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WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Joint Stock Company JSC "Biocom"
Unit number	N/A
Production Block	N/A
Physical address	54, Chapaevsky Passage, Stavropol 355016, Russia
Postal address	As above
Phone Fax	+78652 36 53 56 +78652 36 53 55
Date of inspection	16-18 July 2012
Type of inspection	Routine inspection
Dosage form(s) included in the inspection	Capsules
WHO product numbers covered by the inspection	Product under assessment: TB 222 Cycloserine 250mg capsule
Summary of the activities performed by the manufacturer	Manufacture, quality control and release of: • Tablets, coated and uncoated • Hard gelatin capsules • Secondary packing of solution for injection
Scope and type of inspection	Routine GMP inspection

This inspection report is the property of the WHO
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Part 2: Summary

General information about the company and site

The company JSC Biocom is situated near the administrative border of Stavropol city.

At the time of the inspection, Biocom employed 113 employees, 29 of which worked in pharmaceutical production and 30 in Quality Control (QC).

The product dosage forms manufactured on site included hard gelatin capsules, coated and uncoated tablets. The company manufactures 26 different products, hormones, potent drugs or antibiotics were not manufactured at the site.

History of WHO and/or regulatory agency inspections

The site was inspected by the WHO prequalification programme in 8 - 12 November 2010.

Focus of the inspection

The inspection focused on the production and control of Cycloserine 250 mg capsule.

The inspection covered various sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

2.1 QUALITY ASSURANCE

A system for quality assurance was established.

Finished product release was the responsibility of the Authorized person or designated deputy – head of QC laboratory, hierarchically independent from production. Starting materials, packaging materials and in-process products were released by the head of the QC.

Product Quality Review (PQR)

PQR SOP as well as PQR a specific product was reviewed and some comments were made.

Change Control

A formal system for change control was described in a written procedure and flow chart. Change control SOP and register were spot-checked.

Deviation management

Deviation management was described in a written procedure. Deviations SOP, deviations register for 2011 and a specific deviation were spot-checked. Deviations were classified as:

- Planned
- Unplanned
- Minor deviation
- Major deviation

SOP "Implementation and control of Quality corrective actions" and register for 2012 were spot-checked. The SOP classified corrective actions (CA) as:

- Critical
- Major
- Minor

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

In general good manufacturing practices were implemented. The necessary resources were provided. Manufacturing steps were recorded in batch manufacturing and packaging records. Instructions and procedures were generally written in clear and unambiguous language.

Qualification and validation were performed.

2.3 SANITATION AND HYGIENE

In general, premises and equipment were maintained at an acceptable level of cleanliness. Procedures were in place for personal hygiene.

The company used UV lamps for disinfection following "general cleaning" (once a month or after product change-over).

2.4 QUALIFICATION AND VALIDATION

IQ, OQ, PQ for capsuling machine and metal detector were spot-checked.

Cleaning validation

UV analytical methods used for the cleaning validation were under re-validation during the inspection. Until the date of inspection analytical methods for 11 products were validated. When validation of analytical methods for all products will be finished, the company will start re-validation of cleaning process.

2.5 COMPLAINTS

Complaints SOP and registers for 2011 and 2012 were spot-checked.
There were no complaints registered regarding product quality.

Responsible person for coordinating and processing the complaints was designated - head of the QA department or an appointed deputy.

Complaints were classified as:

- Critical
- Major
- Non critical
- Adverse drug reactions

2.6 PRODUCT RECALLS

Recalls SO and recall register were reviewed.

One recall had been executed in 2011.

Mock recall had been executed in July 2012.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Not inspected during this inspection.

2.8 SELF INSPECTION AND QUALITY AUDIT

Self-inspections were described in SOP. Self-inspection was carried out for all departments according to an audit schedule. Some departments were audited once per year, some twice per year. Check lists were used to carry out audits. Audits were led by head of the QA, excluding the audit of the QA department itself.

Observations were identified as:

- Non compliance
- Remarks
- Recommendations

Audit reports were approved by the executive director. Corrective actions were proposed after the audit and follow-up was carried out by QA personnel.

Management review was carried-out at the beginning of each calendar year and included results of self-inspections.

Approval of vendors

Approval of vendors was described in SOP. Qualification of vendors was carried out using questionnaires. Questionnaires were evaluated by the QA personnel. After the first supply and testing, the evaluation form was completed. Qualified vendors were listed in the approved vendors list. Vendors were re-evaluated and the approved vendors list was updated once in a year.

Five packaging material vendor audits were carried out during 2011-2012. The vendors audit plan for 2012 was presented to the inspectors.

