World Health Organization

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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
of the FPP manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	Strides Shasun Limited (KRS Gardens - Bangalore)
Corporate address of manufacturer	Strides House, Bilekahalli, Bannerghatta Road, Bangalore, India 560076 Phone: 91-80-67840521 Fax: 91-80-67840800 Website: www.stridesshasun.com
Inspected site	
Address of inspected manufacturing site if different from that given above	Strides Shasun Ltd, KRS Gardens, 36/7, Suragajakkanahalli, Indlawadi Cross, Anekal Taluk, Bangalore South, Karnataka, 562 106, India Lat – 12.73638319890914 N Lng - 77.66792920438357 E **WGS 84** X – 8645954.33 m Y – 1429630.55 m
Unit / block / workshop number	Formulation unit
Manufacturing license number	KTK/25/415/98 & KTK/28/301/98, KTK/25F/02/2009 *For manufacture, pack distribute and sale of soft gel capsules, tablets, hard gelatin capsules and sachet dosage forms*
Inspection details	
Dates of inspection	13 – 17 June 2016
Type of inspection	Routine inspection
Introduction	
Brief summary of	Manufacturing, packaging, quality control, stability testing and release

<table>
<tr><td>the manufacturing activities</td><td>of soft gel capsules, tablets, hard gelatin capsules and sachet dosage forms.11 contract laboratories were used for certain tests.
Toxic or hazardous products, β-Lactams, cytotoxic drugs, hormones and steroids were not being manufactured at the site.</td></tr>
<tr><td>General information about the company and site</td><td>Strides Shasun has manufacturing facilities in the following locations:

<table>
<tr><td>Strides Shasun</td><td>FPP</td><td>No 36/7,Suragajakkanahalli,Indlavadi Cross , Anekal Taluk, Bengaluru, Karnataka 562106, India (IND)</td></tr>
<tr><td>Strides Shasun</td><td>API & FPP</td><td>R.S.No 32,33 and 34,PIMS Road and Mathur Road, Periyakalapet, Puducherry,605014, India, Puducherry, Puducherry 605014, India (IND)</td></tr>
<tr><td>Strides Shasun</td><td>API</td><td>A-1/B, Sipcot Industrial Complex, Kudikadu Village, Cuddalore, Tamil Nadu 607 005, India (IND)</td></tr>
<tr><td>Strides Emerging Markets Private Limited</td><td>FPP</td><td>Survey No.19/1 & 19/3, Alibommasandra Mutbanallur post, Anekal Taluk,
Sarjapur Hobli, Bangalore- 560 099</td></tr>
<tr><td>Strides Shasun Limited</td><td>FPP</td><td>Plot No. 9-12, Dewan & Sons Industrial Area, Veoor, Palghar- 401404, Palghar Dist., Maharashtra State. India</td></tr>
<tr><td>Strides Vital Nig. Ltd.</td><td>FPP</td><td>Plot 2 | Ladipo Oluwole Street |
Off. Oba Akran Avenue | Ikeja | Lagos | Nigeria</td></tr>
<tr><td>Strides Pharmacare Factory for Human And Veterinary Medicines</td><td>FPP</td><td>No.3/11 soba Industrial Area Khartoum, Sudan</td></tr>
<tr><td>Strides Pharma Cameroon</td><td>FPP</td><td>S/C B.P 2353 DOUALA AKWA Rue DUBOIS De Saligny Cameroon
Akwa, Douala, Cameroon</td></tr>
<tr><td>Strides Pharma Mozambique Limited</td><td>FPP</td><td>3016 Ave. Angola, Maputo,
Mozambique</td></tr>
</table>

STRIDES SHASUN LIMITED is involved in the development and manufacture of nutritional, active pharmaceutical ingredients and pharmaceutical products.

Strides Arcolab and Shasun pharmaceuticals combined to accelerate strategy and growth in September 2014. After the acquisition the name of the company changed from Strides Arcolab to Strides Shasun Limited.

The inspected site (KRSG) commenced production of soft gelatin capsules in 1998, tablets and hard gelatin capsules in 1999.

There were 4 production departments:
• Tablet & capsule department</td></tr>
</table>

	• Ointment and cream department • Soft gel department • Packaging department Dedicated block for packaging operations which consist of 17 packaging lines and was made operational in 2006. New dedicated block was commissioned in 2015 to manufacture Oral Liquid & Topical dosage form. All the manufacturing blocks were independent with separate personnel entry and connected to each other for material movement.
History	The site was last inspected by WHO in October 2013. The site has also been inspected by the following regulatory authorities: • National Agency for Food and Drug Administration (NAFDAC), Nigeria - 26.08.2013 • ANVISA, Brazil - 04.11.2013 - 08.11.2013 • US Food and Drug Administration o 15.02.2016 – 19.02.2016 o 18.08.2014 - 26.08.2014 o 12.12.2013 - 20.12.2013 • Indian Regulatory Authority (Drug Control Department), India - 13.09.2013 • Tanzania Food and Drugs Authority (TFDA), TANZANIA o 10.04.2014 - 11.04.2014 o 05.05.2016 • Central Drug Standard Control Organization (CDSCO), India - 03.06.2014 - 04.06.2014 • National Drug Authority, Uganda - 27.08.2014 - 28.08.2014 • Pharmacy and Poison Board (PPB), Kenya - 13.10.2014 -14.10.2014 • Medicine Control Agency (ZMCA), Zimbabwe 27.10.2014 - 28.10.2014 • Food Drugs and Board, Ghana - 20.04.2015-21.04.2015 • Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom (UK) - 15,16 &18 May 2015 • MFDS, Korea - 17.08.2015-19.08.2015 • Directorate of Pharmacy and Medicine Laboratory, Ivory Cost - 14.10.2015 • TGA, Australia - February 2016 (desktop review)
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	Inspection covered oral sold dosage forms division, general tablet and capsule block. Manufacture, packaging and quality control of: • Tablet

