

WHO PUBLIC INSPECTION REPORT Finished Product Manufacturer
**WHO PUBLIC INSPECTION REPORT
(WHOPIR)**
Finished Product Manufacturer
Part 1: General information

Name of Manufacturer	Strides Arcolab Limited
Unit number	Oral solid dosage forms division
Production Block	General tablet and capsule block
Physical address	'KRS Gardens' Suragajakkanahalli, Indlawadi Cross, Anekal Taluk, Bangalore South – 562 106 India
Contact address	Mr Umesh Kale, Vice President, QA Email: Umesh.K@stridesarco.com
Date of inspection	19 - 22 October 2013
Type of inspection	Routine inspection
Dosage forms(s) included in the inspection	Tablets and capsules
WHO product categories covered by the inspection	<u>WHO Prequalified products:</u> HA203 Lamivudine 150mg tablets HA268 Nevirapine 200mg tablets HA291 Lamivudine/Zidovudine 150/300mg tablets HA312 Stavudine 30mg capsules HA313 Lamivudine/Stavudine 150/30mg tablets HA389 Efavirenz 200 mg film coated tablets HA390 Efavirenz 600 mg film coated tablets HA494 Abacavir Sulfate 300mg tablets TB202 Rifampicin/Isoniazid 150/75 mg TB216 Rifampicin/Isoniazid/Pyrazinamide/Ethambutol 150/75/400/275mg FDC tablets MA74 Artesunate + Amodiaquine 50 mg+153 mg tablets IN002 Oseltamivir Phosphate 75mg capsule <u>Products under assessment at WHO:</u> HA524 Lamivudine/Nevirapine/Zidovudine 150/200/300mg tablets HA535 Tenofovir Disoproxil Fumarate 300mg tablets

	HA552 Emtricitabine/Tenofovir Disoproxil Fumarate 200/300mg tablets HA553 Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate 600/200/300mg tablets HA557 Lamivudine/Nevirapine/Zidovudine 30/50/60mg tablets MA88 Artemether/Lumefantrine 20/120mg tablets MA110 Artemether/Lumefantrine 20/120mg tablets <u>Contract manufacturing for Sandoz:</u> TB085 Isoniazid/Rifampicin 75/150mg tablets TB090 Ethambutol/Isoniazid/Pyrazinamide/Rifampicin 275/75/400/150mg
Summary of the activities performed by the manufacturer	Production, packaging, control and release of oral solid dosage forms

Part 2: Summary

General information about the company and site

The site inspected was **Strides Arcolab Limited (hereafter Strides), located in KRS Gardens', Suragajakkanahalli Indlawadi Cross, Anekal Taluk Bangalore-South - 562 106 India**. The oral dosage forms (ODF) division of Strides was inspected by a WHO prequalification team on the above mentioned dates.

The ODF Plant is spread over a total land area of about 23 acres (1.0 million sq. ft. approx.). The production at this plant was commenced for soft gelatin capsules from May 1998, tablets and hard gelatin capsules from September 1999. Dedicated Rifampicin block was commissioned in 2003.

The ODF plant was designed to have following production blocks:

- Soft gelatine block
- Tablet/hard gelatine capsule/liquid filled capsule block (multi product)
- Anti-TB block

According to the site master file and company presentation, the site employed approximately 606 full time employees working on site.

History of WHO and/or regulatory agency inspections

The site was previously inspected by WHO Prequalification of Medicines Programme in August 2011. The Strides Oral Dosage Form division had been inspected and approved by various regulatory authorities including:

Regulatory Authority	Last Inspection date	Current Approval Status
WHO	August 2011	Products prequalified
US FDA	July 2011	Approved
MHRA	December 2011	Approved
TGA	October 2011 (Desktop approval)	Approved
ANVISA	October 2007	Approved

Focus of the inspection

The inspection focused on the production and control of various prequalified, currently under assessment and products manufactured for the third parties. The inspection covered most of the sections of the WHO GMP text, including premises,

equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

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

2.1 QUALITY ASSURANCE

A quality assurance system was implemented and maintained.

The QA department was led by the Vice President QA, reporting directly to the Corporate President QA & RA. The QA and QC units were independent from production. Managerial responsibilities were specified in job descriptions.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

The production was performed in a multi-product facility and production equipment was not dedicated for WHO prequalified products. Validations, qualifications were performed according to the corporate/site policy and documented procedures.

Adequate premises and equipment were available for production, in-process controls quality control and storage.

Manufacturing processes and quality control test requirements were generally well defined in approved documents.

The issues raised from this section had been adequately addressed, and will be verified during future inspections.

