

**Prequalification of Medicines Programme
WHO PUBLIC INSPECTION REPORT**

(WHOPIR)

API Manufacturer

Part 1: General information

Name of Manufacturer	Sequent Scientific Limited (SSL)
Unit number	NA
Production Block	Plant No. 2
Physical address	No. 120: A & B, Industrial Area, Baikampady, New Mangalore - 575011, Karnataka, INDIA
Contact persons and email address.	<ol style="list-style-type: none"> 1. Mr. Ashok H.V. General Manager - Operations E-mail: ashok.hv@sequent.in 2. Mr. Venkiteswaran T.K. AGM - Quality E-mail: venkitesh.tk@sequent.in 3. Mr. Naraveera B.P. Sr. Manager - QA E-mail: naraveera.bp@sequent.in
Date of inspection	20, 21, 22 and 23 October 2009
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	<ul style="list-style-type: none"> • Active Pharmaceutical Ingredients against Malaria (MA) and Influenza (IN)
Summary of the activities performed by the manufacturer	Manufacturing, packaging, control and release of: ⇒ Plant 1: pharmaceutical intermediates, chemicals and chemical intermediates. ⇒ Plant 2: active pharmaceutical ingredient (API).

Part 2: Summary

General information about the company and site

The site inspected was **Plant No. 2** of **Sequent Scientific Limited (SSL)**, located at **No. 120: A & B, Industrial Area, Baikampady, New Mangalore - 575011, Karnataka, INDIA**, hereafter called **Sequent** or **SSL**. This site was formerly **Strides Research and Speciality chemicals Ltd**. It was located in Karnataka Industrial Area Development Board, about 10km from Mangalore City. It was bordered on the southern side by a green belt of Bharat

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Petrochemical Corporation Limited, on the northern side by a granite manufacturing unit, on the eastern side by a road and on the western side by an engineering factory.

According to the Site Master File SMF-R1, effective March 2009 and the presentation given at the opening meeting, **Sequent** was incorporated in 1995. It had manufacturing facilities at Mangalore in Karnataka and Panoli, near Baroda in Gujarat. The Mangalore site had two production blocks at Mangalore: -

1. Plant 1 for the manufacture of pharmaceutical intermediates, chemicals and chemical intermediates
2. Plant 2 for the manufacture of active pharmaceutical ingredients.

This inspection focused on Plant 2 which, according to SMF-R1 had a built up area of about 4,200m². Sequent employed 188 people distributed as follows:

Department	Number of employees
Production	76
R&D	44
Regulatory Affairs	02
Quality Assurance	05
Purchase and Warehouse	08
Projects and Maintenance	30
EHS	07
HRA, IT, Accounts & Finance	16
TOTAL	188

The quality control department and laboratory of Sequent Scientific Limited was operated as an independent unit called Sequent Research Limited because it was involved in contract analytical testing for outside clients.

History of WHO and/or regulatory agency inspections

According to the SMF and company presentation, Sequent was licensed by the Drug Control Authority of the State of Karnataka. It was inspected by the Institute for Standardization & Control of Pharmaceuticals, Ministry of Health, Israel in May 2009. This was the first inspection by WHO Prequalification Programme.

Focus of the inspection

The inspection focused on the production and control of Anti malarial and Anti-influenza active pharmaceutical ingredients produced in Plant 2. The inspection covered all the sections of ICH Q7, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1

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The inspection started with an opening meeting in the conference room, where the inspectors introduced themselves and exchanged business cards with the key staff of Sequent. The inspectors explained the procedure for WHO Prequalification Programme, the procedures and standards used for inspection and timelines for the processing the report and company responses to the inspection observations. The procedures for closing the inspection including the WHO public inspection report (WHOPIR), Notice of Concern (NOC), Notice of Suspension (NOS) were explained. The tentative inspection plan was discussed and confirmed. This was followed by a presentation from Sequent about the company and the site to be inspected. The presentation highlighted the capacities, Quality Management Systems and inspection history of the site. The synthesis and purification processes of Artemether, Oseltamivir phosphate and Artesunate were presented highlighting the starting materials, the equipment used (reactors, filters, tanks centrifuges, dryers, mills and blenders) and their location, keys process parameters, and batch sizes at different stages of the process. A copy of the presentation was obtained and will be filed in the company file.