Aluminum foil manufacturer audit report was presented to the inspectors. The audit report was spot-checked, no observations were made.

Approved vendor and supplier lists were available. In most cases API and excipients were received from suppliers.

2.9 PERSONNEL

In general, the personnel met and interviewed during the inspection appeared experienced and skilled. Job description of newly recruited Head of QC laboratory was spot-checked.

2.10 TRAINING

The training needs were identified and training was organized as per SOP. Induction training consisted of two phases. The first phase was theoretical training for one month and the second phase consisted of theoretical and practical training for two months. Training effectiveness was evaluated by verbal tests and written tests which consisted of objective and subjective questions. Periodical training was carried out every year.

Two step analytical chemist qualifications had been introduced and included theoretical exams and observing the analyst's performance on laboratory equipment. Work skills of analysts were not evaluated by practical comparative testing or equivalent (testing of a sample which had been previously tested by an experienced analyst; testing of the same sample by two analysts, etc). This is a repeated issue also discussed during the previous inspection.

Personal training files were maintained. Personal training file for the newly appointed Head of the QC laboratory was spot-checked.

2.11 PERSONAL HYGIENE

Direct contact was avoided between operators' hands and starting materials, primary packaging materials and intermediate or bulk product. All changing rooms were provided with photographs which described the gowning procedures.

2.11 PREMISES

The site has been in operation since 2004. In general, the buildings and facilities used for manufacture and quality control were located, designed, and constructed to facilitate proper cleaning, maintenance and production operations.
The following SOPs were spot-checked:

- SOP "Cleaning of classified and non-classified premises"
- SOP "Usage of the UV lamp for disinfection of production premises¨
- SOP "Cleaning of capsuling machine"
- SOP "Microbiological environmental monitoring of surfaces in clean rooms"

2.12 EQUIPMENT

Balances and other measuring equipment with appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Calibration due-date labels were attached to the equipment.

Utilities
The HVAC system was properly designed and maintained. A single air handling unit (AHU) served the production areas. There were separate AHU's for storage areas, QC and microbiological laboratories. Production areas were supplied with 100% fresh air. There was a HEPA filter installed in the plenum. The HVAC system was running continuously.

Compressed air system had final filters installed centrally, the type of the final filter was appropriate, filter checking records were available.

Purified water (PW) system first validation was completed in 2008. The sampling frequency during validation studies had not been in line with WHO Good Manufacturing Practices; therefore PW system 3 phase re-validation was carried out from April 4, 2011 until May 31, 2012.

PW in Cysloserine capsule production was used only for equipment cleaning. PW was used in tablet production.

2.13 MATERIALS

Materials were stored in high bay racks. Materials were properly quarantined and released by QC. Temperature and RH (T&RH) was controlled. T&RH mapping was carried out twice per year - in winter and summer, reports were available.

Printed packaging materials were stored in a locked area.

Materials were managed by Corporative Informative System (CIS) and on paper records.

There was a common sampling area for starting materials, capsules and primary packaging materials. Dispensing was carried out in the dispensing room located in the production department.

2.14 DOCUMENTATION

In general, the documentation system was established and maintained. Documents were approved, signed and dated by appropriate responsible persons, regularly reviewed and kept up to date. A system for version control was in place. Specifications and testing procedures were available. Documents related to batch release were stored one year after the expiry date of the batch.

2.15 GOOD PRACTICES IN PRODUCTION

Handling of materials and products was done in accordance with written procedures and was recorded; checks on yields and reconciliation of quantities were carried-out. During processing, materials, bulk containers, equipment, rooms and packaging lines were labeled. In-process controls were performed within the classified production area.

Only one product was manufactured at a time because the main production equipment was available in single items (V blender, granulator, tablets compression machine, capsule filling machine). Production was organized in campaigns. During the inspection, manufacturing was not carried out.

2.16 GOOD PRACTICES IN QUALITY CONTROL

The QC function was independent of other departments. Sufficient samples of starting materials and products were retained to permit future examination of the product. Analytical results were checked by the Head of analytical laboratory.

Out of Specification (OOS)

Dealing with OOS was explained in SOP and flowchart. OOS register was maintained..

Stability studies
24 month expiry period was established and proved for Cycloserine 250 mg capsules. Stability test results for 24 months were within the specification limits.

30 months stability studies had been completed.

Reference substances
Primary and working standards were available for cycloserine API. The reference standard for cycloserine dimer was supplied by Sigma. Storage conditions for standards were suitable. Working standards were standardized against primary standards.

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 Joint Stock Company "Biocom" 54, Chapaevsky Passage, Stavropol 355016, Russia 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.