2.3 SANITATION AND HYGIENE

The facilities and procedures for sanitation and hygiene established on the site were found to be adequate to ensure that premises and equipment were properly cleaned so as to avoid contamination and cross-contamination. In general, adequate procedures were in place for the entry and exit of the critical processing areas.

The issues raised from this section had been adequately addressed, and will be verified during future inspections.

2.4 QUALIFICATION AND VALIDATION

Validation master plan was available which provided a general overview of various qualification and validation activities for facilities, equipment, product and computer system. Separate SOPs and plans were available for respective areas (SOP on cleaning validation, computer system validation plan).

SOP on cleaning validation was briefly reviewed which stipulated procedure for carrying out the cleaning validation. Solubility and toxicity criteria were used to assess the cleaning validation. Swab and rinse sampling were used to draw samples for cleaning validation. Cleaning validation also included clean and dirty equipment hold time. In addition, cleaning validation matrix was available which was updated as and when change controls are initiated pertaining to the introduction of new product and other criteria.

Validation master plan for computerised systems was reviewed which covered companywide computerised systems including BMS, SCADA etc. It was noted that the handheld device used to confirm status of materials in the warehouse was not included as part of the computer system validation.

The issues raised from this section had been adequately addressed, and will be verified during future inspections.

2.5 COMPLAINTS

Complaints were managed with SOP. A flow diagram is incorporated into the SOP. Any complaint is initially registered in a log book and then transcribed to Trackwise in order to facilitate progress in the investigation. Any emerging trends may be identified through frequent review of data entered into Trackwise. Root Cause Analysis is used when thought to be applicable. Time limits are set for each phase of the investigation. Records of investigations are retained for one year after the expiry date of the product batch involved.

2.6 PRODUCT RECALLS

The recall procedure was reportedly modelled on the MHRA Guidance Publication. It is a corporate SOP and is designed to be effective for each of the many supply chains used by the company (e.g. Brokers, markets at home and abroad).

2.7 CONTRACT PRODUCTION AND ANALYSIS

It was noted from the site management that Strides which produces contract products for Sandoz for TB business, intend to stop the same by the end of 2013. There were several issues cited by the site, in particular, there had been an inconsistent demand of prequalified products, also there was a supply issue of Rifampicin.

This section was not inspected in detail.

2.8 SELF INSPECTION AND QUALITY AUDIT

Self-inspections were conducted according to corporate QA SOP which required that each manufacturing sites be inspected at least once per year. In addition, a compliance follow up audit be conducted within 3 to 6 months' time from the self-inspection. A schedule was available and detailed checklists were used for the inspections.

The issues raised from this section had been adequately addressed, and will be verified during future inspections.

2.9 PERSONNEL

The people met during inspection appeared competent and had a good understanding of GMP requirements. A companywide organization chart was available. It was also noted that site organogram was available.

The issues raised from this section had been adequately addressed, and will be verified during future inspections.

2.10 TRAINING

Training was conducted according to the training procedure and training records were maintained through learning management system and hard copies. The effectiveness of training was assessed and recorded in the training files. A schedule for on-going training was available. Selected training file's including an analyst and casual workers were checked.

A training coordinator was responsible and based on site for the training of all staff. Currently, training was organised using both learning management system and manual system. It was noted that training was broadly classified into technical induction training, GXP training and master training requirements index (need matrix). In addition, event training management was in place (e.g. complaint). A monthly training plan was reviewed which identified various training on GXP, roles specific, EHS and behaviour. GXP training were provided at least once every year, whereas event training were need based and depend on change controls, OOS, deviations, SOP etc. 100% evaluation criteria was setup for written and practical evaluation. The SOP stated that training should be provided to contract employees in local and English language where necessary.

2.11 PERSONAL HYGIENE

Personnel hygiene was included in the training received by all personal during induction and basic GMP training. Photos describing the gowning procedures were appended to the changing procedures and provided on the walls of changing rooms. The level of hygiene observed and the measures taken to maintain this were considered at a satisfactory level.

2.12 PREMISES

There premises for manufacturing, storage and quality control of the inspected products were generally of a satisfactory standard. Layouts of the facilities were available and up-to-date.

The site had divided various products and their associated activities into four blocks namely soft gelatine capsule production area, tablet & hard gelatine capsule area, Anti-TB area and packaging area.

The inspection of tablet/hard gelatine capsule production which produces multi-products on non-dedicated equipment. In addition, a brief walkthrough was performed of the Anti-TB production area. There was no production activity running in Anti-TB area at the time of inspection.