The inspectors proceeded with a detailed review of the following areas of the quality management systems and related documents and records:

- ⇒ Organization chart
- ⇒ Job descriptions of key personnel
- ⇒ Quality Manual
- ⇒ SOP on Generation, distribution and retrieval of standard operation procedures
- ⇒ Procedure for document and data control
- ⇒ SOP on Item code numbering of raw materials/products and batch numbering of process data sheets. The format of the batch numbering was:
 - Normal batch: CCCYXXX, where CCC was the product code; Y was the last digit of the year of manufacture; XXX serial number starting with 001.
 - Reprocessed batch: CCCY**R**XXX where **R** denoted reprocessed.
 - Blend batch: CCCY**B**XXX where **B** denoted blend.
- ⇒ SOP on Handling of customer complaints and returns
- ⇒ SOP on Product recall and related recall register
- ⇒ SOP on Handling of incidences and related incidence register. Selected incidences were reviewed.
- ⇒ SOP on Handling of deviations
- ⇒ SOP on Change control
- ⇒ SOP on Batch record review
- ⇒ SOP on Batch release
- ⇒ SOP on Training procedure
- ⇒ Purified water specifications

The inspection activities ended late in the evening and the review progress of the activities of the day and giving of feed back was differed to the next day.

Day 2



The inspectors started by reviewing the progress of the inspection, gave feed back on the observations made in the areas inspected the previous day, received preliminary reactions from the management of the company and agreed on the tentative programme for the day. They continued with review of the following GMP areas and related documents:

- ⇒ SOP on Internal audits
- ⇒ SOP on Product quality review and reviewed the APR for the APIs under review:
- ⇒ Validation Master Plan
- ⇒ Preventive maintenance
- ⇒ SOP on Vendor Qualification
- ⇒ SOP on Receiving of in-coming materials
- ⇒ SOP on Sampling of raw materials, packaging materials, intermediates and finished products
- ⇒ Specifications of of the key starting materials for the synthesis of APIs under focus.
- ⇒ Selected deviation
- ⇒ SOP on Reprocess, rework pf out of specification products
- ⇒ Non conforming products register for Finished products 2009. Selected examples were reviewed in detail.
- ⇒ SOP on Recovery and reuse of solvents from APIs and intermediates manufacturing process
- ⇒ In-house specifications for selected fresh and recovered solvents
- ⇒ SOP on Procedure for stability programme for APIs
- ⇒ SOP on Men entry and exit into warehouse.
- ⇒ Stock control, reconciliation and issuance of seleected starting materials using IMS computer database was reviewed.

The inspectors proceeded to inspect the following areas plus related procedures and records:

- ⇒ Warehouse No. 2 for solid and non flammable starting materials plus associated receiving areas, under-test and quarantine areas, rejected materials area, sampling room, approved material area, primary packaging materials storage area and dispensing room.
- ⇒ Warehouse for finished products (APIs) (15⁰ - 30⁰C) cold room (2⁰ - 8⁰C) and a small room reserved for returned goods.
- ⇒ The records for temperature and relative humidity monitoring were reviewed together with the associated balance calibration records.
- ⇒ An old warehouse used to store recovered solvents for sale and/or incineration plus used oil.
- ⇒ The tank farm for solvents plus associated transfer pipes, dip sticks and procedures for receiving and sampling solvents.
- ⇒ Warehouse No. 3 used to store flammable solvents and reagents plus associated sampling/dispensing room.

The inspection ended late in the day so the review of the progress of the activities of the day, and giving the day's feed back was differed to the next day.

Day 3



The inspectors started by reviewing the progress of the inspection, gave feed back on the observations made in the areas inspected the previous day, received preliminary reactions from the management of the company and agreed on the tentative programme for the day. They continued with review of the following areas of plant 2 where the API under focus were manufactured and related documents following the process flow:

- ⇒ Crude production lines
- ⇒ Solvent day tank area
- ⇒ Purification lines
- ⇒ Collection tanks for mother liquors from various centrifuges
- ⇒ Powder processing areas (100kg and 5kg)
- ⇒ Store for finished APIs and intermediates
- ⇒ Records of temperature for the freezer and store for finished APIs
- ⇒ Water generation, purification and distribution system. Procedures and records for operation, monitoring, regeneration and sanitisation of the water generation and distribution system were reviewed in detail
- ⇒ Operation and monitoring of AHU units plus cleaning of prefilters and fine filters
- ⇒ Installations and records of AHUs for the powder processing area were reviewed in detail
- ⇒ SOP on Air handling and ventilation unit filter cleaning
- ⇒ Nitrogen and compressed air generation, filtration and distribution system
- ⇒ SOP on Cleaning of RCVD
- ⇒ SOPs for cleaning several process equipment and the corresponding use and cleaning log books
- ⇒ Records of daily weight verification of balances in various areas.
- ⇒ SOP on Storage of finished goods or intermediates

At the end of the day, the team reviewed progress of the activities of the day, gave feed back on the observations made in the areas inspected, received preliminary reactions from the management of the company and agreed on the tentative programme for the next day.