	• Film coated tablet • Dispersible tablet • Capsule hard gelatin • Capsule soft gelatin
Restrictions	MB laboratory HVAC and tablet and hard capsule department HVAC system were not inspected due to the time constrains
Out of scope	Ointment and cream department was excluded from the inspection.
WHO product numbers covered by the inspection	• USFDA ANDA 09-0457 Lamivudine Tablet 300mg • USFDA ANDA 09-0457 Lamivudine/Zidovudine + Nevirapine - 150mg/300mg + 200mg • USFDA NDA 21-837 a Lamivudine/Nevirapine/Stavudine Tablet 150mg/200mg/30mg • HA203 Lamivudine Tablet, Film-coated 150mg • HA268 Nevirapine Tablet 200mg • HA291 Lamivudine/Zidovudine Tablet, Film-coated 150mg/300mg • HA312 Stavudine Capsules, hard 30mg • HA313 Lamivudine/Stavudine Tablet 150mg/30mg • HA389 Efavirenz Tablet, Film-coated 200mg • HA390 Efavirenz Tablet, coated 600mg • HA494 Abacavir (sulfate) Tablet, Film-coated 300mg • HA524 Lamivudine/Nevirapine/Zidovudine Tablet, Film-coated 150mg/200mg/300mg • HA535 Tenofovir disoproxil (fumarate) Tablet, Film-coated 300mg • HA552 Emtricitabine/Tenofovir disoproxil (fumarate) Tablet, Film-coated 200mg/300mg • HA553 Efavirenz/Emtricitabine/Tenofovir disoproxil (fumarate) Tablet, Film-coated 600mg/200mg/300mg • HA557 Lamivudine/Nevirapine/Zidovudine Tablet, Dispersible 30mg/50mg/60mg • IN 002 Oseltamivir (phosphate) Capsules, hard 75mg • MA074 Amodiaquine (hydrochloride) + Artesunate Amodiaquine Tablet + Artesunate Tablet 153mg + 50mg • MA088 Artemether/Lumefantrine Tablet 20mg/120mg • MA110 Artemether/Lumefantrine Tablet, Dispersible 20mg/120mg *(under prequalification*) • MA123 Artesunate Capsule, Soft, Rectal 100mg *(under prequalification*) • TB085 Isoniazid/Rifampicin Tablet, coated 75mg/150mg • TB090 Ethambutol (hydrochloride)/Isoniazid/Pyrazinamide/Rifampicin Tablet, Film-coated 275mg/75mg/400mg/150mg • TB 202 Isoniazid/Rifampicin Tablet, Film-coated 75mg/150mg • TB216 Ethambutol

	(hydrochloride)/Isoniazid/Pyrazinamide/Rifampicin Tablet, Film-coated 275mg/75mg/400mg/150mg • TB256 Pyrazinamide Tablet 400mg *(under prequalification*)

Abbreviations	SOP – standard operating procedure PQS – pharmaceutical quality system PQR – product quality review QRM – quality risk management CAPA – corrective actions and preventive actions PpK – Process performance index CpK – Process capability index MR – management review BMR – batch manufacturing record BPR – batch packaging record MF – master formulae LAF – laminar air flow AHU – air handling unit FBD – fluid bed dryer HVAC – heating, ventilation and air conditioning CC – change control RA – risk assessment CoA – certificate of analysis HPLC – high-performance liquid chromatograph GC - gas chromatograph UV - ultraviolet-visible spectrophotometer IR – infrared spectrophotometer FTIR - Fourier transform infrared spectrometer TLC – think layer chromatography LOD – loss on drying KF – Karl Fisher NMR - nuclear magnetic resonance spectroscopy NRA – national regulatory agency URS – user requirements specifications DQ – design qualification IQ – installation qualification PQ – performance qualification OQ – operational qualification FAT – factory acceptance test MB – microbiology TAMC – total aerobic microbial count FMEA - failure modes and effects analysis FTA – fault tree analysis PHA - process Hazard Analysis

	HACCP - hazard analysis and critical control points PM - Preventive maintenance WHOPIR – WHO public inspection report EM – environmental monitoring LoD – Limit of detection BDL – Below detection limit

PART 2

Brief summary of the findings and comments

1. Pharmaceutical quality system

Principle

In general PQS was implemented. Production and control operations were specified in written form and GMP requirements were generally followed. Managerial responsibilities were specified in job-descriptions. Product and processes were monitored and the results taken into account in batch release and regular reviews of the quality of pharmaceutical products were conducted. Periodic management reviews were performed.

