

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
API Manufacturer**

Part 1: General information

Name of manufacturer	CKD BiO Corporation
Unit	N/A
Manufacturing block	Plant I
Physical address	CKD BiO Corporation, 454, Moknae-dong, Ansan-city, Kyonggi Province, South Korea
Date of inspection	3 – 6 December 2012
Type of inspection	Routine inspection, covering aspects of GMP
Active Pharmaceutical Ingredient(s) included in the inspection	Rifampicin API
Summary of the activities performed by the manufacturer	Production and quality control of intermediates and finished Active Pharmaceutical Ingredients (APIs)

Part 2: Summary

Background information

Chong Kun Dang Bio Corporation, further referred to in the text below as CKDBio is located 40 km away from Seoul city in the National industrial complex at Ansan city.

Company history:

Founded as GUNGBON pharmacy in 1941

- In 1965 - company was named as CKD Pharm Corp and formulation plant was established
- In 1968 - US FDA inspection for API
- In 1974 - fermentation plant was established
- In 1988 - new fermentation plant was established and Rifampicin API production was started
- In 1996 - Fermentation plant (Seoul plant) was moved to Ansan plant.
- In 2001 - CKD Bio Corporation was spun off from Chong Kun Dang Pharmaceutical Corporation

The total number of employees was about 268. Twenty two employees were involved in Quality assurance (QA) and Quality Control (QC) activities and 177 in production activities.

History of WHO or regulatory agencies inspections

This was the first WHO inspection at this site.

Manufacturing of specific products had been inspected by other organizations and agencies.

Focus of the inspection

This inspection focused on the production and control procedures of Rifampicin API used in TB products. The inspection covered several sections of WHO good manufacturing practices (GMP) for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, production and quality control.

Inspected Areas

- Quality Management
- Qualification and validation
- Complaints and Recalls
- Self-inspection
- Personnel Training
- Premises
- Equipment
- Materials
- Documentation
- Production
- Rejection and reuse of materials
- Quality control

2.1 QUALITY MANAGEMENT

In general, a system for managing quality was established. The quality department was independent of the production department. In general the system was found to be adequate.

Product quality review (PQR)

PQR standard operating procedure (SOP) on Annual Product Review and annual review report for batches manufactured in 2011 were inspected. PQRs were to be completed by the company by the end of March of every year. Regular quality reviews of APIs were conducted with the objective of verifying the consistency of the process. Such reviews were conducted and documented annually.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Root Cause Analysis

SOP was not available.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Corrective action and preventive action (CAPA)

SOP and Flow diagram were reviewed.

SOP was applicable to the following:

- Complaints
- Recall
- Deviation
- OOS
- Internal and external audits
- Others (e.g. supplier audit)

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Responsibilities of the quality and production units

Job descriptions for QA, QC and for Production personnel were available, addressing general responsibilities. The following Job Descriptions were spot checked:

- QA General Manager
- QC Manager
- Production Manager

Job Descriptions inspected were in general found to be acceptable. According to the job description of the general manager QA, he was responsible for the approval of batches. No specific observations were made.

Internal audits (self-inspection)

There was an SOP with a schedule (plan) for internal / self-inspections. CAPAs taken were monitored and the reports were submitted to management. In general the system was found to be adequate.

Supplier approval

SOP addressing the control of suppliers was spot checked. According with the SOP suppliers of critical materials should be audited. Audits were carried out according to the Check lists which were part of the Audit report. In case of observations found during the audit, audited suppliers were requested to submit CAPA. Proposed CAPA were evaluated by the QA manager and audit report was approved by the QA General Manager and the Chief Executive Officer (CEO).

Specific supplier audit was carried out on 19 August 2011, audit report and checklist were spot checked.

Approved suppliers list was available and presented to the inspectors. In general the system was found to be adequate.

Product release

There was an SOP for the release of the final API and a checklist was included as an annex. Checklist was approved by the QA manager, certificate of analysis (CoA) was approved by the QA General Manager.

2.2 PERSONNEL**Personnel qualifications**

There were an adequate number of personnel employed, who were qualified to perform and supervise the manufacture of intermediates and APIs.

Training

The training SOP made provision for teams to provide training. A training schedule was prepared and was authorized. Topics covered included GMP, Environment Health Systems (EHS) and On Job Training - and were scattered over the annual planner. The trainers were selected based on experience and education. Training on GMP was stated to be a total of 8 hours (production) and 3 hours (QA) per year. Training records were maintained (attendance sheet, training material and assessment). Two records of assessment were checked for employees attending the training in October 2012 and found to be acceptable

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Analyst's qualification (validation)

Qualification for personnel file for Mr. Shin (analyst) was spot checked. Mr. Shin received basic training for 5 days and on-job training for 3 months. After training his performance was evaluated and he was qualified to work individually.

Personnel hygiene

Specific attention was not paid by the inspectors during this inspection, to personal hygiene. Direct contact with intermediates or APIs was avoided. In general personnel hygiene was found to be adequate.

Consultants

Not inspected.

