### Part 1: General information

<table>
<thead>
<tr>
<th>Name of Manufacturer</th>
<th>Square Pharmaceuticals Limited (SPL)</th>
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<tbody>
<tr>
<td>Unit number</td>
<td>Dhaka Unit</td>
</tr>
<tr>
<td>Production Block</td>
<td>Unit I (FUI)</td>
</tr>
<tr>
<td>Physical address</td>
<td>Kaliakoir, Gazipur, 1750, Peoples Republic of Bangladesh</td>
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</tbody>
</table>
| Dates of inspections | 18-21 August 2014
18-20 May 2015 |
| Type of inspection   | Special inspection - follow-up implementation of corrective actions and preventive actions |
| Summary of activities of manufacturer (e.g. manufacturing, packing). | Solid dosage forms:  
  - Coated tablets, capsules, oral powders  
  Sterile products  
  - Small volume parenteral products & ophthalmological products  
  - Insulin’s  
  - Pre-filled syringes  
  HFA (Hydrofluoroalkane) based metered dose inhalers |
| Dosage form(s) included in the inspection | Film coated tablets |
| WHO product covered by the inspection | **Product under assessment:** HIV/AIDS |
| Summary of the activities performed by the manufacturer | Manufacturing, packaging, quality control, stability testing |
Part 2: Summary

General information about the company and site

The Square Pharmaceuticals Limited (SPL) Dhaka Unit was established in 1958 in Pabna, Bangladesh. As a result of increased local and export market demand the General production facility was built in 2001. There were four formulation units:

- Formulation Unit 1 (General production building for oral solid dosage forms)
- Formulation Unit 2 (Small volume parenteral and ophthalmic products)
- Formulation Unit 3 (Insulin, metered-dose inhaler (MDI) and pre-filled syringe production)
- Formulation Unit 4 (Parenteral products production -)
- Dedicated facility for Cephalosporin Products

No hormones or cytotoxic were manufactured in Dhaka unit.

Cephalosporin’s (Beta-lactam) products were manufactured at the site in a separate dedicated standalone facility. No penicillin products were manufactured on site.

History of WHO and/or regulatory agency inspections

The site was previously inspected by the WHO team on 18-21 August 2014. This was follow-up inspection focused on implementation of the corrective actions.

The site was audited/inspected by the following authorities:

<table>
<thead>
<tr>
<th>Year</th>
<th>Inspected authority</th>
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<tbody>
<tr>
<td>April 2001</td>
<td>Directorate of Drug Administration &amp; Licensing Authority Peoples Republic of Bangladesh</td>
</tr>
<tr>
<td>March 2001</td>
<td>United Nations Children's Fund (UNICEF)</td>
</tr>
<tr>
<td>August 2005</td>
<td>Libyan Authority</td>
</tr>
<tr>
<td>November 2005</td>
<td>Tanzania Food &amp; Drug Authority</td>
</tr>
<tr>
<td>May 2007</td>
<td>Medicines and Healthcare products Regulatory Agency (MHRA), UK</td>
</tr>
<tr>
<td>January 2008</td>
<td>Kenyan Authority</td>
</tr>
<tr>
<td>December 2008</td>
<td>The Federal Democratic Republic of Ethiopia Authority</td>
</tr>
<tr>
<td>June 2009</td>
<td>United States Agency for International Development (USAID)</td>
</tr>
<tr>
<td>November 2009</td>
<td>Pharmacy, Medicines and Poisons Board, Malawi</td>
</tr>
<tr>
<td>December 2010</td>
<td>Therapeutic Goods Agency (TGA)</td>
</tr>
<tr>
<td>February 2012</td>
<td>Medicines Control Authority of Zimbabwe (MCAZ)</td>
</tr>
<tr>
<td>March 2012</td>
<td>Therapeutic Goods Agency (TGA)</td>
</tr>
<tr>
<td>July 2013</td>
<td>National Medicines &amp; Poison Board, The Republic of Sudan</td>
</tr>
<tr>
<td>March 2014</td>
<td>United Nations Children's Fund (UNICEF)</td>
</tr>
<tr>
<td>August 2014</td>
<td>WHO</td>
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<tr>
<td>January 2015</td>
<td>US Food and Drug Administration</td>
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Focus of the inspection