Quality Risk Management

The SOP "Quality risk management" was discussed. The SOP was applicable to various stages of drug product lifecycle, for example development, manufacture, change management, deviations, complaints etc. The following SOPs referenced to the QRM were also discussed:

- "Guideline for quality risk management
- "Investigation and CAPA management"
- "Change management"

SOP "Guideline for quality risk management" explained risk based prioritization, quality risk indicators, risk scoring, risk prioritization criteria, risk assessment process, risk assessment process, risk identification, risk analysis, risk evaluation, risk control, risk reduction, risk acceptance, risk communication, risk review, risk management methodology.

The "Risk based prioritization plan" for 2016 was discussed. The plan was applicable to existing:

- Products
- Processes
- Equipment & facilities

All products manufactured at the site were listed in the plan; risk prioritization was based on risk ranking (process control, product knowledge, complaints, product history, product volume and potency).

Quality risk assessment & management No's XX for YY were discussed.

Product Quality Review

The SOP "Product quality review" was discussed. The SOP was applicable to products manufactured during the review period. Review period was defined as calendar year and completed by the June next year. PQR was carried our as per yearly (month wise) schedule (Annual Planner) which also contained the accomplishment of the documents. Products not produced during the review period were also included in the PQR schedule.
Critical process parameters were trended.

The SOP "Determination of process performance and process confidence" was discussed. This SOP was applicable for PQR and process validation. Process capability was calculated using CpK index.

PQR trends were presented as tabulated data and graphs.

A specific PQRs were reviewed.

Management review (MR)
The SOP "Quality System Review (QSR)" was discussed. QSR team was led by the Senior Vice President Quality. QSR team consisted of the heads of all departments. QSR was conducted monthly at unit level and at the corporate level.

Deviations
The deviations were recorded in the Trackwise software. The deviation XX records were discussed.

Corrective actions and preventive actions (CAPA)
The CAPAs were managed by means of the Trackwise software based on the SOP "Investigation and CAPA management". The investigation records of CAPAs initiated by the deviation XX were available.

Root cause analysis (RCA)
The trigger for root cause analysis and corresponding investigations were the following events: complaints, OOS/OOT results, recalls, deviations, regulatory inspections, process performance data (PQR), quality risk management, improvement plan, and quality system review.

Change control (CC)
The SOP described the procedure of change control. The changes were initiated by the concerned organizations. The substantial decisions during the investigation (in particular the implementation) were made by the QA head.

The investigation records of the change controls initiated by deviation XX were discussed.

2. Good manufacturing practices for pharmaceutical products

Manufacturing processes were clearly defined and systematically reviewed. Qualifications and validations were performed. Necessary resources were provided and records were made during manufacture. Significant deviations were recorded and investigated, root causes were determined and corrective and preventive action were implemented. A system was available to recall any batch of product from sale or supply and complaints about marketed products were examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products.

3. Sanitation and hygiene

The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facilities. Areas were cleaned frequently in accordance with an approved written program and SOPs. Microbial monitoring was regularly performed.

Fresh controlled area gowning was used at the beginning of the shift and replaced within the shift in case of product changeover. Tyvek protective apparel was used in the concerned facilities when processing high potent materials.

4. Qualification and validation

The key elements of a qualification and validation program were defined and documented in the Validation Master Plan (VMP). VMP was discussed. VMP was revised annually or when major changes happened.

Qualification

Qualification documents for FETTE tablet press compression machine were discussed.

Cleaning validation

The SOP described the policy and requirements of cleaning validation. It considered the equipment list, the API master list, the MACO matrix and the identification of the worst case molecule in certain equipment. The records contained the same and were discussed in case of Softgel area.

Analytical method validation

The analytical methods were developed at the R&D laboratory. In case of finished goods the test methods were formally transferred to the site.

Computer system validation

The list of computerized systems was available and the critical systems were validated.

Temperature mapping

The SOP “Temperature mapping of room/area” was discussed.

The Temperature and RH mapping study room/area: RH & T controlled area No XX for packing materials stores RH & T controlled area was discussed.

Hold time studies

The hold time studies were done when there was no recommendation from the formulation department as per process validation SOP. Hold time and moisture uptake study for solid orals, liquid and topical products work instruction No XX was reviewed. Hold time studies for all semi-finished products including blend, coated and uncoated tablets were described. Studies for XX capsules for batch No were reviewed.

5. Complaints

The SOP "Management of complaints", flow chart and registers for 2015 & 2016 were discussed. Site QA and during his absence, QMS senior group leader were responsible for complaint investigation, response and closing of complaint. Regulatory affairs department was responsible for notification of applicable regulatory agency (if applicable)

Complaints were classified as:

- Critical
- Major
- Minor

"Fish bone" was used for complaint investigations". Trending of complaints was performed once in month.

A number of complain investigations were spot checked.

Market complaint trends – 2015 were reviewed.

The SOP "Customer notification" was spot checked. This procedure explained how to handle product quality related notifications received at Strides from customers / contract giver. The SOP was applicable for products not distributed to the market. Product quality deviation review team was responsible for investigation of root cause and CAPAs.

6. Product recalls

The SOP "Product recall" and flow chart were discussed. Corporate management team was responsible for making decision to recall and give approval to start the recall.
Recalls were classified as following:

- Class I – should be initiated within 24 hours
- Class II - should be initiated within 48 hours
- Class III - should be initiated within 5 days
- Class IV - should be initiated within 5 days

In case there was no real recall performed, recall procedure effectiveness was evaluated every two years by initiating mock recall.

7. Contract production, analysis and other activities

Manufacturing activities for "WHO" products were not contracted out. A number of contract laboratories were used for certain tests.

