Prequalification Team Inspection services  
WHO PUBLIC INSPECTION REPORT  
of the Active Pharmaceutical Ingredient (API) Manufacturer

<table>
<thead>
<tr>
<th>Part 1</th>
<th>General information</th>
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<tbody>
<tr>
<td><strong>Manufacturers Details</strong></td>
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<tr>
<td>Company information</td>
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</tbody>
</table>
| Name of manufacturer and address | Sequent Scientific Ltd  
120 A&B, 36, 120P & 121, Industrial Area, Baikampady, New Mangalore -575011, Karnataka, India.  
N 12.95182°  
E 74.82561°  
676159823 |
| Corporate address of manufacturer | 301, Dosti Pinnacel, 3rd floor, Plot no E7, Road no 22, Wagle Estate, Thane-west – 400604, Maharastra, India  
Tel: +91-22 41114777, Fax: +91 22 21721111 |
| **Inspected site** | |
| Address of inspected manufacturing site if different from that given above | As above |
| **Inspection details** | |
| Dates of inspection | 12 – 15 February 2018 |
| **Introduction** | |
| Brief summary of the manufacturing activities | The manufacturer was involved in manufacturing, packaging, labelling, testing and storage of intermediates and active pharmaceutical ingredients (APIs).  
Sequent Scientific Limited was incorporated in 1995 and is engaged in the development and manufacture of API and intermediates used in finished pharmaceutical products. Sequent have facilities at Mangalore and Mysore in Karnataka, at Tarapur and Mahad in Maharashtra and at Vizag in Andra Pradesh, India.  
The Mangalore facility has 3 production blocks, Plant-1 used for manufacturing of intermediates, Plant-2 and Plant-3 used for the manufacture of APIs. Mangalore facility is ISO: 14001 certified. |

WHO inspection report Sequent Scientific Mangalore, February 2018  
This inspection report is the property of the WHO  
Contact: prequalinspection@who.int
History

The site has been inspected by the following authorities in the recent years:

<table>
<thead>
<tr>
<th>Authority</th>
<th>Date/s of inspection</th>
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<tbody>
<tr>
<td>FDA Karnataka (CDSCO), Zonal office, Bangalore</td>
<td>June 2014</td>
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<tr>
<td>FDA Karnataka (CDSCO), Zonal office, Bangalore</td>
<td>December 2014</td>
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<td>FDA Karnataka (CDSCO), Zonal office, Bangalore</td>
<td>July 2015</td>
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<td>FDA Karnataka (CDSCO), Zonal office, Bangalore</td>
<td>October 2015</td>
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<td>FDA Karnataka</td>
<td>October 2016</td>
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<td>FDA Karnataka</td>
<td>May 2017</td>
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<td>FDA Karnataka</td>
<td>September 2017</td>
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<tr>
<td>FDA Karnataka (CDSCO), Zonal office, Bangalore</td>
<td>November 2017</td>
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<td>WHO</td>
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<td>WHO</td>
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<td>TGA Australia</td>
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<td>USFDA</td>
<td>September 2012</td>
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<td>USFDA</td>
<td>29 June 2015 to 3 July 2015</td>
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<td>EDQM</td>
<td>September 2017</td>
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Brief report of inspection activities undertaken

Scope and limitations

Areas inspected

- Pharmaceutical Quality System
- Documentation system
- Production System
- Facilities and Equipment System
- Laboratory Control System
- Packaging and labelling system

Restrictions

Inspection was focused at manufacture and quality control of API under WHO assessment

WHO products covered by the inspection

APIs prequalified by WHO and under WHO assessment process to be used in HIV, NTD and HP treatment.
<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Description</th>
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<tbody>
<tr>
<td>AHU</td>
<td>air handling unit</td>
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<tr>
<td>ALCOA</td>
<td>attributable, legible, contemporaneous, original and accurate</td>
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<td>AOL</td>
<td>Acceptance quality limit</td>
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<td>API</td>
<td>active pharmaceutical ingredient</td>
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<td>APQR</td>
<td>annual product quality review</td>
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<td>BDL</td>
<td>below detection limit</td>
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<td>BMR</td>
<td>batch manufacturing record</td>
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<td>BPR</td>
<td>batch packaging record</td>
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<td>CAPA</td>
<td>corrective actions and preventive actions</td>
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<td>CC</td>
<td>change control</td>
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<td>CFU</td>
<td>colony-forming unit</td>
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<td>CoA</td>
<td>certificate of analysis</td>
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<td>CpK</td>
<td>process capability index</td>
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<td>DQ</td>
<td>design qualification</td>
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<td>EM</td>
<td>environmental monitoring</td>
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<td>FAT</td>
<td>factory acceptance test</td>
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<td>FBD</td>
<td>fluid bed dryer</td>
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<td>FG</td>
<td>finished goods</td>
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<td>FMEA</td>
<td>failure modes and effects analysis</td>
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<td>FPP</td>
<td>finished pharmaceutical product</td>
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<td>FTA</td>
<td>fault tree analysis</td>
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<td>FTIR</td>
<td>Fourier transform infrared spectrometer</td>
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<td>GC</td>
<td>gas chromatograph</td>
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<td>GMP</td>
<td>good manufacturing practice</td>
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<td>HACCP</td>
<td>hazard analysis and critical control points</td>
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<td>HPLC</td>
<td>high-performance liquid chromatograph</td>
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<td>HVAC</td>
<td>heating, ventilation and air conditioning</td>
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<td>ID</td>
<td>identity</td>
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<td>IR</td>
<td>infrared spectrophotometer</td>
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<td>IPC</td>
<td>In process control</td>
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<td>IQ</td>
<td>installation qualification</td>
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<td>KF</td>
<td>Karl Fisher</td>
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<td>LAF</td>
<td>laminar air flow</td>
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<td>LIMS</td>
<td>laboratory information management system</td>
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<td>LoD</td>
<td>limit of detection</td>
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<td>LOD</td>
<td>loss on drying</td>
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<td>MB</td>
<td>Microbiology</td>
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<td>MBL</td>
<td>microbiology laboratory</td>
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<td>MF</td>
<td>master formulae</td>
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<td>MR</td>
<td>management review</td>
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<td>NIR</td>
<td>near-infrared spectroscopy</td>
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<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>NRA</td>
<td>national regulatory agency</td>
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<td>OQ</td>
<td>operational qualification</td>
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<td>PHA</td>
<td>preliminary hazard analysis</td>
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<td>PM</td>
<td>preventive maintenance</td>
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<td>PpK</td>
<td>process performance index</td>
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<td>performance qualification</td>
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<td>PQR</td>
<td>product quality review</td>
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<td>PQS</td>
<td>pharmaceutical quality system</td>
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<td>PW</td>
<td>purified water</td>
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<td>QA</td>
<td>quality assurance</td>
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<td>QC</td>
<td>quality control</td>
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<td>QCL</td>
<td>quality control laboratory</td>
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<td>QMS</td>
<td>Quality management system</td>
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<td>QRM</td>
<td>quality risk management</td>
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<td>RA</td>
<td>risk assessment</td>
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<td>RCA</td>
<td>root cause analysis</td>
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<td>RH</td>
<td>relative humidity</td>
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<td>RM</td>
<td>raw materials</td>
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<td>RS</td>
<td>reference standard</td>
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<td>SAP</td>
<td>system applications products for data processing</td>
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<td>SFG</td>
<td>semi-finished goods</td>
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<td>SOP</td>
<td>standard operating procedure</td>
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<td>STP</td>
<td>standard test procedure</td>
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<td>T</td>
<td>Temperature</td>
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<td>TAMC</td>
<td>total aerobic microbial count</td>
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<td>TFC</td>
<td>total fungal count</td>
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<td>TLC</td>
<td>thin layer chromatography</td>
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<tr>
<td>TMC</td>
<td>total microbial count</td>
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<tr>
<td>TOC</td>
<td>Total organic carbon</td>
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<td>URS</td>
<td>user requirements specifications</td>
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<tr>
<td>UV</td>
<td>ultraviolet-visible spectrophotometer</td>
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<td>VMP</td>
<td>Validation Master Plan</td>
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<td>WFI</td>
<td>water for injection</td>
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<td>WS</td>
<td>working standard</td>
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Part 2

Brief summary of the findings and comments

1. Pharmaceutical quality system
The quality management system was generally well established, documented and implemented; the system encompassed organizational structure, procedures and processes. QA and QC departments were independent of production. In general, deviations from established procedures were documented and explained. Procedure was in place for notifying responsible management of regulatory inspections, serious GMP deficiencies, product defects and related actions. Quality management system consisted of: Quality Manual, SOPs and Records.

Data integrity
Data integrity policy was described in the document “Policy on Data Integrity”. Document was briefly reviewed. Elements of policy on data integrity were explained based on ALCOA and additional data integrity elements such as:
- Complete
- Consistent
- Enduring
- Available

Document also explained policy on electronic data acquisition systems, electronic access security measures, auditing of quality system etc. Class room training on data integrity policy was provided to all employees. Training effectiveness was evaluated by group discussions. Training records were available.

Product Quality Review (PQR)
An SOP “Product quality review” was briefly reviewed. The PQR covered, but not limited:
- Commercial batch summary
- Batch summary
- Commercial batch data
- Yield summary
- Key quality attributes
- Failed batches
- Changes (permanent)
- Vendor related changed
- Manufacturing process related changes
- Analytical specification and method repeated changes
- Temporary changes
- Recall
- Complaints
- Stability
- Reviewed of CAPAs and their adequacy
- Review of pending actions from previous years PQR
- Conclusion
Statistical evaluation of the trends was carried out using standard deviation and relative standard deviation. According to the SOP PQR should be completed by the end of April of the following year. A number of PQRs were briefly reviewed and discussed.

Management review (MR)
An SOP “Management review” was briefly reviewed. According to the SOP MR Meetings should be held once in a six months. Standard MR Agenda was provided. Latest MR was held in February 2018; minutes were available and were reviewed in details. MR meeting was well documented and covered all topics listed in the standard agenda.

Quality risk management (QRM)
An SOP “Quality Risk Management” was briefly reviewed. According to the SOP QRM was applicable, but not limited to:
- Development
- Facilities/equipment/Utilities
- Manufacturing operations
- Quality control activities
- Storage and distribution
- QMS elements:
  - Quality defects
  - Deviations
  - Internal audits
  - Regulatory inspections
  - PQR
  - Change management
  - Complaints

The following tools were listed in the SOP; however it was indicated that Process Flow Diagram was used for RA:
- FMEA
- Fish bone diagram
- IPO (input process output diagram)
- FTA
- HACCP
- Supporting statistical tools

“Register for Quality Risk Management” was presented to the inspectors.

A number of risk assessments were briefly reviewed.
Change control (CC)
An SOP “Change management activity”, flow chart, CC forms and register for 2017 were briefly reviewed. The SOP described planned temporary changes (planned changes) and permanent changes management. The following change types described:
- Major modifications to facility/equipment/accessories/utilities including IT systems
- Like to unlike changes (e.g. equipment change to different type of equipment)
- Rationalization /simplification of testing
- Outsourcing activities
- Major CAPA introduced after recurring history of failures / complaints etc.

CCs were trended every six months. Annual trending of CC was presented during MR meetings.

A Number of CCs were briefly reviewed.

Deviations
An SOP “Handling of deviations”, its flow chart and register for 2017 were briefly reviewed. Deviation register was department specific. Deviations were classified as:
- Critical
- Non-critical

Deviations from production procedures were recorded in the BMR/BPR and a link was given to a specific deviation investigation form. Process flow charts, 5 Whys and Ishikawa diagram were listed as tools to be used for investigation of deviations. Deviations were trended every six months. Annual trending of deviations was presented during MR meetings.

A number of deviations were briefly reviewed.

Corrective actions and preventive actions (CAPA)
An SOP “Corrective action and preventive action”, its flow chart and CAPA register were briefly reviewed. The SOP was applicable, but not limited to:
- Customer/ regulatory /internal audits
- OOS /deviations / out of calibration (OOC)
- Complaints
- QRM
- Recall

A number of CAPAs were briefly reviewed.

Complaints
An SOP “Handling of customer complaints and returns”, and the complaints and returns register for 2017 were briefly reviewed. All quality related complaints were reviewed by QA. According to the SOP complaints receipt shall be notified to the regulatory authorities whenever applicable.

A number of complaints investigation records were briefly reviewed.
Recalls
An SOP “Product recall” was briefly reviewed. No product recalls were recorded. Recalls were classified as:
- Class I
- Class II
- Class III
According to the SOP class I and II recalls shall be initiated immediately within 48 hours from identification and confirmation to recall. In case of Class I and II recalls regulatory authorities should be informed. Recall effectiveness was evaluated every 2 months for domestic and export market.

Self-inspection
An SOP “Internal Audit” was briefly reviewed. Audit plans for 2017 and 2018 were presented. According to the SOP all departments should be audited once in 4 months. Conflict of interest was addressed. Internal audit check lists were available for all departments. Internal audit check list of Analytical service department was reviewed. Check list had section “Observations”. CAPAs were proposed by Head of department, evaluated by QA. CAPAs implementation was also monitored by QA. Lead auditor was Head of QA department or his designee. Observations were classified as:
- Critical
- Major
- Minor

List of internal auditors was presented to the inspectors. Generally internal audits were well attended to.

Supplier qualification
An SOP “Vendor qualification” was briefly reviewed.
A qualified vendor list was available listing for each product the details of the approved vendors and, when relevant, the details of the manufacturer.

The vendors/manufacturer were classified according to the criticality of the products supplied:
- Key starting materials
- Intermediates
- Critical raw material
- Other RM
- Packaging material

Revalidation of the vendors/ manufacturers was scheduled every 3 years.

A number of Vendors Qualification records were briefly reviewed.
Personnel
The current organization chart of the company was available. The company had sufficient number of personnel with responsibilities according to their respective unit and department. Personnel were wearing suitable clothing for the manufacturing activities.

According to the Company presentation, the site employed approximately 371 full time employees:

Around 152 contract workers were involved in physical operations e.g. transfer of materials and cleaning. Contract workers were not involved in activities performed in clean rooms.

Training
An SOP “Induction of Employee” was briefly reviewed. According to the SOP induction training shall be completed before the person start executing the designed job. The Induction training record for Mr. XX (production) was briefly reviewed.

An SOP “Training of personnel” was briefly reviewed. GMP training was provided at least once per year. Annual training calendar and monthly training plan was presented to the inspectors. The following training modes were specified:
- Self-study
- Group study
- External training
- On job training
- Classroom training

An SOP “Trainers Qualification” was briefly reviewed. Qualified trainers list was presented to the inspectors. Mr. ZZ from production department training file and certification as a qualified trainer was briefly reviewed.

There were 45 training modules available. The following training modules were briefly reviewed:
- “Vendor qualification”
- “Guidance for GMP violations”
- “Awareness of c GMP and safety contract workers”

Data integrity training was presented jointly by SEQUENT & ALIVIRA (veterinary API manufacturing division). These training materials were presented to the inspectors. These training materials were further used for Sequent employers training.

An SOP “Analyst Qualification in LIMS”, analyst competitive skill matrix and signature specimen list (full signature and short signature) were briefly reviewed. Analyst qualification was performed when joining the company and on routine basis – every 3 years. Analysts were given already analysed sample and results were compared. Acceptance criteria between two analyses were specified.

Mr. YY analyst, training file for residual solvents by GC was briefly reviewed.
An SOP “Health checks up and Monitoring” was briefly reviewed. The following medical check-ups were organized by HRA department:

- Pre-employment
- Half yearly
- Annual

Physical fitness certificate of contract worker Mr. VV was presented to the inspectors. Physical fitness checks were performed by Sequent medical doctor.

2. Documentation system

Documentation system was generally well established. Documents related to the manufacture of intermediates and APIs were prepared, reviewed, approved and distributed according to written procedures. The issuance, revision, superseding and withdrawal of documents were controlled with maintenance of revision histories.

Production, control and distribution records were retained for one year after the expiry date of the batch. For APIs with retest dates, records were retained for three years after the batch was completely distributed. Specifications were established for raw materials, intermediates and APIs. The Company had a policy to archive logbooks and other documents. An SOP “Control of records” was briefly reviewed.

An SOP “Batch release” was briefly reviewed. Batch release was done by Head QA or designee. This procedure was applicable for release of intermediates and finished products for dispatch.

An SOP “Batch record review” and check list were briefly reviewed. Quality Assurance personnel were responsible for review of the batch records post completion of the batch, QA head or designee to release the batch post QA review. SOP was applicable for review of completed batch manufacturing and packaging records.

An SOP “Review of analytical documents” and Review Check List for Analytical Service and Review Checklist for QA department were briefly reviewed. Audit trails were reviewed for all analysis.

An SOP “Management of audit trail” was briefly reviewed. According to the SOP Audit trail verification shall be performed once per month. The SOP was applicable for all chromatographic data systems and non-chromatographic data systems. Audit trail requires checks for the system audit trail, method history and sequence history. Monthly audit Trail review log for Chromatographic systems XX for December 2017 was verified. Verification of Audit trails was done by QA & Compliance group.

Certificate of analysis was issued and signed by QA.

An SOP “Generation, Issue and Retrieval of Batch, Manufacturing & Packaging Record” was briefly reviewed. BMRs and BPRs were approved and issued by QA department. Lot numbers and batch numbers were generated automatically by SAP system.
3. Production system
In general, production operations followed defined procedures. Process flows (with IPCs) and routes of synthesis were available. Access to production premises was restricted to authorized personnel. Weighing and measuring devices were of suitable accuracy for the intended use. Closed systems and dedicated pipes were used for material transfers from reactors to centrifuges.

An SOP “Personnel entry and exit, gowning and de-gowning in production Plant-2” was briefly reviewed.

A number of documents related to manufacturing operations were briefly reviewed.

Material management
There were defined areas for:
• Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection,
• Quarantine before release or rejection of intermediates and APIs,
• Holding rejected materials before further disposition (e.g. return, reprocessing or destruction),
• Storage of released materials,

The following SOPs were briefly reviewed:
• SOP “Sampling of raw material, packaging material, intermediates, and finished products”
• SOP “Dispensing and issue of raw material, packaging material, engineering and consumable items”

Validation Mater Plan (VMP)
An SOP “Validation master plan” was briefly reviewed.

Process Validation
The process validation report for XX was briefly reviewed, as well as the following documents:
• Validation protocol for process validation of XX batches failing to meet established specifications
• Process validation report for ZZ of 3 validation batches
• Performance qualification protocol for rotocone vacuum drier

Cleaning validation
Generic protocol for cross over cleaning validation: “Cleaning validation” and SOP “Identification, selection and validation of analytical method for analysing line clearance and cleaning” was briefly reviewed.

These documents were generated for cleaning validation of equipment used for manufacturing API products in multipurpose equipment QA calculates the limits of previous product allowable in the next product considering the batch size and number of equipment to be used in the next campaign. Lowest residual limit derived from 10 ppm/MACO/NOEL is allowed to be carried over to the next product.

Bracketing approach was used considering the solubility matrix of the product, similarity in type and capacity of equipment and similarity of product.
The analytical method used for detecting and/or quantifying the previous product residue was UV spectrophotometry, TOC, TLC analysis HPLC analysis or GC analysis. The method was validated on specificity, linearity, limit of detection and limit of quantification.

A number of cleaning records were briefly reviewed.

4. Facilities and equipment system

Plant 2 and 3 where APIs under assessment were manufactured were covered during inspection. Plant 2 was designed for small batches of less than 50 Kg. In plant 3 larger batch sizes are manufactured. Each plant had a “crude section” and 3 ISO 8 classified lines including a “pure section” and a “powder processing section. All fixed equipment was multipurpose, except the permanently fixed lines which were product specific. Transfer hoses used in the pharma area were product dedicated.

Buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Facilities were designed to minimize potential contamination. Adequate space was provided for orderly placement of equipment and materials to prevent mix-ups and contamination.

Permanently installed pipework was appropriately identified. Solvent pipelines had different colour codes.

Document “Qualification plan for IT infrastructure” was available and briefly reviewed. The scope of the document was limited to qualification of an additional server, workstations & network components like switches at the Sequent Research site, Mangalore.

The qualification documents Chromeleon software version 6.80 were available and briefly reviewed:

- IQ
- OQ
- PQ

IQ and OQ were performed by the service provider, PQ by Sequent employees. Software qualification was performed according to an SOP “Management of Laboratory Instruments and equipment’s in LIMS”.

PQ protocol chromatographic data management system was briefly reviewed.

Open lab version Ez Chrome version A.01.4 qualification documents were available and were similar to Chromeleon software version 6.80 qualification documents, but were not reviewed during the inspection.

Documents “Project validation plan for LIMS system” and “Project validation report for LIMS system” were briefly reviewed. IQ and OQ was executed by corporate office, PQ was executed on site.

Document “PQ protocol for Chromeleon version 6.80 Chromatography Data Management System” was briefly reviewed.

A number of documents related to the SAP system validation were briefly reviewed.
An SOP “Administration on LIMS” was briefly reviewed.

An SOP “Operation of Gas Chromatograph” was briefly reviewed. The following user privileges were specified:

- Analyst
- Reviewer
- QA
- Service engineer
- Administrator

An SOP ASD147-R5 “System administration of Chromeloeon Software” was briefly reviewed. User’s privileges were specified:

**Back up data**

An SOP “Data back-up procedure” was briefly reviewed. Online back-up was used for stand-alone systems. Daily and weekly back-ups were taken on tapes by IT personnel and stored in fire proof cabinet. Daily back-ups were retained for 15 days and afterwards used again. Monthly back-up was taken on two tapes and external hard drive. One tape was stored in of-site location (guest house). Restoration of data was performed according to the annual data restoration schedule what was presented to the inspectors. Data restoration from all instruments was done monthly on a rotational basis with all instruments covered over one year.

A “Disaster recovery plan procedure” was available.

**Utilities**

**Purified water system (PW)**

PW was used for production and for cleaning of equipment and tools. There was one PW generation system on site. The system had 2 distribution loops. Storage tank (2000 L) and loops were made from stainless steel 316 L. PW was in continuous circulation at ambient temperature. Conductivity and flow rate on the return loops were checked on-line. Designed flow rate NTL 1.5 m³/hour, slop was 1:100. PW storage tank and loops were sanitized every 15 days using 80 – 85 °C water for 90 minutes. Samples form return loops were analysed daily, samples from other sampling points were analysed every 15 days on rotational basis. PW trends were presented to the inspectors. Action level for total aerobic microbial counts was 75cfu/ml and alert level was 50cfu/ml.

A number of following documents related to PW system were briefly reviewed.

**HVAC system**

Clean air to Plant 3, line 1 was supplied by AHU XX. Schematic drawing of AHU was reviewed. Recirculated air with 10% fresh air was used. Filter cascade: G4→F9; Terminal HEPA filters H13 were installed. Pressure differentials between G4 and F9 and H13 were monitored daily. HEPA filters integrity tests were performed once per year.
AHU XX was installed in 2010 and was re-qualified every year addressing the following parameters:
- Particle counts (viable and non-viable)
- HEPA filter integrity test
- Air velocity
- T & RH
- Differential pressure
- Fresh air determination
- Area recovery
- Air flow pattern test

AHUs re-qualification was performed by 3rd party. Measuring instruments calibration certificates were available.

AHU XX was inspected during inspection. AHU “Filter Cleaning log sheet” for 2017 and Check list for “Preventive maintenance” were presented to the inspectors. Primary and secondary filters were cleaned every month or in case pressure differentials were out of limits.

Temperature mapping
An SOP “Operation and Calibration of Walk-in Stability Chamber / Humidity Control Ovens” and Yearly Calibration and Mapping / Validation Report” were briefly reviewed.

General approach to the storage areas T & RH mapping was explained in VMP. Finished good warehouse T & RH protocol XX and report YY were briefly reviewed.

Laboratory premises
Laboratory areas were separated from production areas. Microbiological laboratory premises were separated from the QC laboratory.

5. Laboratory control system
Quality control appeared to be adequately organized and equipped. Some in process control (IPC) tests as TLC and pH were performed by operators in the production premises, other tests were performed in Quality control laboratory by dedicated analyst group working in 3 shifts.

HPLCs were operated by Chromeleon software version 6.80 and GCs by Open lab version Ez Chrome version A.01.4.

LIMS system was used to:
- Record samples
- Analyses
- Calculations
- Issuance of CoA
Analytical services were contracted out to Sequent Research Limited. Both companies were part of Sequent group. The following analyses were done by Sequent Research:

- Chemical
- Instrumental
- Stability
- Microbiology

Sequent Research laboratories were located in R&D and Analytical services building. Laboratory also performed stability studies for other companies what are not part of Sequent group.

An SOP “Contractor GMP awareness and agreement” was briefly reviewed.

Analytical Service Agreement between Sequent Scientific Ltd and Sequent Research Limited was reviewed. Service agreement included the following:

- Sampling and analyses of water, raw materials, intermediates and finished products
- Update status of products analyses and issue certificate of analysis
- Stability study as per requirements
- Generation of specifications and analytical methods
- Analytical method development, validation and method transfer
- Analysis of R&D sample and development samples
- Investigation of OOS/OOT
- Any other samples / analysis support as required.

List of approved external service providers, including laboratory services was presented to the inspectors.

Master Service Agreement between Sequent Research Limited and XX and the assessment form for Contract Testing laboratory and Audit Report were briefly reviewed.

An SOP “Sampling of Raw Materials, packaging Materials, Intermediates and Finished products” was briefly reviewed. Samples from KSMs were taken from all containers. Pool sample was prepared from 10 containers.

For purposes of data integrity API XX Batch No YY analytical protocol, electronic metadata, standards usage, printouts and other relevant data were cross checked. No discrepancies were noted.

Environmental monitoring (EM)

An SOP “Monitoring of Microbial Load in Clean Rooms: sampling methods” and EM trends were briefly reviewed. Settle plates method and active air sampling were used for EM. Alert and action limits were set up based on historical data. Samples for EM were taken once a month on different days for different areas.

An SOP “Handling of control samples and withdrawal” was briefly reviewed.
SOPs “Handling of Reference standards and Primary Standards in LIMS” and SOP “Handling of Working Standard, reference standard (in House) and Manufacturers or Suppliers or Customer Standard” were briefly reviewed. Working standards were standardized against Pharmacopoeia standards and dispensed in 13 amber colour vials under LAF, one vial for use within one month. Standards were stored according to specified storage condition in special chamber, deep freezer and in desiccators. T and RH in Thermolab chamber was recorded automatically every 10 minutes and checked daily. Chamber and deep freezer were equipped with audio alarm, what was challenged monthly.

Out of specifications
An SOP “Handling out of specification results” and SOP “Investigation of out of specification products” were briefly reviewed.

A trend analysis of all OOS was conducted every 6 month. A number of OOS and related documents were briefly reviewed.

Stability studies
SOPs “Stability Programme for APIs”, “Stability Testing Protocol” and “Management of Stability Samples” were briefly reviewed.

Stability Protocol API XX, accelerated stability study (finalized) data and long term stability – zone 3 and zone 4 data (36 months finalized) were briefly reviewed.

Stability Master Plan for API XX stability samples was cross-checked with stability sample receipt & issuance register. Cross-checks confirmed that stability schedule was followed. 9 chambers were provided for stability studies. Stand by chamber was available. T and RH in stability chambers was recorded automatically every 30 minutes and checked daily. Chambers were equipped with audio and SMS alarm system, which was challenged every year.

Stability studies for API XX was done under 3 conditions:
- 40°C /75 % over 6 month
- 25°C/25% over 12 month
- 30°C/75% over 12 month

6. Packaging and labelling system
Packaging and labelling operations of finished APIs was done in ISO 8 room under dust extractor. At the time of the inspection no packaging and labelling operations were carried out. Customer specific labels were printed in-house by QA.
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 Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report a decision on the compliance of Sequent Scientific Ltd, located at 120 A&B, 36, 120P & 121, Industrial Area, Baikampady, New Mangalore -575011, Karnataka, India, Plant-1, Plant-2 and Plant-3 was considered to be operating at an acceptable level of compliance with WHO good manufacturing practices for active pharmaceutical ingredients 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.

PART 4

List of GMP guidelines used for assessing compliance

   Short name: WHO TRS No. 957, Annex 2

   Short name: WHO TRS No. 986, Annex 2

   Short name: WHO TRS No. 961, Annex 6
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
   Short name: WHO TRS No. 970, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

   Short name: WHO TRS No. 961, Annex 5
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

   Short name: WHO TRS No. 937, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

   Short name: WHO TRS No. 957, Annex 1

   Short name: WHO TRS No. 957, Annex 3

    Short name: WHO TRS No. 961, Annex 7
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
   Short name: WHO TRS No. 961, Annex 9
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

   Short name: WHO TRS No. 943, Annex 3
   http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

   Short name: WHO TRS No. 961, Annex 2
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

   Short name: WHO TRS No. 981, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

   Short name: WHO TRS No. 981, Annex 3
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

   Short name: WHO TRS No. 961, Annex 14
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

   Short name: WHO TRS No. 992, Annex 3
   Short name: WHO TRS No. 992, Annex 4

   Short name: WHO TRS No. 992, Annex 5

   Short name: WHO TRS No. 992, Annex 6

   Short name: WHO TRS No. 996, Annex 3
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

   Short name: WHO TRS No. 996, Annex 5
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

   Short name: WHO TRS No. 996, Annex 10