the final packing, therefore no storage, labelling is performed in between.

#### Packaging materials

The packaging materials were sampled and stored in the solid warehouse.

### **3.9 STORAGE AND DISTRIBUTION**

#### Warehousing procedures

The QC was responsible for the release and QA was responsible for rejection of the raw materials.

#### Distribution procedures

Always entire (intact) packages of raw materials delivered to the production workshops from the warehouses based on the production plan. The workshops had assigned areas for dispensing and staging raw materials. The production personnel was responsible for the execution and checking of dispensing/weighing of the materials at the production workshops, recorded on material and batch specific Locator Cards.

The SOP “Release of intermediates and API” was discussed. Finished API release was responsibility of the QP who was also quality manager. Check list was used to ensure that all items listed in the SOP had been discussed and verified.

### **3.10 LABORATORY CONTROLS**

#### General controls

The raw materials, intermediates and APIs were tested against written quality specifications containing the requirements and the corresponding test methods. The test results were summarized amongst the ID of the certificate, the requirements, test results, batch number, and reference to the specification ID.

There were computerized analytical instruments used such as High Performance Liquid Chromatographs (HPLC) and Gas Chromatographs (GC).

The Agilent HPLCs and GCs were used amongst other materials for testing of lamivudine and zidovudine intermediates and APIs.

#### Testing of intermediates and APIs

The quality specifications, test methods and test records of the specific materials were discussed.

### Validation of analytical procedures

The instrumental analytical test methods (HPLC, GC) of the lamivudine and zidovudine APIs had been validated.

The validation protocol and report of the residual solvent test in lamivudine API were discussed.

### Certificates of analysis (CoA)

The SOP “Management of CoA” was discussed. CoA was issued by QC analyst, reviewed by the QC group leader and approved by the QC manager (for raw materials and intermediates) and QP by the finished APIs.

### Expiry and retest dating

The SOP “Confirmation of manufacturing date and re-test date”. Re-test dates were established based on the stability studies. Manufacturing date was established from the drying date of the finished API. Re-test dates for the zidovudine and lamivudine were established 2 years.

### Stability monitoring of APIs

The SOP “Stability study” was discussed. Samples were stored under the following conditions:

- 40 °C ± 2°C, 75% ± 5%
- 30 °C ± 2°C, 75% ± 5%
- 25 °C ± 2°C, 60% ± 5%
- 30 °C ± 2°C, 65% ± 5%
- 25 °C ± 2°C, 60% ± 10%
- 6 °C ± 2°C

One chamber was used for degradation studies and one chamber was kept for back-up (qualified meeting the requirements of the chambers in use).

Window periods between withdrawal of samples and analysis were specified.

First batch per year was placed on long term stability monitoring programme. Samples were packed in market simulated conditions.

### Hold time studies

The hold time studies were available for the following intermediates: CME, lamivudine salicylate and crude lamivudine.

### Reserve/retention samples

The reference/retention samples were available in the chambers located in the same floor of the administration building as the QC laboratories.

### Reference standards

The reference materials (compedia standards and working standards) were stored in a dedicated refrigerator (2-8 °C). The inventory containing the receipt, the usage and the recent stock of the reference materials were available (e.g. Zidovudine 4050-WS1501 and

#### Microbiological laboratory (MBL)

Microbial laboratory was not visited during this inspection. The SOP “SOP for Media” was discussed. Upon receipt growth promotion test was carried out for each batch of dry media. Medias were sterilized at 121 °C for 15 minutes. pH was checked before sterilisation, but not after sterilisation.

### **3.11 VALIDATION**

#### Validation policy

The overall validation policy was explained in the document “Validation master plan (VMP) for 2015”. The similar VMPs were available for previous years. VMP covered:

- Equipment qualifications
- Cleaning validation
- Process validation
- Unplanned validation
- Analytical methods
- Computerized systems

Validation approach was explained in the document “SOP of validation management”.

#### Qualification

For the qualification policy and records of the critical equipment was available.

#### Approaches to process validation

The manufacturing process validations discussed, compared to the provided process flowcharts and the production documents during the inspection.

#### Cleaning validation

The cleaning procedure contained batch-to-batch and after campaign/product changeover cleaning. “Validation report for cleaning procedure used for double-tapered rotary vacuum dryer of zidovudine” was discussed. Cleaning validation was carried out in November/December 2013 for 3 consecutive validation batches.

The “SOP of cleaning validation” was discussed. SOP specified the circumstances for the cleaning re-validation.

### **3.12 CHANGE CONTROL (CC)**

SOP “Change Control” was discussed. This SOP was applicable to the following changes:

- Raw materials (changes in the specifications and suppliers)
- Packaging materials (changes in the specifications and suppliers)
- Test methods
- Operation procedures
- Facilities /equipment
- Process’s
- Software

The classification of changes was according to two categories: major and minor.  
A specific CC were discussed

### **3.13 REJECTION AND RE-USE OF MATERIALS**

#### Reprocessing and reworking

No recovering was allowed in case of lamivudine.

The practice of recovered batches in case of zidovudine was restricted for domestic market. No recovering process can be used in case of APIs intended to be marketed in “regulated markets”.

The reprocess/rework policy was described in the SOP. In case of reprocess/rework, specific manufacturing instructions were to be issued and approved by the QA Manager and it was reflected in the batch numbers.

The serial numbers were generated product-wise and restarted annually.

The reprocessed/re-worked batches were recorded in a common logbook together with the “general” batches. Stability testing (long-term, accelerated) was to be initiated in both cases. There was no practice of rework in place; no rework was recorded in the last 3 years

#### Recovery of materials and solvents

The “Management procedure for recovered solvents” was discussed. Company had practice to recover solvents and mother liquors. Consumption of the recovered solvents and mother liquors were recorded in the batch manufacturing records.

Recovered solvents were used for different manufacturing steps of different products. The regeneration can be flash distillation or fractionation. Flash distillation was defined and recorded in the BMR, performed and the regenerated solvent stored in the concerned production facilities. The fractionation was performed according to the SOPs, and the recovered solvents were stored in dedicated tanks. The recovered solvents received internal batch numbers. The “Recovered toluene production sheet” was discussed.

#### Returns

The SOP “Returns” was discussed. According to the SOP returned products were stored in the separate returned products room. Afterwards QC will sample and test the products. If the product complied with the specifications, it was re-packed and released. If returned product did not comply with specifications, it was re-processed.

#### Rejected materials

The SOP MM-007/01 “Management of rejected materials” was discussed. Rejected materials were stored in the separate rejected materials room in the warehouse.

### **3.14 COMPLAINTS AND RECALLS**

The SOP “Handling customer complaints” was discussed. Responsible person was QA manager. This was explained in the related Job descriptions. Complains were categorized as:

- Complaints related to the product quality
- Complaints not related to the product quality

The SOP “Product recall” was discussed. Responsible person was Quality manager. Recalls were classified as:

- Class I – should be executed within 1 day
- Class II – should be executed within 3 days
- Class III – should be executed within 7 days

Till the date of inspection there were not recalls. The SOP effectiveness was evaluated by the mock recall. According to the SOP mock recall should be carried out every year.

### **3.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)**

Manufacturing operations were not contracted out. Two contract laboratories were used specific tests. As an example the Technical agreement (TA) with the XXX laboratory was discussed.

## **PART 4: CONCLUSION**

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned:

- ZidovudineAPIMF264
- LamivudineAPIMF265

manufactured at Anhui Biochem United Pharmaceutical Co., Ltd, located at Zone B, Innovation Avenue, Taihe Industrial Park, Anhui, Peoples republic of China (Buildings No 3 and 5), was considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

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.