The contract with the laboratory XX was discussed.

8. Self-inspection, quality audits and suppliers' audits and approval

Self-inspections were performed routinely according to the self-inspection schedule.

Supplier's audits and approval

The suppliers (including suppliers of the raw materials and contract partners) were qualified according to written procedures.

The suppliers of starting materials were selected, qualified and monitored according to SOPs:

- "Selection and evaluation of vendors"
- "Vendor audit"
- "Vendor quality performance review".

The suppliers had unique identification codes generated by the SAP system initiated by the vendor code generation form.

The qualification and evaluation records of the vendor XX supplying Lumefantrine and Artemether APIs were discussed.

9. Personnel

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Responsible staffs, specific duties were recorded in written job descriptions. Personnel were aware of the principles of GMP and received initial and continuing training, including hygiene instructions, relevant to their needs. Steps were taken to prevent unauthorized people from entering production, storage and QC areas.

Job descriptions

The employee had written job descriptions. The job descriptions of a QA executive and a Team Leader Softgel were available and discussed.

10. Training

The general practice and requirements of trainings were detailed in SOP.
The newly recruited person received general orientation training first. It was followed by the specific trainings according to the "Job role mapping".
The training records of employee XX, job role: Soft gel supervisor were discussed.

The SOP "Technique evaluation of an analyst" was discussed. The SOP explained on-job training and evaluation of new analyst. SOP specified that in case analyst has not performed particular analytical techniques for more than a year or an analyst was absent for more than 6 months, analyst evaluation should be performed before assigning the analysis. Analyst was

given recently analyzed and approved sample and should perform triplicate specified tests. Acceptance criteria were defined. Analyst evaluation matrix was discussed. XX analyst evaluation file was discussed.

11. Personal hygiene

Changing, gowning and hand washing followed written procedures. The protective closing washing operations followed standard operating procedures. To enter the production section operators had to worn "boiler suits", head covers and factory footwear. Personnel suffering from illness such as skin rashes, colds, and open lesions to the body were required to report the department head and were excluded from working in the clean and critical areas. Smoking, eating, drinking, chewing and the storage of food and personal medicines and smoking was prohibited in the manufacturing areas. Regular medical examination was carried out once per year for permanent and contract workers.

The health checks were performed before the employment then regularly annually. The declarations on the health condition by a physician were available.

12. Premises

Exposed surfaces were smooth, impervious and unbroken. Changing rooms were designed as airlocks and used to provide physical separation of the different stages of changing. Changing rooms were flushed with filtered air. Airlock doors were interlocked. Premises were cleaned and disinfected according to written procedures.

Ancillary areas

Rest and refreshment rooms were separate from manufacturing and control areas.

Storage areas

Storage areas were of sufficient capacity. Receiving and dispatch bays protected materials and products from the weather. Segregation was provided for the storage of rejected, recalled, or returned materials or products.

Addition to the raw material warehouse located at the site there were two warehouses used for storage of primary and secondary packaging materials under ambient conditions in another site (about 10 km distance). The incoming materials were always received in the manufacturing site, and then sent out for the external warehouse, if applicable. The stock details including the storage conditions were available in the SAP. The material request and dispensing was also managed by SAP.

Sampling areas

Separate sampling areas were provided for sampling of APIs, inactive materials, primary and secondary packaging materials. APIs, inactive materials and primary materials were sampled under LAF. Line clearance was carried out after each sampling operation by QC executive and verified by QA executive.

Weighing areas

Dispensing for APIs/inactive materials and primary packaging materials was carried out in dispensing rooms under LAF. Dispensing was carried out by stores officer and checked by store executive. Materials were dispensed in poly bags and stored in stainless steel containers. There was a high potent mobile isolator in place for the dispensing of high potent APIs.

Production areas

The premises were laid out in such a way as to allow the production to take place in areas connected in a mostly logical order, corresponding to the sequence of the operations and to the requisite cleanliness levels. The working and in-process storage space did permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different pharmaceutical products or their components, to avoid cross-contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps. Interior surfaces (walls, floors and ceilings) were found to be smooth and free from cracks and open joints. They did permit easy and effective cleaning and disinfection. Production areas were ventilated, with air-control facilities (including filtration of air to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, relative humidity) appropriate to the products handled, to the operations undertaken and to the external environment. These areas were regularly monitored to ensure compliance with their design specifications. The packaging areas for the pharmaceutical products were designed and laid out so as to avoid mix-ups or cross-contamination.

The SOP “Cleaning of production area” was discussed. The SOP was common applicable for all production areas. The SOP explained non-serial and serial cleaning procedures.

The layouts of the facilities were available and discussed.

Quality control areas

Sufficient space was given to avoid mix ups and cross-contamination. Adequate storage space was provided for samples, reference standards, solvents, reagents and records.
The re-construction of the laboratory facilities was on-going at the time of the inspection consisting of the relocation of the microbiology laboratory into a new area (within the existing territory of QC) and the expansion of the QC laboratories to the same falling vacant areas.

13. Equipment

General

Fixed pipework was clearly labelled to indicate the contents and the direction of flow. Balances and other measuring equipment of an appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Balances were verified daily using one weight, weekly balance verification was carried out using minimum and maximum weights. Daily verification of balances was carried out using minimum, middle and maximum weights.

