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

Part 1	**General information**
Manufacturers details	
Name of the manufacturer	Eisai Pharmaceuticals India Pvt. Ltd.
Corporate address of the manufacturer	Plot No. 96, 97, 98, 124 & 126, Visakha Pharmacity Limited (SEZ) Parawada – 531019 Anakapalli District, Andhra Pradesh India Phone: +91 8924 660777, +91 891 3047100 (24 hrs. contact number) Fax: +91 8924 660759. Website: www.eisai.co.in
Inspected site	
Name and address of the inspected manufacturing site, if different from that given above	**As above** **Geographical coordinates:** North latitude: 17°39'36.9" East longitude: 83°05'56.5"
Unit/block / workshop number	Bottle packing line, Drug product facility.
Inspection details	
Dates of inspection	24 – 28 March 2025
Inspection record number	Routine GMP inspection - FPP
Introduction	
Brief description of the manufacturing activities	Eisai Pharmaceuticals India Pvt. Ltd. (EIL) is an integrated facility that includes the manufacturing of Active Pharmaceutical Ingredients, Finished products, and R&D (with a pilot scale facility) within the same premises. The facility includes separate buildings for the manufacturing of oral solid dosage forms (Tablets) and Active pharmaceutical ingredients, along with adequate support services. The unit is located in the "Pharmaceutical Special Economic Zone" with surrounding units engaged in the manufacturing of API & Formulations Units. Adequate measures are in place to prevent the risk of contamination from open sewage, drains, public lavatories, or from disagreeable or obnoxious odors, fumes, excessive soot, dust, smoke, or chemical/biological emissions from nearby factories.
General information about the company and site	EIL is a 100% subsidiary of Japan-based Eisai Co., Ltd. for the manufacturing and marketing of drug substances and drug products. Eisai India's facility was established in 2009 to manufacture Drug Substances APIs, and Drug Products (Oral solid dosage forms- Tablets) for Human consumption only.

<table>
<tr><td></td><td>Eisai Co., Ltd. is a research-based human healthcare company that discovers, develops, and markets pharmaceutical products globally. The Company was established in 1941 and is headquartered in Japan.</td></tr>
<tr><td>History</td><td>In the last five years, the site has been inspected by the following authorities:
<table>
<tr><th>Name of the Authority</th><th>Dates of inspection</th><th>Scope of inspections (e.g. block, workshop etc. inspected)</th><th>Outcome of inspection</th></tr>
<tr><td colspan="4">2024:</td></tr>
<tr><td>FDA, US</td><td>26th - 30th AUG. 2024</td><td>DS block</td><td>Compliance with GMP</td></tr>
<tr><td>DCA, India</td><td>23rd May 2024</td><td>DS & DP blocks</td><td>Compliance with GMP</td></tr>
<tr><td>PMDA, Japan</td><td>March 2024 (Desktop)</td><td>DP block</td><td>Compliance with GMP</td></tr>
<tr><td>PMDA, Japan</td><td>06th - 09th FEB. 2024</td><td>DS block</td><td>Compliance with GMP</td></tr>
<tr><td colspan="4">2023:</td></tr>
<tr><td>PMDA, Japan</td><td>March 2023 (Desktop)</td><td>DS block</td><td>Compliance with GMP</td></tr>
<tr><td>DCA, India</td><td>04th July 2023</td><td>DS & DP blocks</td><td>Compliance with GMP</td></tr>
<tr><td colspan="4">2022:</td></tr>
<tr><td>DCA, India</td><td>7th June 2022</td><td>DS & DP blocks</td><td>Compliance with GMP</td></tr>
<tr><td>PMDA, Japan</td><td>November 2022 (Desktop)</td><td>DS block</td><td>Compliance with GMP</td></tr>
<tr><td colspan="4">2021:</td></tr>
<tr><td>DCA, India</td><td>11th June 2021</td><td>DS & DP blocks</td><td>Compliance with GMP</td></tr>
<tr><td colspan="4">2020:</td></tr>
<tr><td>DCA, India</td><td>26th April 2020</td><td>DS & DP blocks</td><td>Compliance with GMP</td></tr>
<tr><td>PMDA, Japan</td><td>August 2020 (Desktop)</td><td>DS block</td><td>Compliance with GMP</td></tr>
<tr><td>PMDA, Japan</td><td>September 2020 (Desktop)</td><td>DS & DP blocks</td><td>Compliance with GMP</td></tr>
<tr><td colspan="4">2019:</td></tr>
<tr><td>WHO</td><td>September 2019 (Desktop)</td><td>DP block</td><td>Compliance with GMP</td></tr>
</table>
*DS - Drug Substance, * DP- Drug Product</td></tr>
<tr><td colspan="2">Brief report of inspection activities undertaken – Scope and limitations</td></tr>
<tr><td>Areas inspected</td><td>• Pharmaceutical quality system
• Good manufacturing practices for pharmaceutical products</td></tr>
</table>

	• Sanitation and hygiene • Qualification and validation • Complaints • Product recalls • Contract production and analysis • Self-inspection, quality audits and suppliers' audits and approval • Personnel • Training • Personal hygiene • Premises • Equipment • Materials • Documentation • Good practices in production • Good practices in quality control
Restrictions	The scope of the inspection was limited to the FPP products listed in the WHO PQ Program.
Out of scope	FPPs not within the scope of the WHO Prequalification Program
WHO product numbers covered by the inspection	**WHO application no:** NT002 Diethylcarbamazine Citrate 100 mg tablets
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
AQL	Acceptable quality limit
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
HBEL	Health-Based Exposure Limit
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
MLT	Microbial limit test
MR	Management review
NC	Nonconformity
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
SAP	System, applications and products in data processing
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
TAMC	Total aerobic microbial count
TT	Technology transfer
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

Part 2	Summary of the findings and comments

1. Pharmaceutical quality system

Production and control operations were specified in written procedures, and documented accordingly, and GMP requirements were generally met. Products and processes were monitored, and results were verified as part of the batch approval process. The system encompassed aspects of manufacturing, quality control, and distribution to ensure pharmaceutical products' safety, efficacy, and quality.