Day 4

The day was dedicated to inspection of the quality control laboratory and related documentation. The areas inspected included:

- ⇒ The sample receipt area plus related procedures, SOP and registers (for finished products samples, in-process samples, DM water samples).
- ⇒ Sample storage cabinets. Documentation related to selected samples were reviewed.
- ⇒ Stability testing procedures and programme:
 - SOP on Management of stability samples. It provided for samples to be withdrawn from the chambers -7 days or +10 days from the due date under long term studies and -2 days or +5 days under accelerated studies.
 - SOP on Analysis of stability samples and handling of stability data. It provided for initiation of analysis within 10 days from due date and completion within one month from the due date.
 - Stability chambers: 1 walk in chamber of 25⁰C/60%RH, 1 walk in chamber of 40⁰C/75%RH, 1 walk in chamber of 30⁰C/65%RH, 1 walk in chamber of 30⁰C/75%RH and 1 walk in chamber of 5⁰±3⁰C. There was a chamber for



- photostability studies and three standby chambers which had been qualified for all stability conditions.
- Stability sample receipt and issuance register and data related to selected batches was reviewed.
- ⇒ SOP on Receipt, calibration, usage and discard of HPLC columns. The corresponding records for the following selected columns were reviewed.
- ⇒ Records of monitoring the columns including theoretical plates, resolution, tailing factor, retention and relative retention time of benzene and toluene, area of chromatogram due to benzene and toluene, height of chromatogram due to benzene and toluene
- ⇒ SOP on Handling of Reference and Working Standards. Working standards were prepared from approved materials which were fully characterized and potency was assigned using mass balance approach or assay of 6 replicates with RSD NMT 2%, standardized against primary or in-house reference standards. The refrigerators used to store primary and working standards ($2.5^{\circ}\pm 2.5^{\circ}\text{C}$; $5.0^{\circ}\pm 3.0^{\circ}\text{C}$) had been qualified including temperature mapping. Working standards were assigned a 1 year retest period from the date of manufacture but there no time limit specified for the duration of use from the time of first opening of each of the prepares 6 vials. Used vials were resealed after use.
- ⇒ Microbiology laboratory plus related procedures and data:
- Sample register for purified water samples
 - SOP on sampling and analysis of raw and purified water samples.
 - Documents related to standard cultures of bacteria used in positive control and growth promotion studies. Four passages were allowed although the generation of received cultures was not documented.
- ⇒ Process validation for production of the APIs and reasons for validation:
- ⇒ Process validation for production of crude API from key intermediate.
- ⇒ Change control procedure and review of selected cases.
- changes in the purification method and change from plant 1 to plant 2 with related increase in batch size.
 - fixing of drying time to 12 hours.
 - change of process from centrifuge slurry to reactor slurry of wet cake.
 - several changes including change of drying time from 12 hours to 20 hours.
- ⇒ Cleaning validation procedures. The approach to cleaning validation, preparation of solubility matrix (10ppm), swab recovery studies (NLT80%) and reports of ranking of products were reviewed.
- ⇒ Quality of compressed air that comes into contact with the products (at jet mills)
- ⇒ Quality of Nitrogen that is used in the laboratory
- ⇒ Quality of Nitrogen that is used in production

At the end of the day, the team reviewed progress of the activities of the day and the entire inspection, gave feed back on the observations made in the areas inspected and wrap up for the inspection and received reactions from the management of the company. There was consensus on the all the observations made.

2.1 QUALITY MANAGEMENT

Sequent Scientific Limited had documented its quality system in form of a quality manual, organization structure, job descriptions and responsibilities of key personnel and units, standard operating procedures (SOPs) and production data sheets.

There was a documented system for evaluation and release of starting materials, intermediates and APIs; change control, approval of deviations, documenting and investigating out-of-specifications results; internal audits and product quality review. Validation and qualification programmes were documented in the Validation Master Plan.

Some deficiencies were noted in the documentation of some of the procedures and implementation of the policies and procedures but these were subsequently resolved.

2.2 PERSONNEL

Sequent had adequate numbers of personnel to perform the required tasks. The staff had the required basic qualifications and there was a training programme to keep them up to date with new developments and demand of their assignments. There was an organization chart and job descriptions to elaborate on functional and reporting responsibilities. On the basis of the documents and activities evaluated, the GMP consciousness of some staff needed to be strengthened.

Appropriate changing and gowning procedures were in place and there was a canteen which was separate from production and QC areas.