Analytical balances located in the QCL laboratory daily calibration was carried out using 4 standard weights. For example for the balance XX 50 mg, 500 mg, 100 g and 200 g standard weights were used.

Daily verification of balances was carried out using minimum, middle and maximum weights. The following items were checked during monthly calibration:

- Repeatability
- Uncertainty
- Eccentricity
- Linearity
- Linearity error
- Drift

ILAB software was used to record analytical balances calibration, preparation of reagents and solutions.

Production equipment was cleaned on a scheduled basis.

The SOP "Cleaning of equipment and accessories" was discussed. The SOP specified two cleaning procedures:

- Non-serial (product to product)
- Serial (batch to batch)

The SOP "Operation and cleaning of octagonal blender was discussed. The SOP explained setting up and operation procedure as well non-serial and serial cleaning procedures. All steps explained in the SOP were supplemented by the detailed photos. SOP was found to be detailed.

Preventive maintenance

The SOP "Procedure for preventive maintenance" was discussed. PM schedules were generated in SAP. PM was performed using handheld device or hard copy of approved task list. In most cases hand held device was used. Time point widow periods for PM schedule were defined. As an example FETTE XX tablet press compression machine PM was selected and reviewed in the SAP. Spot checks showed that schedule was followed.

Calibration

The SOP "Calibration of measuring & testing instruments, electronic weighing scales & standard weights" was discussed. This SOP was applicable to carry out Calibration of measuring & testing instruments, electronic weighing scales & standard weights by external services. Calibration schedule was maintained by SAP.

The SOP "Operation and calibration of dissolution test apparatus" was discussed. Mechanical calibration was performed every 3 months.

Chemical test ("performance verification") using USP prednisolone 10 mg tablets were performed every 6 months.

Dissolution apparatus XX mechanical and chemical calibration was discussed. Traceability to the USP prednisolone 10 mg tablets batch number and standard Lot number was ensured.

Heating, ventilation and air conditioning system (HVAC)
The environmental conditions in the production areas were controlled by HVAC system.

The production areas of the soft gel capsule plant were supplied with controlled air (classified as Class D) by means of XX AHUs and pressurized ventilation units. The qualification and monitoring protocols and records of Soft gel capsule areas were discussed.

The AHUs were re-qualified annually. The re-qualification policy (PQ) of the HVAC systems was defined.

Purified Water (PW)
PW was generated by ultrafiltration. There were 3 loops supplying PW to the production departments. PW was in continuous circulation at 65 ºC±5 ºC. Sanitization was performed once in month. Temperature was monitored at the return loop. TOC and, conductivity was monitored on-line and also off-line.

MB PW water trends for April 2016 were spot checked. All results were within specified alert limit. Action and alert limits were established based on historical data.

The SOP "Monitoring of water for microbial quality" was discussed.

Compressed air (CA)
The SOP "Qualification of compressed gases" was discussed. Compressed air system qualification was performed once per year and the following tests were carried out for all user points where CA was in contact with product:

- Maximum discharge pressure
- Oil mist
- Pressure dew point
- Particulate matter
- TAMC

0.1 µ pre-filters and 0.01 µ final filters were installed at all user points where CA was in contact with product. Last qualification was performed in March 2016. Results seen were within specified limits, trends were presented as graphs.

14. Materials

General

Incoming starting materials and finished products were quarantined after receipt until they were released for use or distribution. Materials and products were stored under the appropriate conditions. Food grade oil was used for punches and dies lubrications.

Starting materials

Starting materials were purchased from approved suppliers. Approved suppliers lists for starting materials (active and inactive) and packaging materials were available in SAP system. For each consignment, the containers were checked for integrity of package and seal. Damage to containers and any other problem that might adversely affect the quality of a material recorded and reported to the QA department. Check-lists were used for materials receipt. Received goods were compared with purchase order. Upon receipt "Goods receipt" (GR) number was assigned by the SAP system and note was sent to the QC Laboratory, analytical report number (ARN) was automatically generated and sampling was done according to the different materials sampling plan.

Finished products

Finished products were stored in separate warehouse, quarantined and release by SAP.
The materials at the FG Warehouse were managed according to SOPs "Material receipt" and "Material dispatch".

Rejected, recovered, reprocessed and reworked materials

Each warehouse had separate, locked rejected materials storage room. Finished product warehouse had separate rejected and returned goods storage rooms.

Packaging material

Packaging materials were purchased from approved suppliers. Printed packaging materials were stored in secure locations. Each delivery of batch of printed or primary packaging material was given a specific reference number. No more than two splicing's were allowed for the roll labels. Hard capsules and Al foils were stored in controlled environment warehouse. Primary packaging materials were sampled in separate room under LAF.

Reference standards (RS) and working standards (WS)

The SOP "Handling of reference standards, in-house / manufacturers standard, primary standards and calibration standards" and flow chart were discussed. In-house reference standards were used when reference standards were not available. Material having the lowest impurity profile was selected and qualified as in-house standard. All tests according to the STP were performed for qualification of in-house standard and additional tests as identification by NMR, mass spectra, elemental analysis were performed if applicable. In-house standards were dispensed in 14 amber vials. One vial for use in one month and 2 "master vials". In-house standards and WS were dispensed in LAF booth. Standards were stored in fridge (2 ºC to 8 ºC), deep freezer (-15 ºC to – 25 ºC) and in humidity chamber (ambient T)

The SOP "Preparation and handling of working standard (WS)" and flow chart were discussed. Material having the lowest impurity profile was selected and qualified as WS against reference standard.