The premises were designed to have a logical flow of materials and personnel. The production areas had adequate space for the placement of equipment and materials to prevent mix-ups and contamination. The company claimed that there are no highly active products or non-pharmaceutical products are manufactured in the same facility.

Processing areas where products are exposed were supplied with filtered air through EU4, EU9 and H13 filters. Pressure differentials between zones were specified and monitored by Magnehelic gauges. Magnehelic gauges have been installed in the most of the AHUs.

The utilities including the HVAC system and Purified Water (PW) were visited and were considered to be well designed and maintained. AHU were operated according to SOP which included detailed instructions for start-up and shut-down.

In general, premises were found clean and tidy

2.13 EQUIPMENT

Process equipment was installed and maintained in a way that minimizes risk of contamination and cross contamination. There were some exceptions noted. Refer section on observations.

A qualification/calibration and preventive maintenance program was in place and was followed.

Production equipment was identified as to its content or purpose and cleanliness status by label. Maximum hold times had been determined. The protocol and records for determining these times were reviewed.

Cleaning procedures for critical manufacturing equipment were available and had been validated.

2.14 MATERIALS

The warehouse is accessed through an air lock and gowning room fitted with a step over barrier. Washrooms and toilet facilities are located prior to the gowning room. Bootees, bonnet and coat are donned. A hand wash with 70% IPA is performed before final entry. The change procedure is pictorially represented on the wall. Removal of watches is required but prompting was necessary.

Differential pressures between the outer areas, the change room and the warehouse side indicated an airflow giving containment within the room. Storage areas included ambient, below 25°C and 2° to 8°C.

A pest control program is in place but it was not assessed during this inspection. Similarly the areas are temperature mapped but the protocol was not reviewed. The outer loading dock is fitted with a roller shutter door and separated from the warehouse by a heavy-duty plastics curtain. There is no control over overshoes worn when moving from the clean warehouse floor area to the relatively dirty dock floor. The company may wish to consider providing extra overshoes to be worn when re-entering the warehouse.

SOP gives instruction on receipt and handling of raw materials. The SAP system will not allow purchase of goods, which do not have a supplier identity number, programmed into the system. QC are advised that sampling is necessary by supplying them a copy of the GRNQC issue a sequential AR number which identifies and controls the raw material throughout its life cycle.

The database was interrogated for comparison of physical count with the listing on the database. Transaction details are batch specific. No matters of concern were noted with these two aspects of inventory control.

Sampling and Dispensing Area:

Separate rooms for both sampling and dispensing are situated in the warehouse and are accessed through airlocks designed to operate with a negative air pressure differential relative to the warehouse. All are equipped with LAF units. SOP controls maintenance and use. The rooms are designed to operate under negative airflow with respect to the warehouse. The range on the magnehelic gauges used to monitor the pressure was small scale and difficult to interpret. Whilst airflow was physically discernible, the reading was too close to the bottom end of specification to confirm that the rooms were in compliance. Sampling follows SOP. Dispensing follows SOP. Dispensed material is transferred to the manufacturing areas via a covered connecting corridor.

The issues raised from this section had been adequately addressed, and will be verified during future inspections.

2.15 DOCUMENTATION

A comprehensive set of SOP's is available, controlled by corporate management and forming part of the Company Quality Manual. Master copies are held in both hard copy and on protected computer files. A master SOP defines how to prepare and write an SOP.GQA/001/R6 effective 27/9/2012. SOPs are identified by an alpha numeric system which indicates the pertinent department responsible for generating and editing the document. SOP numbering, issue number, effective date, revision history, authorship and approval follow conventional lines. Signatures of authorising personnel matched the references held on file.

Document management follows SOP. Control procedures are in place to manage regular review, distribution, retrieval and destruction. Status (e.g. current, obsolete), is indicated by different coloured stamps applied to the front page. New editions are circulated in their entirety.

A "Use Case" approach is now used when following an SOP's instructions. The object is to focus the attention of the user on the sections pertinent to his/her role in execution of the SOP. It is hierarchical in application. Operators follow the section which equates to a work instruction. Supervisors, the next higher level follow their relevant section as do their line managers followed by QA and finally any cross departmental managers involved in the process. It does not however absolve a user from ignoring sections which are not applicable. User training provides the necessary background to understanding the document as a whole. Detailed flow diagrams for individual SOP's provide adequate description of the process.

The QMS system incorporates a Trackwise software package which can be interrogated to ascertain the progress of CAPAs, OOS investigations, change control, complaints and recalls.

2.16 GOOD PRACTICES IN PRODUCTION

Production operations were guided by approved written procedures in form of manufacturing instructions (MIs) and batch manufacturing records (BMRs). Records reviewed and practices witnessed indicated that records were made promptly in the BMRs and any deviations were also recorded and handled in accordance with an approved procedure.

Line clearance was conducted before and after production and packaging operations. The check list used was not detailed enough to highlight all the checks that needed to be done.

In-process controls were performed and documented at appropriate stages and intervals. There were provisions for checks on yields and reconciliation of quantities.

Materials and equipment were adequately labelled with identity, stage of processing and status as appropriate.

The issues raised from this section had been adequately addressed, and will be verified during future inspections.

2.17 GOOD PRACTICES IN QUALITY CONTROL

All components are purchased using the SAP system. The laboratory is sufficiently equipped to perform necessary testing. Rulers, Verneir callipers, balances, burst strength tester etc are all calibrated and within date. A light box used for detection of pin holes in foil (Al & PVC) is available. Chemical testing is performed using reagents prepared by the chemistry laboratory. Authorised reference standards are available for component dimensions, artwork, colours and colour tolerances.

Microbiology

The major activities centre on environmental monitoring and water testing. Entry to the laboratory is via a change room with a step over barrier. The incubators (32Deg C, 24 Deg C. and a dual 33Deg C/43Deg C. have been validated and temperature read out is constantly recorded. Similarly the refrigerator has been validated and is constantly monitored. The LAF used for plating out is located in a dedicated area and is maintained and sanitised following SOP. It operates with ΔP reading across the HEPA filter of 7-15 mm Water and air flow rates of recorded at 100 ± 3 ft/min (0.5 m/sec).

The MACHIN FABRIC autoclave is used for sterilising media. Operation of the autoclave follows SOP. It has been validated for heat distribution, load patterns and the standard cycle of 122Deg.C for 22 minutes using B stereothermophilus (3×10^6) with a D value of 1.5 minutes, the minimum value of F_0 is easily exceeded. No matters of concern arose regarding the equipment reviewed.

Media preparation follows SOP. A full range of solid media is available and preparation records are maintained. Positive and negative growth promotion tests are performed, the former using the conventional range of test organisms. Standard reference cultures are stored in the refrigerator. Five regenerations are permitted before re-culturing.

Plating out follows Pharmacopoeial requirements together with SOP SD/GP/0539/R1. No matters of concern were noted.

Chemistry

Documentation is controlled by a LIMS system. Raw material receipts are entered and each is fully documented for description, quantity lot number and company AR number. The AR number is unique and is used as the control number. AR numbers are issued sequentially by the LIMS system. Work is allotted by the supervisor on a priority basis to technicians trained in the required testing methods. The WIP is displayed on a wall screen and gives current status.

The analyst will retrieve the test and specifications from LIMS and print off a copy. Testing follows SOPs. All test methods and specifications are programmed by corporate personnel and it is their responsibility to update the data base. Results are entered by hand and checked before entry onto LIMS. Access to defined fields is by password which in turn is hierarchical.

SOP controls material release. Status (Pass, fail etc) is accorded through the bar coding system and COA's are printed off. Regulations permit electronic signature of an authorising person. The training record and job description of the two supervisors authorised to release raw material and finished products confirmed their competence to do so. No matters of concern were noted.

SOP controls cleaning and maintenance. Preparation of volumetric solutions follows SOP ASD/CP/0525/R2. Bench reagents are fully traceable to method of preparation and labelled with an expiry date and the name of the person responsible for the preparation. No matters of concern were noted.

Instrumentation

UV-Visible Spectracord/200 is routinely checked for absorption accuracy (potassium dichromate solution), wavelength accuracy (holmium filter), stray light and base line stability. The cuvettes and sample compartment looked clean and well maintained.

The FTIR is regularly checked for wave number accuracy and peak resolution. KBr mounts are used wherever possible and test spectra are compared with a standard preparation each time. Comparison of the two gives a purity index. A minimum of 98% purity is specified.

High Pressure Liquid Chromatography: 22 Agilent Technologies integrated stacks with dedicated modules. The operation and maintenance of HPLC was chosen at random as an example. IQ and OQ data is available but time did not permit in depth scrutiny. The most recent calibration was performed on 26/7/13. Flow rates, detector linearity and wavelength accuracy and oven temperature controls met specification. Data capture is achieved by setting integrator parameters after assessment of initial chromatograms (baseline, start and finish times.) Once set they are fixed for both sample and standards with bracketing a standard procedure. Manual integration (e.g. peak to peak, valley to valley) for smaller impurity peaks is permitted. Chromelion software was used for maintaining the audit trail. Columns are managed by following SOP. They are job specific and issue is controlled by a supervisor. History of use and performance is recorded in LIMS. HETP values, resolution and peak symmetry are routinely checked. The record for analysis of related substances in Stavudine/Lamivudine 30/50 mg tablets Lot No.7219001 using a reverse phase C₁₈ column No.1070/LC/0447 complied with the requirements. Of those analytical instruments assessed, no matters of concern were noted.

Environmental monitoring:

The production areas are designed to operate at Class 100,000 (ISO 8) when at rest. Room environmental conditions are specified in SOP. Differential air pressures, relative humidity and temperature are given for each work area. 18 AHU's located on

the upper floor supply filtered air to their dedicated workshops directly below. All are conventionally configured with outside air being filtered by 10µ and 5µ prior to feeding terminal ceiling mounted 99.99 HEPA filters. The area housing the AHU's is acceptably clean and tidy. Some electrical cable conduits were broken, resulting in exposed electrical wiring. Ducting was sound with no discernible air leaks.

The AHU serving the tablet compression area were inspected. It was noted that the room number was not cross referenced to the AHU number. Air is supplied with an uncontrolled RH. It is fed through a dehumidifier located next to the to the compression room and thence to the compression machinery. The RH can be adjusted to meet product requirements. Pressure differentials across both filters were within range (6 – 12 mm H₂O for 10 10µ and 3-4 mm H₂O for 5µ). Air flow dampers were securely tightened. The tubing of the primary filter pressure differential gauge on unit 141 was not connected.

Particulate Measurement

Measurement follows SOP PQCVG/002/R5 effective 6/12/2013. It addresses all critical aspects of an HVAC system namely, terminal filter seal integrity. Records show air change rates above 25. All pressure differentials noted throughout the site during the three days of inspection were within the specified range. The particulate measurement trend over the past year was the only parameter reviewed. The LASARIL 310C counter was calibrated and within date. Measurement followed protocol. Worst case locations were selected for measurement e.g. doors and air return grilles. The number of sample points (5) is given by the square root of the room area. The mean particulate value for 0.5µ and 5µ counts is calculated. 0.5µ levels were of the order of 39×10^3 and 5µ were of the order of 8×10^3 per cubic foot. The action limit is set at 35×10^4 for 0.5µ and 29×10^4 for 5µ. Figures returned were well below ISO 8 classification. The action limit is far above levels found in practise. It is recommended to set more realistic alert levels. No other matters of concern were noted.

Viable Particulate Measurement

Active air sampling is the only method used. The SAS sampler collects one cubic meter of air in ten minutes. Instructions for operation of the sampler are given in SOP. Monitoring is carried out according to SOP. Levels found were between 50 and 100 cfu/m³. The warning level is set at 170 and action at 200 the latter being the maximum permitted for ISO 8 at rest conditions. As with particulates, the company may wish to consider revising the action and warning limits to reflect what is routinely found in practise.

Water Testing

Phase III results for the past 3 months were assessed. The sampling routine together with a schematic of the plant is given in SOP. It details frequency of sampling of each point such that all points of use are sampled within 2 weeks with the holding tank and the return pipe work being sampled daily. It provides details on methods of sample vessel preparation and, how to flush each point before sampling. Samples may be stored up to 48 hrs under refrigeration before re sampling is necessitated. 400ml samples are tested using Millipore membrane filtration. Microbial levels for the purified water tank and take off point at work station were all reported as zero,

including tests for pathogens. These levels satisfy Pharmacopoeial standards for purified water. No matters of concern were noted.

Out of specification (OOS):

The established procedure is followed namely phases I, II and III. Statistical treatment of results does not permit outlier tests. A flow diagram of the investigation procedure is incorporated in the SOP. The company is aware of the MHRA guidance document. All OOS incidents are recorded in a log book. The company has chosen to include OOS results from development batches, e.g. blend analysis where optimum blending times are being established. Examples of treatment of OOS results picked at random and listed below showed no matters of concern. Log reference ~~070/OOS-130028~~, ~~Diphenhydramine HCl & Ibuprofen SGC 25/200mg~~, related substances test. Log reference ~~0170OOS/13032~~ ~~Lamivudine Tablets 3000mg~~ hardness test. Log reference ~~OOS-/005/1070/Loperamide RM Lot No 1006060329~~, impurities test failure (Limit 0.10% found 0.113%). It was noted that where trace analysis (LOD & LOQ) is involved, rounding up of results obtained follows SOP CQC001/PF03/WI 007/R3.

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, as well as the corrective actions taken and planned, Strides Arcolab Limited, 'KRS Gardens' Suragajakkanahalli, Indlawadi Cross, Anekal Taluk, Bangalore, India 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.