2.3 BUILDINGS AND FACILITIES

The building and facilities were designed to facilitate logical flow of production activities and to avoid cross contamination. The building and facilities were in a good state of repair and were adequately cleaned.

This was multipurpose plant. The clean areas for purification stage and powder processing were controlled to class 100,000 conditions and were separate from those for the crude synthesis stages. Manufacturing areas were constructed with smooth surfaces for easy cleaning and were supplied with separate AHUs to provide a pressure cascade for the different processing areas. Temperature and relative humidity were regularly monitored.

Utilities like compressed air, nitrogen and purified water were generated and purified on site and the corresponding qualification reports were available. Some deficiencies were observed in the specification of purified water used in relation to the APIs produced and the operation, monitoring and maintenance of the AHUs but these were subsequently resolved.

2.4 PROCESS EQUIPMENT

The process equipment were designed and installed to facilitate containment and logical flow of production. Procedures and records for their operation, cleaning and maintenance were available. There was a system to indicate the status of the equipment although its

implementation needed to be consistently implemented. Supervision of cleaning procedures and the corresponding record keeping needed to be strengthened. This was subsequently addressed.

The corresponding measuring devices were regularly calibrated and the calibration status indicated but not all the service lines and pipelines were labelled with identity content and/or direction of flow. This was subsequently addressed.

2.5 DOCUMENTATION AND RECORDS

There was a system for documentation in form of master production and control procedures, SOPs, manufacturing procedures (Process data sheet, PDS), process flow charts, log books, registers, specifications, testing procedures and analysis records. SOPs were available to the staff that needed them. There was a documented system for their design, approval and control but this needed strengthening. Some weaknesses were observed in the clarity and comprehensiveness of some SOPs; consistency between the process data sheets (PDS) and master production procedures; and non-compliance with the procedures during implementation. These were subsequently addressed.

A computer based inventory management system (IMS) was used to control the stocks and other activities like "virtual quarantining" of materials awaiting approval but it had not been validated. Plans had been initiated to install a new enterprise resource planning software which would be fully validated.

2.6 MATERIALS MANAGEMENT

Materials were sourced from approved suppliers. Most of the key starting materials were synthesized in Plant 1 on the same site. On receipt they were quarantined, sampled and tested before acceptance into approved stores for subsequent use. There were segregated storage areas for starting materials, intermediates and finished APIs and the storage conditions were regularly monitored. There were separate stores for highly flammable solvents and several underground tanks for solvents. There were some deficiencies in the segregation of some materials according the status of approval and the methods used to monitor the storage conditions but these were subsequently resolved.

Materials at different stages processing were identified with a unique batch numbers and stage of processing. There was system

The handling of expired and unserviceable materials was highly inadequate. Large quantities of such materials were found in several buildings and many parts of the compound without adequate control and security. These expired and unserviceable materials plus the handling of certain solvents provided a potential health and safety risk.

2.7 PRODUCTION AND IN-PROCESS CONTROLS



Production processes were guided by documented procedures and instructions outlined in the process data sheets (PDS). There were in-process controls conducted at appropriate stages of synthesis to monitor the quality of the intermediates and APIs. Where blending was practised, it was using batches that had been tested and approved. PDS were based on master production procedures although inconsistencies were frequent. The batch size, process steps, process equipment used and related documentation frequently changed from that validated and/or outlined in the dossiers submitted to WHO and/or described in the master documents and PDS. Some of these changes did not go through a systematic deviation control, change control procedure and revalidation.

Since plant 2 was a multipurpose plant with multipurpose process equipment, production was conducted on campaign basis, with documented cleaning procedures between batches or products and status labelling. The supervision of cleaning activities plus related recording and status relabeling required strengthening. This was subsequently addressed.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Packaging operations were guided by documented and approved procedures using tested and approved packaging materials. Packaging materials supplied by clients were exempted from sampling and testing before use. APIs were packed in a white high molecular high density polyethylene (HM HDPE) bag followed by a black high molecular high density polyethylene (HM HDPE) and finally into blue high density polyethylene (HDPE) container with a lid and a metallic seal.

The container were initially labelled using an in house label and later with a commercial label supplied by or made according to the specifications of a client. There were procedures for line clearance and reconciliation of packaging materials.

2.9 STORAGE AND DISTRIBUTION

Sequent had separate storage warehouses and areas for starting materials, packaging materials, solvents, intermediates, and finished APIs. However, large quantities of expired and unusable materials were found in several buildings and many parts of the compound without adequate control and security.