15. Documentation

In general documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Documents were regularly reviewed and kept up to date. Records were made or completed when any action was taken. Documents were reviewed every 3 years.

Specifications and testing procedures

Approved, signed and dated testing procedures and specifications were available for starting and packaging materials and for finished products as well as for intermediate and bulk products.

Specifications for starting and packaging materials, finished products and intermediates

Specifications for starting and packaging materials, finished products and intermediates were available and contained required information about the materials (e.g. material code

Batch manufacturing records (BMR) / batch packaging records (BPR)

BMRs and BPRs were used for each batch processed. Before any processing begins, checks were made that the equipment and work station were clear of previous products, documents, or materials, and that the equipment was clean and suitable for use. Checks were recorded and were part of the BMR.

The master copy of the MBR was scanned to the DMS (Document Management System). The issuance consisted on the indication the batch number and printing out the requested documents/pages. The issuance of the BMRs from the DMS was controlled by audit trail.

Following to the accomplishment of the production the QA was responsible for the checking and reconciliation of BRs based on BMR completion checklist.

Batch numbering system

Batch numbers are generated according to the SOP. The batch numbers are generated as a never repeating serial number reflecting the site code and the form of the production.

Standard operating procedures (SOP) and records

Generally various SOPs and records of actions taken were available for all activities carried out on site. Records were kept for major and critical equipment.

Expiry date allocation

The SOP "Assigning of manufacturing date, retest and expiry date for semi-finished/intermediate/finished goods" was discussed. Manufacturing and expiry date of the product was generated by the SAP at the time of dispensing raw materials.

Batch record review/batch release procedure / analytical records review

The following SOPs were discussed:

- "Finished product release and archival of BMR/BPR"– this SOP provided procedure for preparation of documents for finished product release and archival of MBR/BPR – responsibilities and tasks. The SOP provided BMR completion check list and finished product release check list.
- "Semi-finished goods / intermediates and finished goods release". According to the SOP QA head or designee was responsible for review of analytical results, review of relevant records and release of semi-finished goods for packaging, review of BMR and authorization for batch release.
- "Testing approval and disposition of in-process, semi-finished and finished goods". This SOP described quality control activities e.g. handling of in-process, semi-finished and finished product samples.
- "Review of QC records". This SOP gave guidelines for analytical results review (API, finished products, stability, HPLC validation, GC validation and CoA).
- "Reviews of audit trail generated for laboratory instruments" was discussed. This SOP was a supplement to the SOP "Operation and calibration of HPLC with Chromeleon software".

16. Good practices in production

General

In general production operations followed defined procedures. Deviations from procedures were recorded and investigated. Checks on yields and reconciliation of quantities were carried out. Materials, bulk containers, major items of equipment, rooms and packaging lines being used, were labelled to identify the product or material being processed and the batch number. Access to production premises was restricted to authorized personnel. In-process controls were performed by operators and by QA personnel within the production area. Friability test, Thickness, hardness, uniformity of weight, weight variation. Locking length and disintegration tests were carried out in IPC laboratory. Weight variation, thickness and hardness tests were performed by operators in the compression cubicles before start of compression of the batch and also on regular intervals.

Before processing operations was started, steps were taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation. Necessary environmental controls were carried out and recorded.

Dispensing operations

Dispensing operations were carried out in warehouse.

Prevention of cross-contamination and bacterial contamination during production
Precautions were taken to prevent the generation and dissemination of dust by provided airlocks, pressure differentials, and air supply and extraction systems. In general contamination and cross-contamination of starting material or of a product by another materials or product were avoided.

Processing operations
Before processing operations were started, steps were taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation. Time limits for storage of equipment after cleaning and before use were stated and based on validation data. Significant deviations from the expected yields were recorded and investigated.

Measuring, weighing, recording, and control equipment and instruments were serviced and calibrated at specified intervals and records maintained.

Tablet / hard capsule block
Separate airlocks were provided for material and personal entrance to the granulation rooms. blending rooms, coating rooms and capsule filing rooms.

Metal detectors were installed to all compression and capsuling machines. Metal detectors were challenged using Fe non-Fe and SS test kits at the beginning and end of the manufacturing operations.

Dedicated finger bags were used for all products. Finger bags integrity checks were carried out after product campaign was over. In addition broken bag detection sensors were installed to all FBDs. Metal sieves integrity checks were performed before and after use.

Separate AHUs provided air to the FBDs and coating machines.

Packaging operations
Before packaging operations begun, steps were taken to ensure that the work area, packaging line, printing machine and other equipment were clean and free from any products, materials or documents used previously. The line clearance was performed and recorded in the BPRs. Production records were reviewed as part of the approval process of batch release before transfer to the authorized person.

Blisters integrity leak tests were carried out regularly.

Reprocessing, reworking and repackaging
The SOP “Reprocessing, reworking and repackaging of drug products” was discussed.

Reprocessing/reworking shall be duly authorized by QA. In case of reprocessing details shall be recorded in respective BMR and separate batch number shall be assigned. Samples of reprocessed batches shall be placed on stability studies. In case of reworking fresh BPR shall be issued and separate batch number shall be assigned. The manufacturing date/expiry date of reworked batch shall be the same as for original batch.