2.3 BUILDINGS AND FACILITIES**Design and construction**

Buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Buildings and facilities had (in general) adequate space for the orderly placement of equipment and materials.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Utilities

Not inspected in detail on site.

Heating, Ventilation, and Air- conditioning (HVAC): Air Handling Units (AHU) re-qualification protocol/report was reviewed.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Water

Purified water (PW) system was inspected and in general found to be well maintained. Water was purified by means of a double Reverse Osmosis (RO) system and Electro-Deionisation (EDI).

PW system SOP, trends for the last 3 months and re-validation report were reviewed. PW system was re-validated after the change control which included the installation of on line Total Organic Carbon (TOC) analyser and heat exchangers.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Containment

Highly sensitizing materials were not manufactured on site.

Lighting

Lighting was adequate.

Sewage and refuse

Not inspected.

Sanitation and maintenance

Specific attention was not paid to the sanitization and maintenance.

2.4 PROCESS EQUIPMENT**Design and construction**

Equipment used in the manufacture of intermediates and APIs was of appropriate design and adequate size, and suitably located for its intended use. Major equipment such as reactors and centrifuges, and permanently installed processing lines used during the production of an intermediate or API were appropriately identified.

The following equipment was used in production process:

- Glass crystallizers
- Reactors and vessels
- Ceramic filtrations
- Nutsche filters
- Resin columns
- Vacuum dryers
- Freeze dryers
- Fluid Bed Dryer (FBD)
- Tray dryers
- PW system

Equipment maintenance and cleaning

Preventive maintenance (PM)

2012 Maintenance & Checking plan of major equipment was spot checked. Check lists were used for every piece of equipment. PM was carried out every three months according with the schedule.

Calibration

Calibration schedule was explained in the Validation Master Plan (VMP) which was prepared annually.

Some calibration records were spot checked:

- Autoclave thermometer calibration
- Dry oven thermometer calibration
- Temperature gauges and pressure gauges

Thermometers, temperature gauges and pressure gauges were calibrated every 6 months. Calibration was traceable to the standard equipment's used for calibration.

Computerized systems

Not inspected in detail.

2.5 DOCUMENTATION AND RECORDS**Documentation system and specifications**

Documents related to the manufacture of intermediates and APIs were prepared, reviewed, and approved. Specifications were established and documented for raw material, intermediates and finished API. Acceptance criteria were established and documented for in-process controls. In general the system was found to be adequate.

Equipment cleaning and use record

Cleaning SOP and records for centrifuge dedicated for Rifampicin were spot checked. Clean in Place (CIP) procedure was included in the cleaning process validation during product change over. Records were checked and in general found to be adequate.

Records of raw materials, intermediates, API labeling and packaging materials

Some records were spot checked and in general found to be adequate.

Master production instructions

Master production instructions had been established and appropriately approved and followed.

Batch production records

Batch production records were prepared for each intermediate and API and included complete information relating to the production and control.

Laboratory control records

Some laboratory records and work sheets were spot checked and found to be adequate.

Batch production record review

Written procedures were established for the review and approval of batch production and laboratory control records.

2.6 MATERIALS MANAGEMENT**General controls**

A system was in place for evaluating the suppliers of critical materials. Materials were purchased from approved suppliers.

Receipt and quarantine

Materials were held under quarantine until they were sampled, tested and released for use.

Sampling and testing of incoming production materials

Containers or bags from which samples were withdrawn were marked to indicate that a sample had been taken. Sampling of materials (e.g. media) was sometimes done in the warehouse and sometimes in a sampling booth. Sampling rods were used to take samples from big bags. Risk assessment was done to identify whether suitable controls were in place for this activity.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

2.7 PRODUCTION AND IN-PROCESS CONTROLS**Production operations**

The inspection covered cell bank maintenance, fermentation, harvesting, isolation and purification.

Working Cell Bank (WCB) was stored in two deep freezers. Temperature (T) in the freezers was monitored and recorded every 2 hours and on continuous charts. Freezers were connected to the UPS system and alarm system was challenged monthly. Access to the cell bank was controlled. Freezers were re-qualified every two years. T mapping was carried out.

Inoculation was carried out in Class “A” LAF cabinet which was surrounded by Class “C” area.

In the culture room - temperature was monitored and recorded every 3 hours. The T monitoring equipment was also connected to the UPS.

Media contamination checks were carried out.

Fermentation process was controlled by the computer system which was said to be validated, but its validation was not reviewed by the inspectors. Fermentation tanks were cleaned and sterilized. Some process parameters were verified by the inspectors by checking the batch record against the electronic data captured at different steps and times.

Computerized data was backed up.

Almost all of the manufacturing process was carried out in closed equipment. Some manual manipulations were done, for example unloading the cake from the centrifuge.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

In-process sampling and controls

In-process sampling was done by the operators; analytical controls were carried out in IPC laboratory located at the production plant.

Blending batches of intermediates or APIs

Blending was recorded in Batch record. The batch record of the blending process allowed traceability back to the individual batches that made up the blend. Blended batches were individually tested for conformance to established specifications before blending.

The expiry date of the blended batch was based on the manufacturing date of the oldest tailings or batch in the blend.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Packaging operations were not inspected at the time as there was no packaging taking place during the inspection days.

Packaging materials

Primary packaging materials were stored in the warehouse in fibre drums.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Label issuance and control

Export label was created according to customer specifications and approved by QC. Labels were printed by production support team. Labels were approved by QA in the Batch packaging record.

2.9 STORAGE AND DISTRIBUTION**Warehousing procedures**

Inspectors made an inspection tour to the warehouse (where media were stored) and to the solvent farm. Facilities were provided for the storage of all materials. Released and rejected materials were stored separately. Quarantine areas were identified.

It was explained that temperature mapping was done, but this was not reviewed by inspectors. Insect and rodent control was in place.

Raw materials were dispensed in the warehouse.

Solvents were delivered in tankers. Tanker cleaning certificates were requested upon receiving of the solvents. Solvents were stored in dedicated tanks. Dedicated lines were provided for the solvents. Lines were labeled with the solvent name and connections were locked with a padlock. According to the company, preventive maintenance of the tanks was performed annually.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Distribution procedures

APIs were released for sale after QA approval. CoA was signed by General Manager QA.

2.10 LABORATORY CONTROLS**Out of Specification (OOS) investigation**

OOS SOP, flow chart and register for 2011 and 2012 were reviewed.

Inspectors made inspection to the Quality Control Laboratory (QCL) and microbiology laboratory.

QCL

Samples for analysis were stored in cabinet under controlled conditions. Temperature and RH were monitored and recorded three times per day.

Analytical balances were calibrated daily with standard weights and every three months by a supportive department.

Reference and working standards were stored in the fridge and deep freezer that was equipped with an alarm system. Alarm system was challenged once per month. Temperature was monitored continuously by temperature charts and recorded once per day. Working standards (WS) were dispensed in amber glass vials at a time. Expiry date was set up one year. One vial was used for one month. Reference and WS registers were available. WS were standardized against USP reference standards.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Microbiological laboratory

Only one section (clean room) of the laboratory was separated from the general and chemistry laboratory.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Testing of intermediates and APIs

Laboratory tests for intermediates were performed in the IPC laboratory located at the production plant. Impurity profiles were established. Finished APIs were tested in QC laboratory that was separated from production areas.

Certificates of analysis

Certificates of analysis (CoA) were issued for each batch of API and signed by the General Manager QA.

Stability monitoring of APIs

Stability samples were stored in two chambers: long term ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$) and accelerated ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$) condition chambers. Temperature was monitored continuously by temperature charts and additionally checked and recorded once per day (manually). The alarm system was connected to the fermentation control room panels.

One batch of Rifampicin API was placed on long term stability annually. Three validation batches were placed on accelerated stability.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Reserve/retention samples

Reserve samples of APIs were stored in the same packaging system in which the bulk APIs were stored. Retention samples were stored for 5 years.

2.11 VALIDATION

Qualification

Qualification of AHU

AHU qualification report/protocol was reviewed.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Process validation programme

Manufacturing process re-validation was done after change control. Three batches were used for the study. All steps were included in the validation.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Cleaning validation

Cleaning validation approach was based on the campaign production of APIs. Cleaning validation was done for every product change-over/campaign. Swab and rinse samples were taken. Material of construction (MOC) of equipment included stainless steel (SS) and glass.

A specific validation report was inspected. The analytical method used in the validation study was HPLC method and according to the company, the analytical method was validated. In general cleaning validation was found to be adequate.

Validation of analytical methods

Not inspected.

2.12 CHANGE CONTROL

An SOP for change control (CC) and CC register were reviewed. Change controls were classified as following

- Major
- Moderate
- Minor

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Deviations

The SOP for handling Deviations, deviation forms and deviations register (2011 – 2012) was reviewed.

Deviations were classified as:

- Major
- Minor

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

2.12 REJECTION AND RE-USE OF MATERIALS

Rejection

Not inspected, SOP was available.

Reprocessing and reworking

Re-processing SOP was checked. Rework was not permitted according with SOP on Deviation control.

Recovery of materials and solvents

Recovered and re-used solvents were used in the production process. Specifications were established for recovered and re-used solvents. Solvents were recovered and reused in the same process. Recovered solvents register was available.

Returns

SOP was reviewed. SOP for returned materials covered all materials.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

2.13 COMPLAINTS AND RECALLS

Complaints

There was an SOP and flow chart for complaint handling and investigation. The SOP, complaint register for 2011, as well as one complaint was reviewed. QA manager was responsible for handling of complaints

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Recalls

There was an SOP and flow chart for handling recalls. There were no recalls registered till the date of the inspection.

2.14 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

N/A

Part 3: Conclusion

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 a decision on the compliance of manufacture of Rifampicin API at CKD BiO Corporation (Plant I) CKD BiO Corporation, 454, Moknae-dong, Ansan-city, Kyonggi Province, South Korea was considered to be operating at an acceptable level of compliance with WHO GMP guidelines 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.