The inspection (May 18-20, 2015) focused on the production and control of HIV-AIDS tablet under the prequalification. A particular attention was paid on implementation of corrective actions and preventive actions (CAPA). Note: This WHOPIR is based on two inspection reports.
Inspected Areas

- Quality Assurance
- Sanitization and hygiene
- Qualification and validation
- Complaints
- Recalls
- Supplier qualification
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

3.1 PHARMACEUTICAL QUALITY SYSTEM (PQS)

Principle
In general a PQS was implemented to ensure that pharmaceutical products fit for their intended use. Production and control operations were specified in written form and GMP requirements were generally followed. Managerial responsibilities were specified in job descriptions. The organisation chart was available and reviewed. Job descriptions of the Quality Assurance (QA) General Manager, the Assistant General Manager of QA and the Production General Manager were reviewed.

Quality Risk Management (QRM)
QRM principles were applied to evaluate of the risk to product quality. The SOP “Quality Risk Management” was reviewed. The SOP was revised after the previous WHO inspection. The SOP was applicable to:

- Development
- Manufacturing
- Distribution
- Inspection/auditing
- Testing
- Regulatory submissions
- Qualification & validation
- Complaints
- CC
- Calibration
- Quality Investigation Reports (QIR)/deviations
- Maintenance
- OOS
- CAPAs
- Supplier qualification
Reworking/reprocessing
Storage condition

The risks were classified as:
- Critical
- Major
- Minor

Product Quality Review (PQR)
The SOP “Annual product review” was reviewed. PQR was performed based on a rolling review, whereas all products were divided into 12 months and certain number of products was taken for monthly review. The SOP was revised after the previous WHO inspection.

Management review
The SOP “Execution of Quality Management Review meeting” was checked. According with the SOP Quality Management System (QMS) review should be performed at least annually.

Change control (CC)
The SOP “Change control” was revised after the previous WHO. The deviation was raised following the previous WHO inspection pertaining to stability samples not tested within timeline.

Deviation management
The SOP “Quality investigation report (QIR)” was reviewed. Quality incident was defined as: “The site events which if not detected early enough and responded to correct will possibly compromise safety, quality and efficacy (unplanned deviations)”. Deviations were classified as:
- Critical
- Major
- Minor

According with the SOP and investigation report (QIR) – the root cause should be identified and CAPAs proposed. QIR should be closed within 30 days; if it was not possible then the Quality Assurance (QA) justification for extension was required. QIR trending should be performed every six months. A review of outstanding QIR and Preventive Actions (PA) progress should be monitored regularly and reported quarterly.

The deviations register for 2014 was checked.

3.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS
In general good manufacturing practices were implemented. The necessary resources were generally provided. Manufacturing steps were recorded in batch manufacturing and packaging records. Instructions and procedures were generally written in clear and unambiguous language. Qualifications and validations were performed, adequate premises
and equipment were available for production, in-process controls and storage, and operators were trained.

3.3 SANITATION AND HYGIENE
Premises and equipment were maintained at an acceptable level of cleanliness. The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facility. The SOP “Personal hygiene and usage of personnel protection measure” was reviewed.

3.4 QUALIFICATION AND VALIDATION
The key elements of a qualification and validation programme were defined and documented in the validation master plan. The validation master plan was checked.

Process validation (PV):
Only one API source of Azithromycin was currently qualified. It was noted that process validation protocol was revised based on the last inspection deficiency, and PV will be done before commercialization of the product as committed to the WHO.

Cleaning validation
SOP “Cleaning validation”, matrix table and cleaning validation protocol / report were presented to the inspectors. The worst case approach was used for cleaning validation. The criterion was based on comparison of the daily dose and 10 ppm, whichever was lower. Cleaning validation studies were performed for two batches, the third batch studies were on-going.

Computer validation
GMP computerised systems were validated and managed based on the V-model (software development), Good Automated Manufacturing Practice 5 (GAMP 5) and company guidelines. The validation protocol for a specific computer system was briefly reviewed due to the time constrains.

Equipment qualification
The SOP “Planned preventive maintenance system” was reviewed. The qualification status of equipment was available for review and considered acceptable. An example of the FBD maintenance record was reviewed.

3.5 COMPLAINTS
Complaints and other information concerning potentially defective products were reviewed according to written procedures and the corrective actions were taken. A person responsible for handling the complaints and deciding the measures to be taken was designated.

The SOP “Investigating and analysing of customer complaints” was reviewed. The SOP was revised after previous WHO inspection. The Head of QA or his deputy was responsible for handling the customer complaints, ensure that corrective actions and preventive actions (CAPA) were taken effectively and also for the complaints quarterly review.
The complaints registers were unit based. The complaint register for the Unit I for 2015 and specific complaints were checked.

3.6 PRODUCT RECALLS

The SOP “Product recall” and a specific recall report were reviewed. The recall was done following the SOP. Product reconciliation was performed. According with the SOP mock recall should be performed at least once in two years.

3.7 CONTRACT PRODUCTION AND ANALYSIS

The manufacturing and Quality control operations of the inspected product were not contracted out.

3.8 SELF INSPECTION AND QUALITY AUDIT

The self-inspection according with the Check lists was performed every 3 months, each area was inspected at least once in a year. The observations were addressed through the CAPA system. The self-inspection plan for 2014 was reviewed and records showed that self-inspections had been performed as per the plan.

Supplier’s audits and approval

The SOP “Vendor qualification for raw and packaging materials” and flow chart was reviewed.

The supplier’s audits were scheduled based on the risk matrix:

- The high risk products (sterile API) – every two years
- The medium risk products (non-sterile API) – every three years
- The low risk products (excipients other than animal origin) – every five years.

3.9 PERSONNEL

In general the manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. The responsible staffs’ specific duties were recorded in written job descriptions. Personnel were aware of the principles of GMP and received initial and continuing training.

3.10 TRAINING

The training was performed according with an SOP. The Quality Control Laboratory (QCL) analysts training and validation was performed according with a specific SOP. The training file for a newly qualified analyst was reviewed. Reviewed training record was detailed.

3.11 PERSONAL HYGIENE

Direct contact was avoided between the operator’s hands and starting materials, primary packaging materials and intermediate or bulk product. Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking material and personal medicines was not permitted in production, laboratory and storage areas. Wrist-watches, cosmetics and jewellery were not being worn in clean areas. The level of hygiene observed and the measures taken to maintain hygiene were considered sufficient. The changing rooms were provided with photos describing the gowned procedures.
3.12 PREMISES
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 premises were designed to ensure the logical flow of materials and personnel. The in-process laboratory was located in the production block. The quality control laboratories were separated from production areas. The sufficient space was given to avoid mix-ups and cross-contamination. The premises were protected from entry by insects, birds and animals. The premises were clean and well maintained.

Storage areas
The receiving and dispatch bays protected materials and products from the weather. The segregation was provided for the storage of rejected, recalled, or returned materials or products.

The warehouse for the storage of different materials was found to be adequate. The temperature mapping was performed.

Production areas
In general, the production area was laid out to allow the production steps to take place in a logical order. In general the surfaces were smooth and free from cracks. The equipment and materials were orderly positioned to minimize the risk of confusion between the different pharmaceutical products or their components.

The temperature, relative humidity and pressure differentials were regularly monitored.

Quality control areas
The quality control areas were separated from production areas. The sufficient space was provided for samples, reference standards, solvents and reagents.

3.13 EQUIPMENT
The balances and other measuring equipment were available for production and control operations and were calibrated on a scheduled basis. The calibration due-date labels were attached to the equipment. The calibrated standard weights used for in-house verification of the balances were available.

The laboratory instrument/equipment (High Performance Liquid Chromatograph - HPLC), used for the stability study testing verification was checked.

Equipment calibration
The SOP “Calibration of Sartorius balances” was checked. The SOP was applicable for the balance located in the production and laboratory.

Utilities
HVAC
The following SOPs related to the HVAC were checked:
• “Pre, bag & HEPA filter replacement of HVAC systems”
**HVAC re-qualification**

A specific air handling unit (AHU) re-qualification report was checked. The following tests were performed:

- Installed filter leakage test
- Air flow and air change
- Room differential air pressure
- Air flow direction test
- Temperature and Relative Humidity

**Purified Water (PW)**

The procedure “Periodic sanitisation of purified water system” was checked. The SOP was applicable to the main loop and PW storage tank. The sanitization was done automatically. The sanitization temperature was 85 °C for 90 minutes. The sanitization was performed monthly and sanitization records were spot checked and were found to be acceptable.