17. Good practices in quality control

The QC function was independent of other departments. Adequate resources were available to ensure that all the QC arrangements are effectively and reliably carried out. QC personnel had access to production areas for sampling and investigation as appropriate.

Class "A" volumetric glassware was used.

Availability of instrument calibration standards was checked – spot checks showed that required calibration standards were available along with CoA specifying expiry dates.

The chromatographic software's were controlled by Chromeleon connected to LIMS.

The general instructions on the system suitability parameters of chromatographic methods were available in SOP.

The list of users, the user groups and user privileges was available, up-to-date and strictly controlled. The SOP detailed the basic principles of chromatogram integration.

The analytical equipment was regularly qualified / calibrated and maintained. The qualification records of HPLC XX were discussed.

In-process control (IPC)

IPC laboratory belonged to the QA department. IPC tests were carried out by production personnel and QA personnel. IPC tests were carried out routinely according to the product specific BMR/BPRs.

Test requirements - finished products

For each batch of medicines product, there was an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

Certificate of analysis (CoA)

CoA were printed by QA personnel from SAP and authorized by QA head or designee.

Stability studies

The SOP "Testing and reporting of results of stability samples" and SOP "Preparation, approval of stability protocol" were discussed.

The following conditions were applied for accelerated studies:

- T 40 ºC ± 2 ºC, RH 75% ± 5%

and long term:

- T 25 ºC ± 2 ºC, RH 60% ± 5%
- T 30 ºC ± 2 ºC, RH 65% ± 5%
- T 30 ºC ± 2 ºC, RH 75% ± 5%
- T 5 ºC ± 3 ºC (APIs)

Stability samples' testing was performed by dedicated team.

One batch per year was placed on long term stability monitoring programme. Samples were packed in market simulated conditions.

Stability chambers were connected to the software and in case of power failure, an alarm was triggered. T/RH in the chambers was continuously monitored and recorded every 10 minutes by 8 sensors (each chamber). Printouts were taken daily and checked. Chambers had sound, visual and SMS alarm system.

Out of trend and specification results (OOT/OOS)

The OOT and OOS results were recorded, investigated and addressed based on the following SOPs:

- "OOT results"
- CQC/007/R2

The procedures were illustrated with the corresponding process flows as follows:

- for raw material testing
- for IPC testing
- for finished product testing
- for stability testing
- for testing of packaging materials (physical)
- for testing of packaging materials (chemical)
- for finished goods (physical)
- for blend university
- for water testing

Retention samples

The SOP "Management of control samples" was discussed.
The retention samples were handled by means of LIMS system.

Sampling procedure

The SOP "Sampling, testing and approval of raw materials" and the SOP "Sampling of non-sterile packaging material" were discussed. AQL was used for primary packaging materials sampling. Critical, major and minor defects were defined.

Microbiological laboratory (MB)

The MB laboratory was not inspected.

The MB laboratory performed the following tests:
Microbial limit tests (FPP, raw materials, in-process sample and hard gelatin capsules), water analysis, environmental monitoring (active air sampling).

The SOP "MB evaluation of controlled environments" was discussed. EM trends for blending room No 3 for 2015 were discussed.

PART 3

List of deficiencies

Unless otherwise indicated, references below are to the WHO good manufacturing practices: main principles for pharmaceutical products. WHO good manufacturing practices for pharmaceutical products: main principles. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report* Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2 (document 1 in Part 5 above). Where another document is referenced, its Part 3 document number is indicated in Italic-script and listed in the section GMP guidelines used for assessing compliance above.

Note: the coding e.g. ***(AW)*** following the heading to each deficiency is a WHO internal reference code used by the Prequalification Inspection Team for deficiency analysis and reporting purposes and should be ignored by the recipients of this report.

The following deficiencies were made during the inspection		***References***
1. Critical		
None during this inspection		
2. Major		
2.1	**Possible contamination and cross-contamination:** 2.1.1. A lot of powder was observed on the floor and stairs in the blending room. It was noted that after blending the room was cleaned, however operators enter the common corridor wearing the same shoes and garments 2.1.2. Several screen gaskets were seen to be poorly maintained. During inspection on June 15 it was observed that one screen (30 mesh ID T/303#/55/15) awaiting cleaning had lost a cuprum earthing stud. The company was requested to do an investigation and raised on the same day a deviation report to find out at what stage the cuprum earthing stud had been lost and to investigate the possible impact to the products manufactured using this sieve from the beginning of the campaign on June 3. (The company is requested to submit the full investigation report for review as part of its CAPA). 2.1.4. Environmental monitoring alert and action limits were not set based on knowledge and experience, and historical data and later revised based on actual data over a period of time. Moreover Action limit	12.2, 12.3, 12.4, 12.30, 13.1, 13.2, 16.10, 16.11

