

**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	+78652 36 53 56
Fax	+78652 36 53 55
Date of inspection	8 - 12 November 2010
Type of inspection	Routine inspection
Dosage form(s) included in the inspection	Capsules
Summary of the activities performed by the manufacturer	Manufacture, quality control and release of: <ul style="list-style-type: none"> <li>• Tablets, coated and uncoated</li> <li>• Hard gelatin capsules</li> </ul>
Scope and type of inspection	Routine GMP inspection
Programme	Prequalification of Medicines Programme

## **Part 2: Summary**

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

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

At the time of the inspection Biocom employed 112 employees, 19 of which worked in pharmaceutical production and 23 in Quality Control (QC).

The product dosage forms manufactured on site included hard gelatin capsules, coated and uncoated tablets.

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

The Biocom site was not previously inspected by WHO.

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

The inspection focused on the production and control of prequalified products. The inspection covered all the 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, hierarchically independent from production. Starting materials, packaging materials and in-process products were released by the head of the QC.

Quality manual approved by the Executive director was presented. QM was written in accordance with ISO 9000. The site was ISO 9000 certified.

### **Change Control**

A formal system for change control was described in a written procedure and flow chart. Change control register was available.

### **Deviation management**

Deviation management was described in a written procedure. Deviation register was available. Deviations were classified as:

- Class I - deviations what could have possible impact on processes, quality and analysis
- Class II - deviations what do not have impact on processes, quality and analysis.

Deviations were recorded in the BPR's and in the deviations register.

It was noticed that the majority of the deviations recorded in the register were not actually related to production processes.



### Product Quality Review (PQR)

PQR SOP and specific product PQR for 2009 were reviewed.

## **2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS**

Good manufacturing practices were implemented. The necessary resources were generally provided. Manufacturing steps were recorded in batch manufacturing and packaging records; records were made during manufacture. 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.

## **2.4 QUALIFICATION AND VALIDATION**

### Validation Master Plan (VMP)

The VMP included elements of qualification, as well as validation of processes, including Cleaning Validation and Computer Validation.

### Process validation

Sufficient data was available to demonstrate process consistency. Process validation was carried out for 3 consecutive production batches.

### Cleaning validation

The same cleaning procedure was used for all products. The approach was to validate cleaning after each product. Cleaning was verified after every campaign of each product applying the same scope as in validation. Discussion was held over this approach.

Cleaning validation for 8 products had been completed and was on-going for another 8 products.

Microbiological tests were used in cleaning validation for operator garments.

### Re-qualification

Re-qualification was conducted for HVAC every two years. During re-qualification the following parameters were checked:

- particle count / size
- air change per hour
- air velocity
- pressure differentials
- temperature & relative humidity (T&RH)



## **2.5 COMPLAINTS**

Dealing with complaints was explained in the SOP. Complaint register was available and shown to inspectors. Responsible person for coordinating and processing the complaints was designated - head of the QA department/designated deputy.

Complaints were classified as:

- critical
- major
- non critical
- adverse drug reactions

## **2.6 PRODUCT RECALLS**

Dealing with recalls was explained in the SOP. The head of the QA department/designated deputy was responsible for the recall coordination.

## **2.7 CONTRACT PRODUCTION AND ANALYSIS**

Production activities were not contracted out. Some analysis were carried out in a contract laboratory and the contract was presented to inspectors.

## **2.8 SELF INSPECTION AND QUALITY AUDIT**

Self inspections were described in an 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 lead 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 an 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 updated once in a year.

Five packaging material vendors audits were carried out, three audit reports were presented to the inspectors; no remarks.



## **2.9 PERSONNEL**

In general, the personnel met and interviewed during the inspection appeared experienced and skilled. Job descriptions of key persons were available and the following were reviewed, no remarks were made by inspectors:

- Quality Director
- Qualified person
- Chief of QA department
- Chief of QC
- Head of production
- Research and Development Director
- 

## **2.10 TRAINING**

The training needs were identified and training was organized as per SOPs. 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. Training programmes were drafted for job positions.

Personal training files were maintained.

## **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. SOP "Personnel hygiene" was reviewed; no remarks were made by inspectors. Medical checks were carried out before employment and once per year. Personal medicines were not permitted in production, laboratory and storage areas.

## **2.12 PREMISES**

The site is in operation from 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. A pest control procedure was in place.

### Storage area

Storage areas were designed and maintained to ensure good storage conditions. The warehouse was clean, dry and maintained within acceptable temperature limits. Receiving and dispatch bays were separated and protected materials and products from the weather.

### Production areas

Manufacturing areas were designed and maintained to minimize the risk of mix-up of different pharmaceutical products or their components and to avoid cross-contamination. Walls, floors and ceilings were smooth and free from cracks and open joints. Production areas were effectively ventilated.



### Quality control (QC) areas

Quality control laboratories were separated from production areas. All analytical tests (chemical and instrumental) were carried out in a single, quite small room. Microbiology laboratory was separated from chemical laboratory. Sufficient space was provided for samples, reference standards, solvents and reagents. Reference and working standards were stored in the fridge. Retention samples of API's and FPP's were stored appropriately in a separate room.

### **2.13 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. Calibrated standard weights used for in-house checking of balances were available. Calibration due-date labels were attached to the equipment.

Equipment after cleaning was stored in a separate room. It was noticed that the cleaned equipment did not bear status labels and the room itself was not labeled with an indication to the clean equipment storage.

Equipment calibration schedule and planned preventive maintenance program (PM) of equipment and systems was in place. Spot checks showed that the schedules had been followed and records were maintained.

### Utilities

HVAC system was properly designed and maintained. One air handling unit (AHU) served the production areas. There were separate AHU's for storage areas, QC and microbiological laboratories. Systems were in place to ensure low humidity in the production environment.

Purified water (PW) system validation was completed in 2008.

### **2.14 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 Corporate Informative System (CIS) and on hard copies. Computers were password protected.

Materials and locations in the warehouse corresponded to the electronic database.

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. Entrance to the sampling room was via a common air-lock for materials and personnel; entrance to the dispensing rooms was via separate airlocks for personnel and materials.



SOP "Classification of defects for packaging materials and AQL" was reviewed, no remarks were made by inspectors.

AQL was applied for printed packaging materials sampling. Classification of defects was as following:

- critical, class I - AQL - 0.010%
- critical, class II- AQL - 0.15%
- major AQL - 0.65%
- other AQL - 2.5%

Microbiological analyses were carried out for each batch of starting materials and primary packaging materials.

In general, storage and labeling of materials were acceptable.

### **2.15 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 the batch release were stored one year after the expiry date of the batch.

### **2.16 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 production area.

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.

Environmental air temperature, RH and pressure differentials were monitored twice per day. Portable digital Thermo/hygrometer IVA-6A was used for Measuring temperature and RH. Processes appeared to be under control.

### **2.17 GOOD PRACTICES IN QUALITY CONTROL**

The QC function was independent of other departments. Samples of starting materials, packaging materials, intermediate products, bulk products and finished products were taken by approved methods. Sufficient samples of starting materials and products were retained to permit future examination of the product. Analytical results were checked by the supervisor.

HPLC chromatograms for stability studies and method validation for stability studies and comparative dissolution studies were checked on paper.



Out of Specification (OOS)

Dealing with OOS was explained in the SOP and flow chart.

Stability studies

Stability schedule was presented to inspectors. The schedule was followed. At the time of the inspection 12 months long-term results were available. Results were within specification limits. Analytical raw data was available for inspectors.

Reference substances

Primary and working standards were available. 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.