The procedure “Integrity test procedure of ventilation filters” and integrity test result from was spot checked and was found to be acceptable.

The calibration of temperature sensors, conductivity meters and water flow meter was performed once per year, last calibration records were presented to the inspectors.

**PW trends**

The PW trend analysis (Unit FUI) were spot checked. All results were within alert limits.

### 3.14 MATERIALS

The materials in the warehouse were appropriately stored in a clean and orderly manner. The receiving and dispatch bays were separated.

The procedures describing the receipt, quarantine, storage, handling, sampling, testing and approval or rejection of materials were available. The temperature and Relative humidity were controlled: 15 to 25 °C and 40 to 65% RH respectively. The materials in the warehouse were handled partially by the Systems Applications and Products system (SAP).

### 3.15 DOCUMENTATION

In general the documents were designed, prepared, reviewed and distributed with care. In general, documents were approved, signed and dated by the appropriate responsible persons. The documents were laid out in an orderly fashion and were easy to check. The reproduced documents were clear and legible. The documents were regularly reviewed and kept up to date.
Batch release
The SOP was checked. The Head of QA or his deputy was responsible for decision to release/reject the finished pharmaceutical products in SAP system and approve the release for sale certificate and if required issue the GMP compliance certificate, review and check batch related documents, change the batch status of the finished product from unrestricted to restricted stock. The review of batch documents was performed using “Check list for batch documents”.

Batch numbering system
The SOP “Procedure for product batch number issuing & handling of BMR & BPR” was checked. Batch Manufacturing Records (BMR) & Batch Packaging Records (BPR) were issued by the executive of QA.

Reprocessing and rework
The SOP “Procedure for manufacturing reprocess” was checked. SOP point 7.1 stated: Take prior approval from regulatory authority and/or marketing authorization holder as appropriate.

3.16 GOOD PRACTICES IN PRODUCTION
In general the production facilities surfaces were smooth and free from cracks. The equipment and materials were orderly positioned to minimize the risk of confusion between the different pharmaceutical products or their components.

The temperature, relative humidity and pressure differentials were regularly monitored.

The metal detectors were installed to all compression machines. During the inspection the Certificates of inspection were seen for 0.3 mm ferrous test samples, 0.5 mm SS316 test samples and 0.5 mm brass test sample.

Every production Unit had its own garment laundry. The SOP “Washing procedure of laundry” was spot checked.

The in-process controls were performed at the production floor at the in-process laboratory.

3.17 GOOD PRACTICES IN QUALITY CONTROL
The quality control function was independent from other departments. The samples of starting materials, packaging materials, intermediate products, bulk products and finished products were taken by the approved methods.

The SOP “Sampling of starting materials” and sampling log book were reviewed.

The sampling procedure of the packaging materials was based on √n +1 and acceptable quality limit. The approved specifications and testing procedures were available.

The Pharmacopoeia reference standards (RS) and working standards (WS) were available. Usage of the reference standards was recorded in the log book. The procedure for preparing WS was reviewed.
Out of Specification (OOS)
The SOP “Investigation of out of specification” and OOS registers were reviewed.

The specific OOS investigation reports were reviewed.

Out of trend (OOT)
The SOP “Investigation of out of trend” was checked.

Stability studies
During the inspection special attention was paid to the stability studies and data integrity related to the stability studies.

The specific stability studies reports for 40/75% (1, 2, 3 and 6 month) and 30/65% & 30/75% (3, 6, 12, 18, 24 and 36 months) were reviewed.

The SOP “Stability testing” was reviewed.

There were a number of HPLC systems dedicated for the stability testing. It was noted that during the inspection stability laboratory employed 23 analysts in three shifts.

Verification of electronic data
The Chromeleon was used for Agilent & Dionex / thermo Scientific HPLCs and Empower 3 was used for Water systems HPLCs. It was noted that currently the laboratory did not have the Laboratory Information Management System (LIMS) and intend to implement the LIMS in few years’ time.

During the inspection electronic data, audit trails and HPLCs access controls were verified.

Part 4: 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 Square Pharmaceuticals Limited (SPL), Dhaka Unit, Unit I (FUI), located at Kaliakoir, Gazipur, 1750, Peoples Republic of Bangladesh, was considered to be operating at an acceptable level of compliance with WHO good manufacturing Practices for pharmaceutical products.

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.