The company's Quality Manual described and documented the quality management system framework implemented at Eisai-India, Visakhapatnam. The manual outlined the philosophy and components of the QMS. It specified the requirements to be followed to achieve customer satisfaction, comply with applicable regulatory and customer expectations, and align with the principles of the ICH Q10 guideline.

Management Review

Periodic management reviews of the operation of the PQS were conducted with the involvement of senior management to identify opportunities for the continual improvement of products, processes, and the system itself.

Management review was conducted in accordance with SOP for “Management review”. According to the SOP, Management Reviews should be conducted at least once in three months. An annual meeting schedule was prepared by the QA representative in April for the next financial year. The last MR meeting was held on 23/01/2025. The MR meeting presentation and the site-level MR summary report were discussed. The meeting was held according to the standard agenda. The following global KPIs and criteria were specified:

- Critical/major complaints
- Deviations
- CAPA
- Recalls/Incidents
- Supplier management (audits)
- OOS

The site-level MR summary report was prepared by the Head QA and approved by the site Head. The meeting was chaired by the site Head.

Product quality review (PQR)

Product Quality Review (PQR) was conducted regularly and documented on an annual basis. Batches manufactured and other quality attributes related to the previous year (from January to December) were considered in the review. As per the SOP, the PQR should be completed by the end of March each year.

PQR was conducted in accordance with the applicable SOP. The 'Product Quality Review' was discussed, and it was noted that the following tools were used to evaluate the results:

- Control charts
- Process capability was assessed using Cp and Cpk values. A Cpk of 1.33 (4 sigma) or higher was considered capable and acceptable. If the Cpk was between 1.00 and 1.33, it was considered marginally capable. A Cpk below 1.00 required further evaluation. A minimum of six batches was required for statistical evaluation. Cpk was used for:
    - Assay
    - LOD
    - Tablet weight
    - Thickness
    - Hardness
    - Impurities

Selected PQRs were reviewed and discussed during the inspection.

Quality risk management (QRM)

QRM was conducted in accordance with SOP for "Risk management". The procedure covered different stages and phases of QRM. Risk assessment consisted of risk identification, risk analysis, risk evaluation, risk control, risk reduction, risk acceptance, risk communication, and risk review. The following tools could be used:

- Control charts
- DOE
- Pareto charts
- Process capability analysis
- Histograms
- FMEA (5 ranking was used for RPN)
- FMECA
- FTA
- HACCP
- HAZOP
- PHA
- Flowcharts etc.

According to the SOP, RA should be reviewed every 3 years. The risk register was reviewed, and randomly selected risk assessments were spot-checked.

Handling of deviations

The facility followed a comprehensive deviation management process as outlined in the respective SOP. The SOP defined the handling of deviations from manufacturing instructions and quality-related procedures, encompassing the investigation, quality impact assessment, root cause analysis (RCA), corrective and preventive actions (CAPA), and monitoring of deviations' status. Deviations were categorized into three classifications based on their potential impact on patients and the likelihood of occurrence:

- Critical
- Major
- Minor

Deviation review and trending were conducted regularly to identify recurring causes and assess the appropriateness of CAPA measures. Critical and major deviations were discussed in site-level management review meetings, while deviation trending was included in the Annual Product Quality Review (APQR) as per the facility's SOP for management review.

Several deviations were reviewed during the inspection.

All deviations were required to be closed within 30 days, as specified in the SOP. The deviation trend analysis categorized errors by type (man, machine, material, method, etc.). Further analysis focused on human error-related deviations, including operator oversight and other specific issues.

In summary, the facility adhered to a structured deviation management process. However, improvements in the clarity of trend reporting and increased focus on operator-related errors could further enhance the overall system.

Root cause analysis
The facility followed a structured approach for identifying the root causes of deviations, out-of-trend results, non-conformances, and out-of-specification results. This process was governed by an applicable SOP, ensuring a consistent and systematic method for root cause analysis. Subject Matter Experts (SMEs) across various departments, including Quality Assurance, Production, and Quality Control, were trained to conduct effective investigations. The training was incorporated into their designated training matrix to ensure competency in performing RCA.

The RCA investigation team was composed of members from key departments, such as QA, Production, and QC. The head of QA played a critical role in ensuring compliance with the procedures and maintaining oversight of the Corrective and Preventive Actions resulting from investigations. The primary objectives of RCA investigations were to determine the causes of failures, evaluate their potential impact on product quality, identify any similar occurrences, and assess whether regulatory requirements were met. Data for investigations was collected from various sources, including batch records, process control data, Standard Operating Procedures (SOPs), Certificates of Analysis, and equipment logs. The team employed various RCA tools and techniques to analyze the issues, such as the 5 Whys, Fishbone (Ishikawa) diagram, Failure Mode and Effects Analysis (FMEA), brainstorming, and 1H-5W analysis.

The application of these RCA tools and techniques was thoroughly described in the respective SOP, ensuring a standardized approach to RCA across the facility.

CAPA management
The Corrective and Preventive Action (CAPA) process at the facility was governed by the applicable SOP. This SOP applied to deviations, laboratory incidents, out-of-specification (OOS) results, Annual Product Quality Review (APQR), complaints, rejections, and other related issues, ensuring a comprehensive approach to CAPA.