	was set up 200 CFU/m³ and 100 CFU/4 hours 90 mm plate – these limits according to the ISO 14644 are maximum allowed limits for microbial contamination for the specified cleanliness class (grade D).	
2.2.	**Contract testing:** 2.2.1. Contact laboratory Higher Pharmatech Pvt. Ltd was used for finished products stability testing and finished goods testing. Use of contract laboratory was not notified to the WHO – variation guideline was not followed. In addition contract laboratory was not inspected/approved by WHO or other stringent authority.	*WHO TRS, No. 981, Annex 3*
3. Other		
3.1	**Materials** 3.1.1. There was no justification (risk assessment) given supporting the procedure/practice of composite sample preparation from undefined number of sampled units. According to the SOP GQC/022/R0 "Sampling, testing and approval of raw materials" pool sample used for assay tests could contain 1 to 20 individual samples. Number of containers pooled for composite sample was not validated to prove that composite sample did not mask (hide) any OOS results of the raw materials	17.13 *WHO TRS, No. 981, Annex 2*
3.2	**Temperature mapping studies of the packing materials stores RH & T controlled area (this deficiency is applicable also to other T mapping studies:** 3.2.1. Room dimensions were not considered for the T mapping studies and location of the T sensors 3.2.2. T and RH were recorded every 2 minutes for 24 hours only 3.2.3. T mapping studies were not carried out following WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products which is already available from 2011.	*WHO TRS, No. 961, Annex 9 and WHO Technical Report Series, No. 992, Annex 5*
3.3	**Documentation:** 3.3.1. The SOP WI/PDN/T101F/R0 "PDT007/PF01/WI001/R2 "Cleaning of production area" section 13/060 stated "cleaning of walls is done by moping wet cloth horizontally top to bottom and each stroke shall overlap previous stroke. The SOP was not written in accordance to the actual procedure used for walls cleaning what was: moping by wet cloth horizontally top to bottom. 3.3.2. Due to efivarenz 200 mg and 600 mg tablets blend lumping during granulation, CC No PC-ODF-2014/674 was initiated to replace the peristaltic pump (the pump did not have RPM display) - step 4.3 of the BMR. However the new BMR No BMP/2001491L616/R11 issued was not updated accordingly, since the statement to record	15.2

	the RPM of the peristaltic pump was not removed.	
3.4	**Testing:** 3.4.1. Although the testing procedure No ASD/FPSTP/3130/R3 indicated the sample should be analyzed immediately, it would be expected that samples at 9 hours should have similar results (reported results - BDL, 0.09% and 0.79%): explanation about differences was not available. 3.4.2. Upon review of the extraction method, it was noted that the discarded filtrate of the placebo and the sample was not carried out during the method validation.	*WHO TRS, No. 937, Annex 4, appendix 4*
3.5	**Analytical test method validation:** 3.5.1. Analytical test methods (raw materials, including APIs) not formally validated/transferred at the site.	*WHO TRS, No. 937, Annex 4, appendix 4* *WHO Technical Report Series, No. 961), Annex 7*
3.6	**Cleaning procedures, cleaning validation:** 3.6.1. It was not obvious in the cleaning procedures and the cleaning validation whether the PW were to be used at high temperature (as circulated) or chilled before use. 3.6.2. The analytical test method used for testing of cleaning validation samples was not defined in the validation protocol (KRS/CV/CALSGC/01/PQ, R0). 3.6.3. There was no record available on the personnel (contract housekeepers provided by Duster) cleaning the sampling and dispensing facilities.	*WHO Technical Report Series, No. 937), Annex 4, Appendix 3*
3.7	**Air handling systems:** 3.7.1. The change rooms of the Softgel plant did were not supplied with air of controlled quality.	*WHO Technical Report Series, No. 961), Annex 5*
3.8	**Deviation:** 3.8.1. During inspection T in the capsule weight check room was out of limits: T - 30.5 ºC. It was noted that T excursion was fixed during the inspection.	2.1.f), 16.3
3.9	**Contracts:**	7

	3.9.1. The contract with the housekeeping services (DUSTER) did not specify the concerned facilities.	

Comments:
During inspection it was noted that the company was not well familiar with related WHO guidelines. It was advised that company should regularly keep track on WHO guidelines.

PART 4
Initial conclusion – inspection outcome
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 Strides Shasun (KRS Gardens - Bangalore), located at KRS Gardens, 36/7, Suragajakkanahalli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, 562 106, India 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.

PART 5
List of GMP guidelines referenced in the inspection report
1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   Short name: WHO TRS No. 986, Annex 2

2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
   Short name: WHO TRS No. 957, Annex 2
   http://www.who.int/medicines/publications/44threport/en/

   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2

Short name: WHO TRS No. 970, Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
Short name: WHO TRS No. 929, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
Short name: WHO TRS No. 961, Annex 5
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
Short name: WHO TRS No. 937, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

7. WHO Good Practices for Pharmaceutical Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
Short name: WHO TRS No. 961, 957), Annex 1
http://www.who.int/medicines/publications/44threport/en/

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
Short name: WHO TRS No. 957, Annex 2
http://www.who.int/medicines/publications/44threport/en/

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
Short name: WHO TRS No. 961, Annex 6

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
    Short name: WHO TRS No. 961, Annex 7
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9
    ***Short name: WHO TRS No. 961, Annex* 9**
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
    Short name: WHO TRS No. 943, Annex 3
    http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2
    Short name: WHO TRS No. 961, Annex 2
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2
    Short name: WHO TRS No. 981, Annex 2
    http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3
    Short name: WHO TRS No. 981, Annex 3
    http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14
Short name: WHO TRS No. 961, Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3
Short name: WHO TRS No. 992, Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4
Short name: WHO TRS No. 992, Annex 4
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5
Short name: WHO TRS No. 992, Annex 5
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
Short name: WHO TRS No. 992, Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
Short name: WHO TRS No. 996, Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

22. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
Short name: WHO TRS No. 996, Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10
Short name: WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
Short name: WHO TRS No. 996, Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf