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Prequalification Unit Inspection Services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Senador Laboratories Private Limited (formerly known as Mylan Laboratories Limited)
Corporate address of manufacturer	Plot 2B & 2C, Biotech Park, Phase II, Medchal Malkajgiri, Lalgadi Malakpet, Hyderabad, Telangana, India, 500101, INDIA
Inspected site	
Name & address of inspected manufacturing site	Plot No. 1606-1609, G.I.D.C., Sarigam, Taluka: Umbergaon, District: Valsad, Gujarat, 396 155, India GPS coordinates: 20.2999◦ N 72.8475◦ E D-U-N-S number: 862627630
Unit / block / workshop number	▪ Building I (manufacturing including production, packaging and quality control) ▪ Building II (packaging) ▪ Building III (Storage)
Manufacturing license number	▪ License number G/25/1476 issued by Food & Drugs Control Administration Gujarat State on 23 February 2024 and valid through 22 February 2029. ▪ License number G/28/1072 issued by Food & Drugs Control Administration Gujarat State on 23 February 2024 and valid through 22 February 2029. ▪ GMP certificate number 22063369 issued by Food & Drugs Control Administration Gujarat State on 15 June 2022 based on the inspection carried out on 21 – 22 April 2022 and 09 June 2022. The certificate is valid through 14 June 2025.
Inspection details	
Dates of inspection	3, 4 and 7 October 2024
Type of inspection	Routine inspection
Introduction	
Brief description of the manufacturing Activities	Senador Laboratories Private Limited, Sarigam facility is engaged in the manufacturing of oral contraceptive pills (i.e., hormonal oral solid dosage forms), placebo tablets and ferrous fumarate tablets for women's healthcare. The facility has dedicated and segregated areas for oral contraceptive pills manufacturing, placebo/ferrous fumarate Tablets manufacturing, including packing, quality assurance, quality control, and release, as well as a warehouse for raw materials, packaging materials, and finished goods. The site comprises a total plot area of about 10530 m^2 and a built-up area of about 10764 m^2.

<table>
<tr><td>General information about the company and site</td><td>Senador Laboratories Private Limited (formerly known as Mylan Laboratories Limited) is a group of lnsud Pharma. lnsud Pharma is a leading Spanish multinational pharmaceutical company. With head offices located in Madrid, Lugano and Buenos Aires, lnsud Pharma has built a broad, balanced manufacturing and sales network. Senador Laboratories Private Limited has its Corporate registered Office located at Hyderabad, Telangana and has its manufacturing sites located at Sarigam and Ahmedabad in India. Senador Laboratories Private Limited, Sarigam, is about 19 km away from Vapi railway station and approximately 170 km from Mumbai International Airport.

Historically, the site name and ownership have been changed several times over the years since 1999. Former names/owners of the site included:
▪ Phimex International (before 1999),
▪ Famy Care (1999 – April 2015),
▪ Jai Pharma (April 2015 – November 2015),
▪ Mylan Laboratories Limited (November 2015 – November 2020),
▪ Viatris (November 2020 - October 2023),
▪ Senador Laboratories Private Limited (From October 2023).</td></tr>
<tr><td>History</td><td>Four earlier on-site WHO inspections were performed in 2011, 2014, 2016 and 2021. The last WHO inspection concluded that the site was compliant with GMP after the completion of the necessary CAPA in response to the few raised “other” deficiencies.

The site was inspected by the following authorities:
<table>
<tr><th>Regulatory / Health Authority</th><th>Year</th></tr>
<tr><td>World Health Organization (WHO), Geneva</td><td>2011, 2014, 2016, 2022</td></tr>
<tr><td>Food and Drug Control Administration (FDCA), Gujarat, India</td><td>2011, 2014, 2017, 2019, 2022</td></tr>
<tr><td>National Institute of Pharmacy and Nutrition (NIPN), Hungary</td><td>2020</td></tr>
<tr><td>Therapeutic Goods Administration (TGA), Australia (desktop assessment)</td><td>2020, 2023</td></tr>
<tr><td>National Drug Authority (NDA) - Uganda</td><td>2013, 2019, 2024</td></tr>
<tr><td>TMDA - Tanzania</td><td>2012, 2024</td></tr>
<tr><td>Food and Drug Administration, Philippines</td><td>2023</td></tr>
<tr><td>Liberia Medicines & Health Products Regulatory Authority (LMHRA), Liberia</td><td>2023</td></tr>
<tr><td>Medicines Control Authority of Zimbabwe (MCAZ)</td><td>2017, 2022</td></tr>
<tr><td>Ministry of Health, Pharmacy and Poisons Board (PPB), Kenya</td><td>2015, 2021</td></tr>
<tr><td>FMHACA, Ethiopia</td><td>2021</td></tr>
<tr><td>Health Canada</td><td>2013, 2019</td></tr>
<tr><td>Ministry of Health, Cambodia</td><td>2019</td></tr>
<tr><td>National Authority of Medicines and Health Products (NAMHP), Infarmed, Portugal</td><td>2010, 2014, 2017</td></tr>
</table></td></tr>
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	US FDA	2012, 2016
	MCC - South Africa	2009

Major changes since the last WHO inspection

A few major changes were introduced since the last WHO inspection, including:

- **Company name**: from Mylan Laboratories Limited to Senador Laboratories Private Limited.
- **Key electronic systems**

Mylan System	Insud Pharma System
D2 (EDMD2) Documentum	TrackWise Digital System - Document Management System (DMS)
MyUniversity (Learning Management System)	TrackWise Digital System - Training Management System (TMS)
TrackWise System (EQMS)	TrackWise Digital System – EQMS and Audits

- **Facility**:
  - Construction of new effluent treatment plant (ETP) block, utility block (filter cleaning & drying area, OHC), underground Fire hydrant tank, and change rooms at building 2, solvent store, HR office, and scrap area.
  - Demolition of old ETP block, filter cleaning & filter drying area, OHC Room, overhead fire hydrant, change rooms at building 2, solvent store, HR Office, and scrap area.
- **Equipment/Instruments**:
  - Production: Replacement of existing compression machine with new compression machine (Like to Like change) at 1st Floor OCP Compression-I area.
  - Quality Control: installation of new "Dissolution Test Apparatus" (Make: Lab India, Model: DS14000).
- **Personnel**:
  - Change of the Head of Quality.
  - Change of the Lead IT.

Brief report of inspection activities undertaken – Scope and limitations

Areas inspected

The following GMP subjects were covered during the inspection:

1. Pharmaceutical quality system
2. Good manufacturing practices for pharmaceutical products
3. Sanitation and hygiene
4. Qualification and validation
5. Complaints
6. Product recalls
7. Contract production, analysis and other activities
8. Self-inspection, quality audits and suppliers' audits and approval
9. Personnel
10. Training
11. Personal hygiene
12. Premises
13. Equipment

	14. Materials 15. Documentation 16. Good practices in production 17. Good practices in quality control
Restrictions	N/A
Out of scope	Products and facilities not related to WHO prequalification
WHO products numbers covered by the inspection	▪ **RH013:** Ethinylestradiol/Levonorgestrel (1 Tablet, Sugar coated 30mcg/150mcg) ▪ **RH035:** Ethinylestradiol/Levonorgestrel (1 + Placebo Tablet, Sugar coated 30mcg/150mcg + 0mg) ▪ **RH038:** Ethinylestradiol/Levonorgestrel (1 + Ferrous Fumarate 30mcg/150mcg + 75mg)
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CFU	Colony-forming unit
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
GPT	Growth promotion test
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MFT	Media fill Test
MR	Management review
NC	Non conformity

NCA	National control authority
NCL	National control laboratory
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

Part 2	**Summary of the findings and comments**

1. Pharmaceutical quality system

Senador Laboratories established a quality policy that describes the company's overall intentions and direction regarding quality. The site quality manual was reviewed. The manual covered, among other things, quality policy, quality responsibilities, organization, documentation hierarchy, quality principles, and system functions.

The Head of Quality was responsible for evolving, implementing and monitoring activities having an impact on the quality of the product. The Head of Quality operated independently of the Site Manager. The former reported to Corporate Quality and Compliance, while the latter reported to Corporate Operations. The Head of Quality led the Quality Unit at the site. The Quality Unit comprised the Quality Assurance and Quality Control , which were independent from Manufacturing and authorized to take appropriate decisions on quality matters.

The quality system was supported by adequate quality documentation system, including technology transfer documents, batch manufacturing records, batch packing records, raw materials, in-process, packaging materials and finished product specifications.

A procedure for the management of data integrity and data governance was in place. The document guided data integrity aspects, including data lifecycle and data integrity risk assessment (DIRA). The DIRA of granulation, testing and product release were spot-checked.

The change management procedure ensured control over changes to documents, procedures, specifications, materials, equipment, systems, facilities, and products. The procedure guided the classification of the proposed changes based on the evaluation of their impact on product quality into 3 categories, namely major, moderate, and minor changes. The SOP also provided for permanent changes, "changes that are permanent in nature and that might affect validated status or regulatory compliance," and temporary changes, "changes that are isolated events having no regulatory impact that is evaluated prior to change being implemented with no prior intent to make it a permanent change". Change control management (initiation, approval, implementation, documentation, and closure) was carried out in the TrackWise digital system as per the procedure defined in the respective SOP. After the implementation of the change, a CC effectiveness check was required to be performed for moderate and major changes.

A list of changes for the years 2023 and 2024 (year to date) was reviewed and several changes were spot-checked.

Quality risk management

The concepts and principles of QRM were well employed in different areas of operations including production, control, and storage. The SOP for QRM was well in place. The procedure provided for initiation, evaluation, assessment and control of risks along with risk communication and documentation. The procedure also provided guidance on two main types of risk assessments, namely planned quality risk assessment (proactive), conducted in advance of the operations to mitigate or eliminate the relevant risks, and unplanned quality risk assessment (retrospective), conducted after an activity has occurred. Various tools were used for QRM, including Failure Mode Effect Analysis (FMEA), Risk Ranking and Filtering, Fault Tree Analysis, Hazard Operability Analysis (HAZOP), Hazard Analysis and Critical Control Points (HACCP). The planned quality risk management register was reviewed and a couple of risk assessments were spot-checked, namely QRM of manufacturing and packaging operations and QRM of reference and working standards management.

Product quality review

The SOP for APQR was in place. The product quality review was conducted on an annual rolling period basis, as applicable, for all approved and commercialized drug products that were manufactured at the site. The APQR of the year 2024 was reviewed and found acceptable. The APQR included trending of the process parameters, critical quality attributes and stability data as well as marketing authorization variations/ regulatory submissions, post-marketing commitments, regulatory authority notifications, raw materials and packing materials, quality events (incidents, deviation and OOS), batch rejections, complaints, recalls, returns and change controls.

2. Good manufacturing practices for pharmaceutical products

Manufacturing practices were clearly defined and reviewed in accordance with operating procedures. There were no issues regarding resources, as a sufficient number of appropriately trained personnel were employed. The premises were well-equipped with appropriate equipment, and qualification and validation were generally in place. Laboratories were equipped with the required instruments to

perform the necessary tests. Proper storage for raw materials and finished products was in place. Records for manufacturing operations were available.

3. Sanitation and hygiene

Generally, good sanitation and hygiene practices were applied throughout the facility. The facility and equipment were cleaned in accordance with approved operating procedures. Hand washing and sanitization facilities were provided for all personnel.

The cleaning procedure for the fluid bed processor was reviewed. The SOP was detailed and included the cleaning of the inner duct for the exhaust and the air inlet. It also discussed the disassembly process, as well as the cleaning of gaskets and seals. A cleaning checklist with pictures and status, verified by production, was incorporated into the documentation. Additionally, a shorter checklist for visual cleaning checks, completed by production and IPQC, was available. This checklist was cross-referenced in the batch processing records for ferrous fumarate tablets. A signature list was included as part of the batch documentation.

The design of the fluid bed processor included a 10.0 µ filter, a fine filter (3.0 µ), and a HEPA filter (0.3 µ). Although there was no filter for outgoing air, this is mitigated by the fact that ferrous fumarate is a low-risk product.

The usage and cleaning procedure for the In-Process Container [IPC] indicated that after unloading the lubricated blend, the IPC wheel and outer surface were cleaned before transferring the blend to the storage area from the blending area.

4. Qualification and validation

The VMP was in place. The VMP provided guidance on validation and qualification activities, including the approaches and methodology for qualification of facility, equipment, instrument, processes, calibration, and revalidation. The 2024 validation and qualification planners were reviewed and spot-checked.

Periodic review schedules of computerized systems in production and QC areas were checked.

Temperature mapping for the post dispensing hold area was reviewed. The number of data loggers used was based on the size of the room, with eight data loggers utilized in this case. Calibration certificates for these data loggers were available and confirmed to be compliant. The data loggers were placed in the middle, top, and bottom areas across the entire room. The acceptance criteria were set at 22°C ± 5°C and relative humidity (RH) NMT 60%. Hot and cold spots were identified, and permanent data loggers were placed at these points.

5. Complaints

The SOP for complaint management was in place. The SOP provided for notification of health authorities in case of critical complaints, which were suspected to result in a potential serious risk to patients, and/or which may result in product recall. The SOP indicated three categories of complaints, namely (1) critical complaints [e.g., the wrong active ingredient, non-compliance with specifications]; (2) major complaints [e.g., unusual odor, discolored alveoli (blister pocket)]; and (3) minor complaints [e.g., minor typographical errors in labeling]. The complaint management process involved complaint creation, logging the complaint in TrackWise® digital system, complaint evaluation, including initial

classification, investigation, retain sample assessment, review of the APQR, complaint sample retrieval and assessment, root cause determination, along with CAPA (if applicable) and final conclusion. The complaint documentation process involved a complaint report, complaint approval, and complaint closure. The timeline indicated in the mentioned SOP for complaint investigation was 30 calendar days. If the complaint required additional time, the complaint coordinator had to communicate a preliminary investigation report to the complainant.

A couple of major complaints were reviewed. As part of the investigation of these complaints by the inspection team, the following activities were performed:

- Review of the batch packing records of the relevant product batches. The camera inspection challenge test was verified and no abnormalities were observed. The challenge test was conducted at the beginning of the process and every two hours thereafter.
- The SOP for the blister inspection system was reviewed.
- Retention room was visited and the concerned batches were checked.
- The relevant packaging process validation protocol of and packaging process validation report were reviewed. The packaging PV involved three different speeds (low speed, optimum speed and high speed) at three different temperatures (low temperature, optimum temperature and high temperature of the sealing roller). The process was concluded as being validated.
- Review of the packaging material release specifications of PVC film-coated and printed foil.
- Packaging material suppliers of the above-mentioned PVC film and printed foil were reviewed and found to be included within the approved vendors list.
- Suppliers' qualification of the PVC and printed foil suppliers were reviewed.
- Blister inspection system requalification reports on lines III and IV.
- The initial operational qualification report of the blister inspection system of line III was reviewed.
- The initial performance qualification report of the blister inspection system of line III was reviewed.
- Initial operational qualification report of the blister inspection system of line IV was reviewed.
- Initial performance qualification report of the blister inspection system of line IV.
- Requalification report of the blister pack machine of the blistering machine at line III.
- The computer system validation of the camera inspection system of line III was reviewed.
- The SOP for risk assessment of computerized systems and the SOP for periodic review of GxP computerized systems were reviewed.
- Observation of the challenge test by the operators.
- Complaints trend analysis for the years 2023 and 2022 were reviewed.
- The SOP for preventive maintenance of the blistering machines was reviewed.
- The machine breakdown log was checked, and four incidents were spotted.

Another minor complaint was reviewed.

6. Product recalls

The SOP for product recall and withdrawal was in place. No recall was needed over the last years. The SOP provided for mock recall on an annual basis per region/continent.

7. Contract production, analysis and other activities

Senador laboratories maintained several approved supplier lists, including API, packing materials, excipients and printed packing materials and consumables for QC and Microbiology Laboratories. Suppliers were evaluated through onsite audits for APIs, excipients, and packaging materials. The global audit unit was responsible for auditing APIs, while Senador conducted audits for excipients and packaging materials.

Vendor Management was discussed. Onsite inspections were typically conducted for the following scenarios: new material from a new or existing vendor, existing material from a new vendor, change in the manufacturing site of a vendor, change in the route of synthesis of material, resumption of vendors after suspension/disqualification, including API manufacturers, printed packaging materials manufacturers, primary packaging material manufacturers, excipient manufacturers (only those with a high-risk profile as per excipient risk assessment), and suppliers performing re-packing activities. These inspections were conducted every three years, not exceeding four years.

The procedure described the disqualification criteria which included commercial reasons, results of annual evaluation, import alerts/warning letters for major regulatory non-compliances issued to the vendor by the RA, risk assessment reports, confirmed critical customer complaints due to materials supplied to Senador and recommendations by the Quality Head.

The audit schedule was reviewed. This was controlled by SAP, preventing any orders from being placed for the affected material codes until the suppliers were re-audited, however it was confirmed that alternative suppliers were available for the materials in question. Printed Packaging material Audit Tracker was reviewed.

Contracts with several API suppliers were in place, including contracts with Bayer AG for Levonorgestrel and Ethinylestradiol.

Although all technical agreements were still under the name of Mylan, a process was underway to transfer all technical agreements to Senador. The responsibilities of both the contract giver and the contract acceptor were clearly specified.

The audit reports for the suppliers of PVC and foil were thoroughly reviewed to ensure compliance.

PVC Supplier:
The audit of this supplier was conducted through a desktop review due to travel restrictions imposed following the COVID-19 pandemic. The supplier was approved based on the findings of the desktop audit. The audit confirmed that the supplier met the necessary compliance and quality standards and observations were noted and promptly addressed by the supplier.

Foil Supplier:
The supplier was audited remotely. The audit was performed against ISO 15378:2017 and ISO 9001:2015.

Both aforementioned suppliers' audits were conducted by the global team of Insud Pharma (the mother company of Senador Laboratories), ensuring that the suppliers met the required quality and compliance standards. The findings from these audits were discussed in detail.

As part of the approval process, several documents were reviewed in addition to the audit such as certificate of compliance for foils, declaration for nitrosamine alu-alu laminates, plain aluminum, printed products, elemental impurity (declaration), finish goods certificates, residual solvents and TSE/BSE certificates.

In addition to material suppliers, the list of external service providers was reviewed and included contract validation services, calibration, pest and rodent control, etc.

Contract Laboratories
The responsibilities of the contract giver and acceptor were clearly specified.

8. Self-inspection, quality audits and suppliers' audits and approval
The self-inspection procedure was reviewed. It stated that a dedicated QA person would prepare the self-inspection plan annually in the Trackwise Digital System, which would be approved by the Site Quality Head/Designee in the first month of the year.

Self-inspections were conducted by a team consisting of a lead auditor and a co-auditor, both of whom must be certified quality personnel. Certification of self-inspectors was performed by the Head of Quality Assurance/Designee. The list of certified inspectors, along with their certification dates, included personnel from various departments such as production, QA, engineering, QC, and the warehouse.

Observations were classified as critical, major, minor, or recommendations. The CAPA plan was maintained in Trackwise electronic system, with tasks sent through notifications to the appropriate person.

Checklists for each department were reviewed and covered aspects such as data integrity, personnel, and training, amongst others.

9. Personnel
The company ensured that an adequate number of personnel with the necessary qualifications and practical experience were employed. Several organization charts were presented and reviewed, clearly delineating the separation between production and quality assurance.

Job descriptions
Individual responsibilities were clearly defined and documented as written job descriptions. Several job descriptions were reviewed. For key positions, delegated personnel were appointed, and the required experience and qualifications for each position were listed. The following job descriptions were reviewed and found to be acceptable: Site Director - Production, General Manager of Production, Head of OSD Quality, and Head of Quality Control. Four personnel had release responsibility, including the Quality Head, Head of Quality Assurance, Assistant Manager QA, and Manager QA.

10. Training

The SOP for the training of personnel outlined the various types of training, including:

- Induction
- Introductory training
- Job-specific training-1 (functional and cross-functional training required for the employee to perform their primary activities)
- Job-specific training-2 (functional and cross-functional training to create general awareness for the employee, not directly linked to primary activities)
- Planned training programs
- GxP Training
- Unplanned training
- External training
- Retraining

The training was managed through the "My University" e-learning system. Trainers were required to be qualified and approved to conduct training. Training records for several operators, analysts, and microbiologists were reviewed and found to align with their job descriptions. Additionally, on-the-job training was conducted and assessed using checklists completed during observations.

On the Job Training Form for the coating solution preparation was checked, and the completed and signed checklist for an Operator as part of the on-the-job training assessment was reviewed.

The certification of microbiologist (SOP-000461218) involved three phases:

- Phase 1: Interaction with the Microbiologist
- Phase 2: Observation of the activity
- Phase 3: Certification, which included observing three tests: Microbial enumeration tests, tests for specified organisms, and identification of microflora.

The Microbiologist trainer/supervisor completed the Phase 3 checklist observing activities and comparing them with documented procedures to ensure the actual test procedures were followed.

Qualification for Visual Inspectors was discussed with the company. A list of qualification dates and re-qualification due dates was available for all the visual inspectors.

The operating procedure listed and described several defects (critical, major, and minor) supported by the pictures provided. These defects included:

- Foreign particles on tablets
- Wrong embossing details
- Heat-deformed blisters
- Missing embossing details
- Improper sealing
- Improper I-Mark
- Damaged tablets
- Rough surface on tablets
- Duplex tablets

- Defaced tablets
- Deformed tablets
- Hairline cracks in tablets
- Broken tablets
- Discolored blisters
- Newly observed or identified defects are added as they are discovered.

The inspection kit used for qualification contained 500 good blisters and 80 defects, with at least 2 of each type of potential defect.

The Protocol for qualification of blister inspector on the blister packaging line was available and reviewed. It listed the defects and explained how the kit was to be prepared. The acceptance criteria were 100%, with three qualifications or re-qualifications required every year.

11. Personal hygiene

Health examinations prior to employment and thereafter were addressed in the SOP for personal hygiene and sickness reporting. Personnel performing visual inspections were required to undergo eye tests on regular basis. Hand washing facilities were available at the entrance of the facility, with hand sanitization stations located at various gowning areas.

Personnel working in production areas were provided with appropriate gowning, as outlined in the procedure for entry and exit of employees. No eating, drinking, smoking, or chewing was observed in the production facility.

In rooms where hormonal active pharmaceutical ingredients were handled up to the coating stage, operators donned pressure suits connected to a central compressed breathing air system. Test results for an operator, specifically hormone testing, were reviewed and all results indicated normal levels.

12. Premises

The premises of Senador Laboratories comprised three buildings namely building 1, building 2 and building 3. The manufacturing activities at each building are below summarized.

Building	Floor	Activity
Building 1	Ground floor	oral contraceptive pills (OCP) manufacturing
		lactose granules, ferrous fumarate tablets / placebo tablets manufacturing
		raw material storage, finished goods storage and service floor
		ETP block, utility block, Occupational Health Centre (OHC), offices
	First floor	oral contraceptive pills (OCP) manufacturing and packaging lines
		lactose granules and placebo tablets manufacturing
		raw material storage and packing material storage
		quality control laboratory
	Second floor	excipients storage
		quality assurance office, engineering office
		purified water system, service floor
Building 2	Ground floor	packaging lines and primary packing material storage
	First floor	retain samples, pm testing, stability area, training hall and service floor
Building 3	Ground floor	excipients storage, finished goods storage and conference room

First floor	secondary packing material storage, documents storage room and offices
Second floor	tertiary packing material storage and documents storage room

In general, the premises were fit for the production and control activities. The facility was dedicated to the manufacture of oral contraceptive pills (OCP) along with the associated placebo or ferrous fumarate as applicable. The placebo and ferrous fumarate pills were manufactured in dedicated areas apart from those used for the manufacture of OCP. The facility provided linear movement of material at different production areas. The hormonal active pharmaceutical ingredients were stored, sampled, and dispensed in dedicated areas at the production suites, rather than the warehouses for safety reasons.

The OCP production areas were served by two breathing air units. The breathing air system was designed to supply "breathing quality" compressed air to enable personnel wearing Supplied Air Respirator (SAR) or respirators to enter and work in hormone contaminated or potentially contaminated areas of the plant.

Trends of the environmental monitoring covering the period from January to December 2023, testing of the water for pharmaceutical use covering the period from January to December 2023 were reviewed.

13. Equipment

Equipment used in the manufacturing, including production and control, were of appropriate design, adequate size, and suitably located to facilitate operation for their intended use, cleaning and maintenance. All the equipment in use was qualified as per the respective procedures. The major processing equipment in the manufacturing area included vibratory sifters, paste preparation vessel rapid mixture granulator, fluid bed processor, multi-mill, double cone blender, compression machine coupled with de-dusters and metal detectors, auto-coater, inspection belts, blister packing machine, cartonator, checkweigher, and serialization and aggregation system or track and trace system.

An annual preventive maintenance plan of equipment was drawn out and routine maintenance including, lubrication of machine and its parts were done accordingly. The maintenance department was responsible for carrying out preventive maintenance as per the established schedule. Records of preventive maintenance jobs were maintained in SAP by the maintenance department and the same were spot-checked for the blistering line III and IV. The SOP for preventive maintenance of the blistering machines was reviewed.

The machine breakdown log in SAP was checked and four incidents were spot-checked.

The Quality Control department has been provided with all necessary equipment and instruments including HPLC, UPLC, UV-visible spectrophotometer, dissolution test apparatus, FTIR spectrophotometer, KF Titrator, gas chromatography, stability chamber, and particle size analyzer. The microbiology laboratory, on the other hand, was equipped with a laminar flow clean air workstation, biosafety cabinet, autoclave, dry heat ovens, incubators maintained at 20 – 25°C, 30 – 35°C, 42 – 44°C and 55 – 60°C, sampling devices including those for environmental monitoring and deep freezer and cooling cabinet for preservation of cultures and media.

Preventative Maintenance

Preventative maintenance was managed in SAP. When new equipment was received, a transaction code was required to schedule preventative maintenance activities in SAP. Generally, these actions were set on a quarterly basis. The system automatically generated manual checklists, which were completed by the maintenance personnel and supervisors. Upon completion, maintenance persons and supervisors signed the checklists and the information was transcribed into the SAP system.

The register on the system was reviewed, and no outstanding preventative actions were observed. The latest preventative maintenance for the fluid bed processor was reviewed. The operation of the inlet volume control damper was confirmed to have been checked.

14. Materials

Incoming raw materials and packaging materials were received and quarantined in accordance with the receipt, identification, storage, and movement of raw and packaging materials in the warehouse. The consignment had to be verified against the approved supplier list, and the following checklists were required to be completed: “vehicle checklist”, “observation on consignment of packaging material”, and “observation on pack”.

A process was in place for verifying the weight, dedusting containers, and preparing a Goods Receipt Note (GRN), after which the materials were immediately taken to the applicable storage areas. Shellac (excipient for coating solution) was stored between 8°C - 15°C and transferred immediately after receipt and GRN generation.

Quarantine was maintained in the SAP system, and release was performed for raw materials by QC in the SAP as well. When picking materials for a production order, a radio frequency (RF) gun was used to scan the materials.

Sampling and dispensing for APIs were conducted in production areas designated for oral contraceptive pills (OCP) in two common sampling/dispensing areas. Excipient sampling was performed in two sampling rooms at the warehouse (one on the ground floor and one on the first floor of building 1), while ferrous fumarate sampling/dispensing took place in a dedicated common area within the warehouse, which had separate material and personnel airlocks.

Sampling was carried out by QC upon receipt of a GRN note. There was 100% sampling for both excipients and API raw materials from each container, and 100% sampling for all other tests, performed in accordance with test specifications. These samples were pooled in accordance with the P-plan. Samples were taken using SS sampling tools.

Sampling and dispensing of primary packaging material occurred on the first floor of Building 1 and the ground floor of Building 2, in accordance with the respective SOP. Sampling was conducted up to 100 containers, after which the $\sqrt{n}+1$ was applied.

QC release was performed in accordance with the procedure for analysis and release of raw materials and packaging materials. Approval was given in the laboratory information management system (LIMS).

The procedure for returned goods and salvaged drug products outlined the conditions under which returned goods could be accepted or rejected. It was the joint responsibility of the production and QA teams to investigate and identify the root cause. Products could only be reworked and redistributed if they had been stored under appropriate conditions and had passed all testing. The investigation had to consider the following aspects: analysis of samples for identity, strength, quality, and purity; review of storage and packaging conditions; examination of labeling; and assessment of potential tampering, counterfeiting, physical or chemical degradation, and adulteration not detected during visual inspection.

No retesting was permitted after the expiry date or the manufacturer's retest date. This was managed through the SOP for retesting of raw materials and packaging materials. This SOP pertained only to retesting within the shelf-life. Retesting was to be conducted annually for APIs, biennially for excipients, and every six months for lactose. If a failure occurred during these tests, an Out of Specification (OOS) was raised, and the standard OOS process was followed.

Reprocessing and reworking were governed by a dedicated procedure. Reprocessing was not allowed; only reworking, which was defined as repacking of secondary packaging, like carton, pouch, or tertiary packaging. QA approval of repacking documents was required, and stability considerations were necessary.

Nitrosamine Assessment
Confirmation of no risk of nitrosamine presence was identified. For the product, Zinnia P, containing Levonorgestrel and Ethinylestradiol tablets (150 mcg and 30 mcg), the risk assessment included the Nitrosamine questionnaire, which showed no risk. The production process flow, including ingredients and packaging materials, as well as declarations from API manufacturers, were considered.

Hold time studies were performed in accordance with the procedure outlined in the hold time study program. The hold time study protocol for dispensed raw material was spot-checked.

An assessment was conducted using a matrix, considering characteristics such as hygroscopicity, support for microbial growth, natural/animal/plant origin, and potency. The materials chosen were as follows:

- API: Ethinyl Estradiol, due to its high potency.
- IPI: Magnesium Stearate, Acacia, and Maize Starch are considered worst-case based on the criteria.

The report was reviewed and all results were within the specified limits.

Hold time study protocol for Lubricated granules, compressed and coated tablets of ferrous fumarate tablets 75 mg was reviewed. The Manufacturing process included sifting, granulation, drying, lubrication, compression, coating, and final packaging. Stage-wise hold time study involved simulated container. Sampling quantities for each test and timeline were outlined in the document. All results were within the specified limits.

15. Documentation

All documents were well designed, prepared, and reviewed as applicable. Systems for issuing documents in a controlled manner were in place, and no superseded documents were observed to be in use during the inspection. Records were generally made or completed at the time of action and were readily available upon request.

The procedure for assigning batch number to materials and products was reviewed. The batch number was automatically generated in the SAP system when the process order was submitted by the supply chain. The batch number was then printed by QA on the batch manufacturing and packaging instructions. The issue log for the batch manufacturing record (BMR) and the verification register was available. Each stage of manufacturing was issued a separate batch instruction, which was verified by QA to ensure batch numbers were not re-issued. The batch number for the packaging part became the final product (FP) batch number. Registers were reviewed and found to be adequate.

Batch processing records were maintained for each part of the batch processed, as well as for batch packaging. The batch processing record for one batch of Ferrous Fumarate was reviewed. The hold times for the different steps were checked and confirmed not to exceed the specified limits.

In general, the batch records were comprehensive, with all relevant information recorded or affixed to the batch processing records.

16. Good practices in production

Production operations followed defined procedures. Deviations from instructions and procedures were recorded and investigated. Checks, yields, and reconciliation of printed packaging materials were calculated and recorded in batch manufacturing records. Dedicated sampling, dispensing, and manufacturing areas were available for OCP and ferrous fumarate tablets. Rooms, packaging lines, and equipment were appropriately labelled, indicated statuses, product or material being processed, batch number, and strength. Access to production rooms was restricted to authorized personnel only.

The ferrous fumarate manufacturing process occurred mainly in one room, including sifting, blending, and granulation. Material was primarily transferred manually into different equipment for each processing step. Line clearances were performed and recorded. Equipment cleaning was conducted within the processing area, with Type A cleaning performed between batches in a campaign and Type B cleaning before starting a new campaign.

The filter bags and sieves used for the production of ferrous fumarate were inspected before use and after cleaning. Compression and coating of ferrous fumarate tablets occurred in separate areas. The punches and dies were cleaned, maintained, and issued in accordance with written procedures. The punch and die log was reviewed, and no issues were cited. Hold times were determined and validated.

17. Good practices in quality control

The Quality Control department operated as an independent department responsible for physical, chemical and microbiological testing (wherever applicable) of raw/packaging materials, in-process controls, stability studies and finished products testing. All materials incoming to QC for testing were sampled in accordance with a set sampling plan and were given a unique analytical report number. The analytical testing, for the raw material, packaging materials, in-process control, stability study, finished

products were allocated to an analyst by the Section Head. All analyses were recorded in analytical worksheets, which were checked by the reviewer and the responsible supervisor.

The SOP for batch release was in place. Four persons had the right to perform batch release as per an established list of responsible releaser persons. Criteria for batch release personnel included a minimum of graduate qualification (science or pharmacy) and a minimum of 5 years' experience, along with training on batch release procedure.

The SOP for Empower 3 chromatography 3 data software application was in place for the management of the software of HPLC instruments. The SOP stated that the manual integration was not allowed. However, the same SOP was provided for what was called "force integration". Force integration meant that the analyst could set the integration parameters. The SOP also mandated the operator in the latter case to obtain approval of the senior management (Head QA or designee). The user privileges of the analysts at the laboratory included the possibility to alter the integration parameters. The SOP also required a brief audit trail to be completed by the QC reviewer after each analysis. The brief audit trail report included check of force peak integration event.

The procedure for Analytical Method Validation and the SOP for analytical method verification of compendial methods were in place. The AMV report of the determination of residual solvent in ethinyl estradiol sourced by one supplier was spot-checked.

The SOP for laboratory investigation report was in place. The SOP provided for phase I and phase II investigation involving quality control and manufacturing activities. The list of OOS in 2023 was reviewed and some OOS were spot-checked.

The SOP for stability studies was in place. The SOP provided for stability studies documentation in terms of stability protocols, selection of batches for inclusion in the stability testing program, sampling, labelling and charging of batches for stability testing. The mentioned SOP, along with the SOP for communication of critical quality events, guided the notification of the regulatory authorities in case of OOT/OOS results related to the stability monitoring program.

A Report to establish the validity of ethinyl estradiol USP/Ph. Eur. working standard when stored below 25°C in a desiccator and opened/closed multiple times over 15 days was reviewed. For shelf-life confirmation, tests were performed on 5 batches at the end of their labelled shelf-life. The receiving and issuing of primary and working standards were maintained in the LIMS.

Verification of Test Glassware: Glassware was randomly selected for verification.

Part 3	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, ***Senador Laboratories Private Limited (Sarigam) [formerly known as Mylan Laboratories Limited]*** located at ***Plot No. 1606-1609, G.I.D.C., Sarigam, Tal-Umbergaon, Dist. Valsad, Gujarat, 396 155, India*** was considered to be operating at an acceptable level of compliance with WHO guidelines on 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 4	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-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   Short name: WHO TRS No. 986, Annex 2
   https://www.who.int/publications/m/item/trs986-annex2

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
   https://www.who.int/publications/m/item/annex-2-trs-957

3. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9.
   Short name: WHO TRS 1010, Annex 9
   https://www.who.int/publications/m/item/trs1010-annex9

4. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3.
   Short name: WHO TRS No. 1033, Annex 3
   https://www.who.int/publications/m/item/annex-3-trs-1033

5. 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
https://www.who.int/publications/m/item/annex-4-trs-929

6. WHO good practices for pharmaceutical quality control laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-seventh Report. Geneva, World Health Organization, 2024 (WHO Technical Report Series, No. 1052), Annex 4.
Short name: WHO TRS No. 1052, Annex 4
https://www.who.int/publications/i/item/9789240091030

7. 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 3.
Short name: WHO TRS No. 957, Annex 3
https://www.who.int/publications/m/item/trs957-annex3

8. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8.
Short name: WHO TRS No. 1010, Annex 8
https://www.who.int/publications/m/item/Annex-8-trs-1010

9. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1019), Annex 2.
Short name: WHO TRS No. 1019, Annex 2
https://www.who.int/publications/m/item/trs1019-annex2

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 4.
Short name: WHO TRS No. 1044, Annex 4
https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1044-annex4-technology-transfer-in-pharmaceutical-manufacturing.pdf

11. WHO good manufacturing practices for sterile pharmaceutical products. Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 4.
Short name: WHO TRS No. 1044, Annex 2
https://www.who.int/publications/m/item/trs1044-annex2

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***
https://www.who.int/publications/m/item/trs943-annex3

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
https://www.who.int/publications/m/item/trs961-annex2

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
https://www.who.int/publications/m/item/trs981-annex2

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
https://www.who.int/publications/m/item/annex-3-trs-981

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
https://www.who.int/publications/m/item/tr961-annex14

17. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3.
Short name: WHO TRS No. 1019, Annex 3
https://www.who.int/publications/m/item/trs1019-annex3

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
https://www.who.int/publications/m/item/trs992-annex4

19. 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
https://www.who.int/publications/m/item/trs961-annex9-modelguidanceforstoragetransport

20. 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
https://www.who.int/publications/m/item/trs992-annex5

21. WHO Recommendations for quality requirements when plant – derived artemisinin is used as a starting material in the production 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
https://www.who.int/publications/m/item/trs-992-annex-6

22. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4.
Short name: WHO TRS No. 1033, Annex 4
https://www.who.int/publications/m/item/annex-4-trs-1033

23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10.
Short name: WHO TRS No. 996, Annex 10
https://www.who.int/publications/m/item/trs966-annex10

24. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10.
Short name: WHO TRS No. 1010, Annex 10
https://www.who.int/publications/m/item/trs1010-annex10

25. Points to consider when including Health-Based Exposure Limits in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2.
Short name: WHO TRS No. 1033, Annex 2
https://www.who.int/publications/m/item/annex-2-trs-1033

26. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6.
Short name: WHO TRS No. 1025, Annex 6
https://www.who.int/publications/m/item/trs-1025-annex-6

27. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3.
Short name: WHO TRS No. 1025, Annex 3
https://www.who.int/publications/m/item/trs-1025-annex-3-water-for-injection

27. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS No. 1025, Annex 4
https://www.who.int/publications/m/item/trs1025-annex4

28. Good trade and distribution practices for pharmaceutical starting materials. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 6.
Short name: WHO TRS No. 996, Annex 6
https://www.who.int/publications/m/item/annex-6-trs-996

29. WHO guidelines for preparing a laboratory information file. *WHO Expert Committee on Specifications for Pharmaceutical Preparations.* Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 13.
Short name: WHO TRS No. 961, Annex 13
https://www.who.int/publications/m/item/trs961-annex13

30. WHO good manufacturing practices for excipients used in pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-seventh Report. Geneva, World Health Organization, 2024 (WHO Technical Report Series, No. 1052), Annex 1.
Short name: WHO TRS No. 1052, Annex 1
https://www.who.int/publications/i/item/9789240091030