Conditions of storage were monitored but the methods used and records maintained in some cases could not guarantee monitoring the extreme conditions to which materials were actually exposed. Sometimes, intermediates or APIs awaiting approval were not effectively segregated from approved ones. This was subsequently addressed.

Appropriate records for stock and distribution were maintained and the records could support traceability of the batches distributed. The majority of the APIs produced by SSL were supplied to Strides.

2.10 LABORATORY CONTROLS

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Quality control services of Sequent Scientific Limited (SSL) were provided by the analytical services department (ASD) of Sequent Research Limited (SRL), an independent unit on the same site. This was initially the QC laboratory for SSL/Strides but was now managed as an independent business because it was involved in contract analytical testing for outside clients. Their relationship was managed through a Quality Agreement.

The premises of SRL plus related facilities and utilities were separate from production and were in a good state of repair. There were dedicated rooms for activities like sample receipt and storage, wet chemistry, instrumentation, hot areas and balance room. The microbiology laboratory was separate from the chemical laboratory. There were adequate pieces of equipment with up to date calibration status.

SRL-ASD was responsible for preparing specifications and test procedures for input materials, packaging materials, intermediates and APIs. This was done in consultation with R&D, production and QA and the specifications and test procedures were approved by the SSL QA. Any changes to the specifications and test procedures were controlled by SSL change control procedures.

SRL-ASD was responsible for sampling and testing of raw materials, packaging materials, intermediates and APIs, validation, water analysis, stability testing. Records of sample receipt and allocation, analysis were maintained. Records of analysis could facilitate traceability of the reagents, standards and equipment used. Working standards were standardized against either primary reference standards or in-house references standards prepared by the R&D section of the SRL. The final release of APIs was done by SSL QA following review of production and QC records.

There were stability chambers for the different storage conditions ($5^{\circ}\text{C}/60\%RH$, $40^{\circ}\text{C}/75\%RH$, $30^{\circ}\text{C}/65\%RH$, $30^{\circ}\text{C}/75\%RH$ and $5^{\circ}\pm 3^{\circ}\text{C}$) and records of charging and withdrawal of samples for testing. Results of stability testing were used in determining the expiry/retest dates of APIs and on-going monitoring their quality.

2.11 VALIDATION

The qualification and validation policies of SSL were summarized in the Validation Master Plan (VMP) and each exercise was guided by an approved protocol. Qualification followed the steps of design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). It was a requirement that each process should be validated and appropriately revalidated, either periodically or following amendments to the process. Validation reports were available for However, it was established that certain changes were not followed by validation and sometimes many batches (>30) were produced and distributed before validation was done. This was subsequently addressed.

Cleaning procedures had been validated. The approach to cleaning validation involved preparation of solubility matrix (10ppm), swab recovery studies (NLT80%) and ranking of products according to solubility in different solvents. This was used to select the worst case

API, the corresponding solvent and the limits to use during cleaning validation and routine monitoring.

2.12 CHANGE CONTROL

There was a procedure for change control which included evaluation of the impact of the change on the validation status of the system and prescribed appropriate control measures to minimize the impact and preserve the validated status. There was a change control register and appropriate records were maintained.

Not all the changes and/or deviations were handled through the established change control or deviation handling procedure. The introduction of new products in a workshop was not done through a well documented change control procedure. These deficiencies were subsequently addressed.

2.13 REJECTION AND RE-USE OF MATERIALS

There were rooms for quarantine and storage of rejected materials and returned goods. The company had polices and procedures for reprocessing and reworking of intermediates and APIs. Some reprocessing procedures had been incorporated into the standard manufacturing process.

Recovery and reuse of solvents and materials was practiced at the site and specifications for recovered solvents and materials were available. Clarity was required in the maximum number of reprocessing cycles allowed, the stability study policy for reprocessed/reworked materials and qualification of the recovered materials for impurity profile. This was subsequently addressed.

Most of the solvents and mother liquor were recovered and sold to an outside party and the residues incinerated or handled otherwise through the effluent treatment plant

2.14 COMPLAINTS AND RECALLS

There were procedures for handling customer/market complaints and product recalls. Only few market complaints had been encountered and none had resulted into a recall. Requirements for improvements in documentation and evaluation of effectiveness of these procedures were observed.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

There was no contract manufacturing done for SSL. All QC services were contracted out to the sister unit (SRL-ASD) and a quality agreement was in place. There was no formal contract with the vendor to whom the waste solvents were sold.



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, **Plant 2 of Sequent Scientific Limited (SSL)**, located at **Plot No. 120: A & B, Industrial Area, Baikampady, New Mangalore - 575011, Karnataka, 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.