Corrective actions were required to be implemented within 30 days, unless an extension was requested and approved by the Quality Assurance (QA) department. Preventive actions were assigned varying timeframes depending on the nature of the issue, with short-term actions due within 30 days, medium-term actions within 90 days, and long-term actions within 180 days. These timeframes account for the complexity of the issues, such as document-related issues, Standard Operating Procedure (SOP) changes, or major investments.

QA staff were responsible for conducting effectiveness control by trending recurring deviations and incidents as outlined in the SOP. This ensured that the CAPA taken was suitable for addressing the identified issues and their associated root cause analysis (RCA). CAPA implementation was tracked and traced through the Quality Management System using a software system. The selected records were reviewed and found to have been handled appropriately.

The performance of CAPA actions was reviewed at the management level to identify trends and make informed decisions. This review process was conducted in accordance with the respective SOP. Quality system trend reviews were held quarterly, with participation from department heads and QA staff to ensure that trends were identified and addressed effectively.

Batch document review
The batch document review was conducted in accordance with SOP “Batch document review”. The SOP was applicable for the review of BMR/BPR, cleaning, and analytical records review to certify the compliance of the batch with respect to process control and quality control specification of the drug product and drug substance. Checklists were used for BMR/BPR and batch analytical records review. BMR/BPR reviews were done by the production supervisor and the QA supervisor. Batch analytical records were reviewed by the QC Supervisor and QA Supervisor, partially through LIMS and partially on hard copies.

Batch release
The batch release procedure was conducted in accordance with SOP “Batch release procedure for drug substance” and batch release flow chart. SOP applied to finished product release to the market. A checklist was used for release purposes. Checks were performed by both production and QA supervisors.

Certificate of Analysis
The CoA was issued in accordance with SOP "Preparation, Issuance and Control of Analysis CoA". Analysts performing the tests entered data into the LIMS, and all calculations were handled by the respective software application, and no manual calculations were performed. The data in the LIMS were reviewed by an independent review team. The final release of raw and packaging materials was carried out by the Head of QC. The finished pharmaceutical product data was verified by the Analytical QA Reviewer, and the FPP release was completed by the Head of QA. The CoA was generated by the LIMS and electronically signed by the Head of QC.

Change Controls (CC)
A list of major Change Controls from 2022 – 2024 was submitted before the WHO inspection.

SOP “Change Control Procedure” was reviewed. The procedure applied to all changes with potential impact on GMP compliance, regulatory requirements, product quality, safety, efficacy, stability, and the validated state of processes, facilities, and equipment at Eisai-India, Visakhapatnam. The SOP explicitly excluded the following from its scope: the exchange of like-for-like components during routine maintenance activities. Such replacements referred to equipment parts or components that functioned in a manner identical to those being replaced. These could either bear the same part number or meet the same design specifications. Like-for-like replacements were not expected to alter the operational or performance characteristics of the equipment in which they were installed. The replaced parts or components were required to be verified against the design specifications or to be a documented, acceptable alternative. Furthermore, the procedure defined changes as either permanent or temporary. Change requests were managed through the respective software system, in alignment with other QMS processes. Each change was further categorized as major or minor, based on its

potential impact on product quality, with a corresponding checklist available in the software system. A risk analysis was required for all major changes. Closure timelines were defined based on the type of change request. Provisions were also included for handling change controls arising from equipment breakdowns. Several change control requests were randomly selected from the list provided prior to the inspection and reviewed for compliance and documentation status.

Furthermore, the overview of change control requests was reviewed in the system. The reasons for requests remaining open beyond their defined deadlines, along with the associated extension justifications, were discussed and confirmed with the responsible person.

Data integrity
The following SOPs were discussed:

- SOP "Backup Management Procedure" that specified procedures for the restoration of electronic data. A multi-layered backup strategy was employed, including three types of backups for the Empower application:
    - Daily and monthly backup on 2 tapes. Every month, one tape was kept on site, and the second one was locked in the bank.
    - Veeam backup (immutable). A combination of software and hardware features
    - VCDR (cloud back-up)

Stand-alone instruments had a separate backup server, exclusively used for QC purposes. Daily and monthly backups were automatic. Once a month manual backup was taken on two tapes.

Restoration of QC equipment data was carried out in two ways: as per the annual schedule and upon request. Data restoration was performed on a project-by-project basis. Restored data was compared with the original data to ensure accuracy and integrity.

PLCs connected to production equipment, such as the compression machine, were integrated with the Human-Machine Interface (HMI). Backup of data files from the HMI system was performed by IT once per quarter, using a USB transfer to the server, followed by a transfer from the server to tapes. These tapes were used for data restoration exercises.

Furthermore, the following procedures were reviewed and discussed:

- Business Continuity Plan, Revision 6": The BCMS (Business Continuity Management System) Annual Plan for 2024–2025 was presented.
- IT disaster recovery plan.
- SOP "Review of Electronic Records and Audit Trail in QC Laboratory".
- SOP “User management”

2. Good manufacturing practices for pharmaceutical products
Manufacturing processes were clearly defined, validated, and systematically reviewed to confirm compliance with established specifications. Adequate resources were provided, including qualified personnel, appropriate facilities, equipment, materials, and documented procedures. Production and quality control activities were conducted according to written instructions, with records maintained to demonstrate compliance. Any deviations were documented, investigated, and addressed through corrective and preventive actions (CAPA). Batch records ensured traceability of manufacturing and distribution.

3. Sanitation and hygiene

The facility followed SOP for cleaning and sanitization, ensuring compliance with hygiene standards. One SOP covered the cleaning and sanitization of entry/exit change rooms and production corridors, while the other SOP governed the cleaning and sanitization of manufacturing areas, including primary packaging.

Cleaning activities were categorized into two types: daily and weekly, or as needed. Type A cleaning was performed during batch-to-batch changeovers, while Type B cleaning was more comprehensive, and carried out during product changeovers, weekly, or as required. Three Disinfectants were identified and were rotated weekly to ensure effective sanitization.

Housekeeping personnel were responsible for performing cleaning tasks, with the head of production overseeing the adherence to procedures. Cleaning activities were logged in area-specific logbooks for documentation purposes. After each cleaning, visual verification of cleanliness was conducted by the supervisor. The cleanliness status was recorded in the cleaning logbooks, and a fixed clean area status label was applied to indicate the area's readiness for use.

Microbiological alerts triggered additional cleaning actions, with production resuming only after three consecutive satisfactory microbiological test results for the affected area. Cleaning procedures were closely monitored through logbooks and status labels, ensuring compliance with the defined protocols.

4. Qualification and validation

Validation and qualification activities were performed according to the established policies and documented procedures. The key elements of a qualification and validation program were clearly defined and documented in a validation master plan.

The company maintained separate Validation Master Plans (VMPs) for different categories. One of the VMPs which provided a written plan to establish documented evidence of the suitability, reliability, and consistency of the facility, equipment, utilities, and processes, was reviewed. The plan was reviewed every two years and included:

- Area Qualification
- Utilities Qualification:
    - HVAC
    - Water system
    - Compressed air
    - Nitrogen gas
- Process validation
- Cleaning validation

Computerized systems were covered under a separate document ('Computer System Validation Master Plan' – CSVMP), while electronic QMS and document management systems were addressed in the 'respective Validation Master Plan, aligned with GAMP 5 and 21 CFR Part 11.

The validation master plan for computerized systems applied to:

- Computer systems handling GMP, including LIMS
- PLC-based process control system
- SCADA (supervisory control and data acquisition system)
- DDC (direct digital controller) - BMS

Continued process verification was conducted according to the SOP "Continued process verification". The SOP was applicable to the new products, TT products, revalidation of existing commercial products throughout the product lifecycle, and ongoing process verification. Continued process verification was performed every 6 months for all batches manufactured.

Continued process verification report for Diethylcarbamazine Citrate 100 mg tablets, review period: January to June 2023 was discussed.

Cleaning validation
The applicable SOP described the cleaning validation procedures for manufacturing equipment to ensure consistent removal of residues to predefined acceptable levels.

The scope included cleaning procedure validation, revalidation, cleaning verification, campaign length establishment, and periodic monitoring of equipment and vessels used in the manufacturing of drug products, drug substances, and drug intermediates at Eisai-India, Visakhapatnam.

The SOP defined the selection and validation of sampling procedures, including swab sampling for chemical residues, swab sampling for microbiological testing, and rinse sampling. The selection of sampling points was also addressed.

The annual chemical cleaning verification report was reviewed. The objective of the report was to provide documented evidence that the cleaning procedures for equipment used in the manufacturing and packing of DEC 100 mg USP were adequate to reduce DEC API residues within the defined acceptance limits. This verification was performed annually.

The acceptance criteria for cleaning validation in the drug product facility were defined in the Product Matrix, with the latest version dated 29/11/2024, following the introduction of medicinal products for blister packaging. This matrix was based on the Residue Limits – Supporting Data report associated with the respective Change Control.

MACO calculations were performed using the an application, incorporating product-specific parameters such as HBEL values, solubility, safety factors (e.g., maximum and minimum daily doses), equipment surface areas, swab areas, rinse volumes, and batch sizes. The output values (L1 to L4a-c), particularly L4a (surface residue limit for bioburden), were reviewed for Diethylcarbamazine across relevant equipment for two batch sizes.

The worst-case scenario was identified between the two applicable substances, and the lowest MACO was selected as the acceptance criterion for the product portfolio. This approach was in line with the cleaning validation SOP.

Additionally, the equipment cleaning checklist for Type Cleaning (between products) related to cleaning between the respective production, dated 27/04/2024 and 17/03/2025, was available and reviewed. The checklist was identifiable.

SOP for method development and validation of analytical test methods for residue analysis, was available and discussed. The SOP outlined procedures for developing and validating analytical methods for API and cleaning agent residues in the QC department, including rinse and swab recovery methods. The company used UV-VIS spectrophotometry equipment, and the validation parameters included system suitability, specificity, precision, ruggedness, robustness, linearity, accuracy, and solution stability. The analytical method validation protocol for DEC residue and the corresponding report were reviewed. Changes to the SOP since 2011 were also examined to confirm that the validated method did not need any amendment.

Analytical procedure validation
Refer to the respective information under section 17 titled "Good practices in quality control".

Validation of computerized systems
SOP for validation of computerized systems was available and reviewed. The SOP outlined provisions to ensure that computerized systems used in manufacturing were validated based on quality risk management principles, with the extent of validation aligned with the identified risks, system complexity, and intended use.

The list of computerized systems used onsite was provided in accordance with the applicable SOP. Documentation relevant to the validation of selected computerized systems was spot-checked.

The traceability matrix associated with the selected computerized system was not available, as the applicable SOP had been revised after the initial system qualification. However, during the review of the performance qualification related to the eLN revalidation, it was confirmed that requirements for system security, data backup, and audit trail had been adequately addressed.

Procedures were in place for the GxP computerized systems, defining their use and control. Appropriate segregation of roles between personnel responsible for operational processes and those managing system administration and maintenance was observed.

Details of user-profiles and access rights to networks, servers, computerized systems, and software were documented. An up-to-date list of individual user rights for each software, system, and network was maintained and managed under change control.

Suitable security measures were in place to prevent unauthorized access, manipulation, or deletion of data from computerized systems. A system for regular audit trail review was established, applicable to all computerized instruments, equipment, and LIMS used in the Quality Control laboratory at Eisai India, Visakhapatnam.

For eLN data review, standard procedures were established. Provisions to protect audit trails from alteration or unauthorized deletion were included in the respective URS.

Computerized systems were periodically reviewed to confirm their validated state or to determine the need for revalidation, in accordance with SOP "Equipment/System Re-qualification". The annual qualification status review and requalification plan for equipment and software systems for 2025 were available and discussed. It was also noted that the temperature monitoring system in the API warehouse had been decommissioned nearly one year ago, in line with the CS validation SOP.

Hold time studies
The facility had a defined procedure for conducting hold time studies, documented in the applicable SOP. The procedure outlined the methodology for determining the maximum acceptable hold periods for in-process intermediates, bulk products, and recovered materials at various stages of the manufacturing process. The aim was to assess whether holding tablets for extended periods, under defined conditions (such as temperature and humidity), impacted their quality attributes, including potency, dissolution, appearance, and microbial load.

The responsibilities for the hold time study process were clearly outlined: QA was responsible for preparing the hold time study protocol and report; QC was involved in reviewing the protocol and performing the necessary testing; and production was responsible for reviewing both the protocol and the report. The establishment of the hold time period was based on factors such as analytical data trends and the results from previous study intervals (n-1).

Hold time studies at the facility were typically conducted at various stages of tablet production, including after granulation, after compression, before packaging, as well as after packaging when the finished product was awaiting distribution or shipment.

During the inspection, the hold time study protocol and report for Diethylcarbamazine Citrate Tablets 200mg USP(wet granules) were reviewed. The study involved a batch size of 2,000,000 tablets, with participation from QA, QC, and production staff. The study design included identifying time intervals for sampling and testing the tablets (e.g., 0, 4, 12, 24, and 28 hours), with test parameters including assay, description, related substances, individual impurities, total impurities, and microbial contamination. The tablets were stored under controlled conditions of no more than 25°C and relative humidity not exceeding 55%.

Samples of tablets were withdrawn at the defined time points during the hold time and subjected to quality testing as outlined in the protocol. A review of the in-process analysis reports showed that all results had fallen within the acceptable limits defined in the product's specifications, as specified in the study protocol.

The conclusion of the study indicated that the wet granules could be held for up to 28 hours. However, it was recommended that the granules be stored for no more than 12 hours at temperatures not exceeding 25°C and relative humidity below 55%. The study was deemed adequate and relevant based on the results reviewed, ensuring that the hold time did not negatively impact the product quality.

5. Complaints
The facility followed a well-established procedure for handling product complaints. Complaints were categorized based on their potential impact on patients into the following categories:
- Critical
- Major
- Minor

The Quality Assurance department was responsible for logging and classifying complaints to ensure proper documentation and follow-up.

For investigation and closure, critical complaints were required to be investigated and resolved within 7 days. For major and minor complaints, an initial report was to be completed within 7 days, followed by three additional reports to track progress and ensure a thorough investigation. If a complaint was found to impact product quality, a product recall could be initiated.

Complaints-related samples were stored in the control sample room, with full segregation to maintain sample integrity and avoid contamination. The investigation team, appointed by QA, comprises members from key departments such as Production, Quality Control, Engineering, and Research & Development (R&D), ensuring a comprehensive and multi-departmental approach to complaint resolution.

Complaint trending was performed quarterly, focusing on the number of complaints and the average resolution time. From the first quarter (Q1) to the fourth quarter (Q4) of 2024, three complaints were logged, all classified as minor. The trend report, which included the QMS document number, was used to support and guide QA improvement initiatives.

Standard procedures governed the preparation and review of quality systems trends. Quarterly meetings were held to discuss trends with key department Heads. The minutes and agenda of the most recent meeting, held in Q4 2024, were reviewed.

A specific complaint case was reviewed during the inspection to assess the handling process and resolution of the issue, and it was found to be adequately handled.

6. Product recalls

The facility followed a comprehensive procedure for product recall as outlined in the SOP which governed the handling of product recalls and withdrawals of drug products. A Recall Committee was tasked with overseeing all recall activities, ensuring thorough investigations were conducted whenever a recall was initiated.

Recalls were classified into two main types:

- Voluntary Recall, initiated by the licensee, typically in response to post-marketing stability studies or market complaints
- Statutory Recall, initiated by Drug Control Authorities.

The severity of the recall was classified into Class I to Class III, with Class I recalls being the most serious (e.g., potential for serious health consequences or death), and Class III being less serious (e.g., unlikely to cause adverse health consequences). Recalls were further categorized by level, with Level I reaching the consumer level and Level II reaching the wholesale level.

The recall plan, prepared by the Recall Committee, outlined the recall depth, the need for a public warning, and the extent of the recall. Regulatory authorities were to be informed prior to or at the initiation of the recall to ensure compliance with applicable regulations. Returned goods were to be managed in accordance with an SOP that governs the handling of returned and rejected batches.

A mock recall was to be conducted every three years if no actual recall had occurred during that period.

Overall, the Quality Assurance Office held the ultimate responsibility for ensuring compliance with the SOP and for managing all aspects of product recall procedures.

7. Contract production, analysis, and other activities

The site followed a well-defined Vendor Qualification process. The SOP covered the approval and qualification of raw material and packaging material vendors, ensuring that all vendors met the necessary quality and GMP standards. Vendors were qualified through various methods, including sample testing, vendor qualification questionnaires, and GMP audits, which might be onsite, virtual, or paper-based.

Requalification of vendors was conducted periodically, with critical material manufacturers requiring requalification every two years, while non-critical manufacturers were requalified every three years. Requalification schedules were prepared at the beginning of each financial year to ensure timely reviews and evaluations.

An annual vendor evaluation was carried out based on key factors such as batches received, released, rejected, out-of-specification (OOS) results, and customer complaints. This evaluation was specifically important for assessing the performance of API and intermediate vendors.

The site maintained an Approved Vendor List (AVL) for raw materials. During the inspection, a review of the contract and agreement between Eisai Pharmaceuticals Ltd and selected vendors was conducted.

A list of contract laboratories was available and reviewed.

Audits of contract acceptors—including contract laboratories and packaging material manufacturers—were conducted every three years, as per the annual audit schedule.

The respective audit reports were also reviewed.

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

Self-inspections were conducted in accordance with SOP for "Internal Audit". A qualified audit team carried out the inspections objectively, ensuring alignment with GMP requirements. As per the procedure, at least one representative from the QA team was designated as the lead auditor, unless the QA function itself was under inspection**.**

A departmental list of internal auditors identified qualified personnel eligible to participate in audits of their respective areas. Auditor objectivity was considered in this list to avoid potential conflicts of interest, thereby maintaining the impartiality of the process. All internal audit records were maintained in the software system.

Internal audits were conducted routinely, as well as under special circumstances such as product recalls, repeated batch rejections, or regulatory inspections. The scope of self-inspection followed the respective SOP and covered critical areas such as personnel, premises, equipment maintenance, storage, production controls, quality control, documentation, sanitation, validation, recall management, complaint handling, and labeling.

Annual inspection plans were prepared in advance; the plans for both 2024 and 2025 were requested and reviewed during the inspection. Audit records, including those corresponding to the audit executed on 19/03/2025 for the Quality Control laboratory, were reviewed in the respective software system. This audit was conducted using a checklist annexed to the applicable SOP. The corresponding inspection plan had been prepared on 2/01/2025 and approved by the Head of QA.

A report summarizing audit findings, evaluations, and corrective actions was generated in the system following each audit. The Head of QA reviewed the audit reports and associated corrective actions to ensure continuous improvement of the system.

Timelines for audit report preparation and response generation were defined in the relevant SOP. The electronic system had a provision to flag and manage missed deadlines by flagging them on the dashboard, and it was monitored by the QA internal coordinator or his deputy. However, the timelines for the implementation of potential CAPAs were governed by the separate SOP on CAPA plan management.

9. Personnel

The manufacturer maintained an adequate number of personnel with the necessary qualifications and relevant practical experience. In general, responsible staff had clearly defined duties documented in written job descriptions and were granted sufficient authority to effectively carry out their responsibilities. This was verified on a sampling basis through the review of selected roles across the organization, with particular attention given to personnel within the Quality Control laboratory.

The site operated under a structured organizational framework encompassing quality management, production, quality control, storage, and distribution functions. An organizational chart was established, clearly defining key roles such as Responsible Pharmacists, and the respective line of reporting to keep the independence of the QA team. The organograms were incorporated into the respective SOP and were available for review. They were appropriately dated and approved by the authorized individual, demonstrating formal control over the organizational structure.

Randomly selected job descriptions, including those for the Qualified Person and the Head of Drug Product Manufacturing, were requested and reviewed. The documentation was available in the respective software system.

The confidentiality agreement was implemented in accordance with the company's applicable policy. Employees were required to sign a self-declaration using an electronic signature, along with a Data Integrity Agreement and a Confidentiality Agreement. Randomly selected evidence of signed agreements was requested and reviewed. Each employee received a Joining Kit, which included various forms to be signed, such as the Secrecy Agreement, HR Privacy Notice, Declaration of Business Interests, and the Ethical Conduct and Data Integrity Agreement. Relevant documentation for two employees was reviewed during the assessment. A Conflict-of-Interest Policy was also in place, requiring employees to acknowledge it through a signed declaration.

10.Training

Training was provided in accordance with a written program for all personnel whose duties took them into manufacturing areas or into control laboratories and for other personnel as required. SOP for "Training Management" described the procedure for training personnel across the organization. A system was established for managing training activities, supported by the application, which included two modules: Document Management System (DMS) and Learning Management System (LMS).

The training program consisted of three types of training: initial, on-the-job, and external training. Job Descriptions were provided in a generic format, with each role assigned to a corresponding job function within the system. Each employee maintained a personal training binder to store evidence of classroom-based training and other relevant records, where such documentation was not already captured in the LMS.

The Training Management System in the LMS was used to plan, conduct, track, and document employee training activities in alignment with the site's Quality Management System. The system incorporated a structured Training Manual that included training materials, questionnaires, and certification criteria. Training sessions involved an evaluation component in the form of a questionnaire. Furthermore, training was scheduled in the LMS based on employee roles, departmental needs, and procedure revisions. The system generated automated notifications and reminders for upcoming or overdue training. Attendance and completion status were tracked in real-time, ensuring timely compliance and allowing supervisors to monitor training progress.

In the LMS, an overview of seasonal employees with temporary contracts was available under the module for System/Non-System Users. These employees were assigned distinct employee codes or usernames, differentiating them from permanent staff.

Upon arrival, the inspectors were provided with relevant safety information pertaining to site-specific requirements and procedures.

Firefighting and first aid training were provided to relevant personnel, and records of the training were maintained in the LMS.

11.Personal hygiene

The facility followed a structured approach to ensure employee health and hygiene, with relevant Standard Operating Procedures (SOPs) in place. A standard procedure outlined the employee health check-up procedure, which included pre-joining and annual medical check-ups for all employees to assess their health status. The health check-ups covered diseases such as tuberculosis (TB), skin conditions, communicable diseases, and eyesight issues, and required X-ray screenings every three years.

An SOP governed personnel hygiene and cleanliness practices, with specific training provided to production staff. Regular monitoring was conducted to ensure ongoing compliance with hygiene standards across the facility. Supervisors are responsible for reporting any infectious diseases, and employees with skin conditions are not permitted to work in drug product production areas to prevent contamination risks.

In addition, employees' fitness was to be re-evaluated upon their return to work after an illness to ensure they were fit for duty. Personal hygiene practices were strictly enforced, requiring staff to maintain cleanliness, including keeping nails short, regular bathing, and clean shaves. Smoking, eating, or drinking was prohibited in the production, laboratory, and storage areas to avoid any potential contamination. Jewelry was not permitted in production areas to maintain a clean environment. During the inspection of the facility, these procedures were noted to be followed by employees.

12.Premises

Production

Premises were located, designed, constructed, adapted, and maintained to suit the operations to be carried out. The layout and design of the premises were to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, and build-up of dust or dirt. Where dust was generated (e.g. during sampling, weighing, mixing and processing operations, or packaging of powder), measures were taken to avoid cross-contamination and facilitate cleaning: entrance to those areas was via separate material entrance/exit areas and main entrance/exit areas. Premises used for the manufacture of finished products were designed and constructed to facilitate good sanitation. Premises were maintained with good sanitation

standards and were well maintained. The premises were designed to ensure the logical flow of materials and personnel. Entrance to the premises was controlled by access cards. The premises were seen as clean and well-maintained.

During the inspection, the inspectors visited the Drug product facility. Entrance to the production rooms was via a cascade of change rooms. Change rooms had gowning pictorial presentations.

The following areas were visited, and the following activities were observed:
- Dispensing Room/Booth
- Clean Bin Storage Area
- Dispensed Raw Materials Storage Area
- Granulation Area
- Granulate quarantine Area and Clean Bin holding Area with separate material and personnel entry
- Blending Area
- Compression Area
- Tablet Tooling Area
- Work in Process (WIP) Area
- Change Parts Area
- Tablets Quarantine Area
- Equipment Cleaning
- IPQC
- Primary Packaging Area (bottles)
- Secondary Packaging Area

Warehouses
Separate warehouses were designated for Raw Materials, Primary and Secondary Packaging Materials, and Finished Goods. Environmental conditions were maintained across all stores, with temperature consistently below 25 °C. Temperature mapping was conducted every three years; hotspots were identified, and conditions were controlled through the BMS (Building Management System). Materials in the warehouses were stored in a high rack system. The SAP system was used for materials management. Warehouses were considered clean and maintained in good order. Receiving and dispatch bays were separated and protected materials and products from the weather. Rejected materials were segregated and stored under lock and key.

Quality Control Laboratory (QCL)
QC laboratories were separated from production areas and were designed to suit the operations to be carried out. Sufficient space was given to avoid mix-ups and cross-contamination. Adequate and suitable storage space was provided for samples, reference standards, solvents, reagents, and records. Samples to the laboratory were delivered via pass box and stored in separate closed cabinets for raw materials, drug products, and drug substances. QC laboratories were equipped for chemical, instrumental, and microbiological testing and were maintained under controlled temperature and humidity conditions. There were separate laboratories for instrumental tests and chemical tests. Laboratories were considered clean and maintained in good order.

Microbiology laboratory (MB)
The MB laboratory was separated from the QCL. Entrance to the laboratory testing area for MLT and preparation of strains was via the change room cascade. The RLAF booth was used for MLTs (class "A", ISO 5) and a biosafety cabinet (grade "A", ISO 5) for work with live strains. RLAF and biosafety cabinet were located in class "D", ISO 8 area. Separate autoclaves were provided for media sterilization and destruction.

There was a clear separation of activities, such as the MLT testing room, incubation rooms, and media preparation rooms, which were all located in separate rooms. The laboratory was equipped with appropriate environmental controls, including thermohygrometers, and temperature and humidity conditions were maintained and regularly monitored.

A total of eight staff members worked in the microbiology laboratory, all holding a master's degree in microbiology.

13.Equipment
Equipment Design and Suitability: Equipment was appropriately located, designed, constructed, adapted, and maintained to support the intended operations. The equipment observed appeared to be of suitable design and construction for its allocated processes. Fixed pipework was clearly labeled to ensure proper identification.

Balances and other measuring instruments, with suitable range and precision, were available for both production and control operations and were calibrated according to a defined schedule. Laboratory equipment and instruments were appropriate for the testing procedures performed.

Current drawings of critical equipment and support systems were maintained. Instruments in the QC laboratory were clearly labeled with calibration status, qualification status, preventive maintenance status, and instrument identification labels, ensuring traceability and compliance.

Among the laboratory equipment observed were four incubators set at different conditions (41-45°C, 20-25°C, and 30-35°C), two autoclaves (one for decontamination of garments, accessories, and media, and one for sterilization purposes), and one freezer set at -20 to -30°C.

The alarm system for monitoring excursions was tested for the freezer and was found to be adequate. Records of equipment and instrument usage were maintained through the LIMS system. The inspectors were able to trace the pH usage logs and data for the previous day. Additionally, logbooks were maintained for some equipment, such as the dynamic pass box which was used to transport samples and other accessories to and from the Microbial Limit Testing (MLT) room. The respective logbook included recorded data such as differential pressure (DP), UV lamp burning hours, cleaning status of the pass box, and relevant checks. The logbook was found to be adequately filled.

During the facility inspection, the production equipment appeared to have been well-maintained, with PM stickers visible on the various pieces of equipment, indicating that the scheduled maintenance had been performed. In addition, the SOP for the Equipment Maintenance Program was reviewed. This document outlined the overall maintenance program for critical equipment and systems within the facility, including a tracking system through the software application. Engineering staff were responsible for executing maintenance tasks, while Production and QA staff were tasked with verifying the impact assessments of these activities. The program included calibration, inspection, and checks for wear and tear on components such as

seals, filters, and gaskets. The maintenance was scheduled according to specific timeframes: every 6 months for most production equipment, quarterly for Air Handling Units (AHUs), and monthly for filters.

The SOP also specified that equipment might require requalification following major repairs, modifications, or extended periods of inactivity, and this process was managed through change control procedures. Overall, the facility had a comprehensive and well-documented and followed preventive maintenance program in place, ensuring that equipment remained in good working condition and that maintenance activities were conducted on schedule. The inspection confirmed that the Rapid Mixer Granulator and other equipment had been properly maintained, with all relevant documentation and maintenance checks up to date.

The following selected equipment used in the quality control and production areas was verified during the inspection:

- FTIR Analytical balance
- HPLC with the respective chromatography software application.
- Disintegration apparatus located in the compression area
- Autoclave used for decontamination
- Incubator

The usage of the equipment was logged in the respective LIMS, which served as an electronic logbook (eLogbook).

Utilities

Purified water system (PW)

The PW system was visited during the inspection. The source of the potable water was a river. The river water was treated by the area developer:

- Filtration
- Chlorination

Potable water was delivered to the EISAI water pre-treatment plant:

- Chlorination
- Multi-grade filtration
- Ultrafiltration
- Ion exchange
- Ozonation
- Ozone destruction UV unit (continuous intensities monitoring) NML 300 mv
- Sodium meta-bisulfate dosing for chlorine removal
- Oxidation and reduction potential (ORP) measures for residual chlorine level.

Potable water was stored in two stainless steel tanks. The "Hot Potable Water Tank" supplied water via a distribution loop to the production area, where it was used primarily for equipment cleaning. The water in this loop was maintained in continuous circulation to prevent stagnation and ensure quality. Water from the second "Potable Water Tank" was treated to produce Purified Water (PW), which was used in the formulation block (Block 1).

- 1st stage RO: 6 membranes
- 2nd stage RO: 4 membranes
- EDI: 2 units
- Storage tank 5000 L
- Distribution loop

The storage tank was equipped with a 0.1 µm hydrophobic filter, for which integrity tests were performed biannually, and filters were replaced every 4 years. The PW in the distribution loop was maintained in continuous circulation at ambient temperature to ensure water quality. Sanitization of the loop and storage tank was carried out every 15 days using hot water at 80 °C for 1 hour. The following parameters were monitored at the return line before the storage tank:

- Conductivity NMT 1.2 µs/cm
- TOC NMT 500 ppp
- Flow rate NLT 3.8 m^3/m
- pH 5 - 7

The general system was also monitored online:

- Conductivity
- RO1
- RO2
- EDI outlet
- pH inlet RO2

The PW generation system was equipped with audio/visual alarm system and was seen to be clean and well-maintained.

Replacement of filters in the water system was performed in accordance with the respective procedures. Evidence of the integrity check of the vent filter for the PW storage tank in the drug product facility (PW distribution system) was randomly selected for verification. The integrity test of 0.2 µm filters was scheduled twice yearly, in March and September. The selected filter was tested on 7 Mar 2025, and the activity was recorded in the respective logbook. The test report, generated by the engineering group using an inbuilt application for bubble point testing, was reviewed. The filter was indicated as hydrophobic, and the results were within the defined specifications.

The manufacturing facility followed an SOP for the sampling, testing, and release of water samples, documented under the applicable SOP. The microbiologists were responsible for the sampling and testing of water, while the Head of Quality Control (QC) oversaw the review and release of the water sample reports. The SOP also outlined the preparation of sampling containers, with the sampling plan being extracted from the LIMS. The LIMS system allows for traceability of samples and test results, including the printing of labels.

Water samples were tested for chemical analysis, Total Organic Carbon, and microbiological analysis. The sampling procedure prioritized the collection of microbiological samples first, followed by TOC samples, and then samples for chemical analysis. Alert and action limits for raw water, potable water, and purified water were specified in the SOP, with these limits being based on historical data and trending results. These limits apply to TAMC and TOC. Upon completing the review of test data, QC personnel prepared a Certificate of Analysis which was submitted to Quality Assurance for approval.

Monthly trend analyses for purified water, raw water, and potable water were conducted, with quarterly discussions held among a cross-functional team to review the results. The outcomes of these discussions were sent to QA for further action. The facility followed a structured process for managing excursions, as described in the SOP on trend monitoring and handling of out-of-trend (OOT) and out-of-specification (OOS) results. This process included a phased approach to investigating issues—Phase I involved laboratory investigation, Phase II involved sampling, and Phase III included manufacturing investigation. Any excursions in chemical analysis were addressed by assessing the impact, identifying the root cause, and developing a Corrective and Preventive Action plan. Actions may include additional sampling, testing, and risk assessments on the impact on produced batches.

The review of the selected data and test records for the sampling point, specifically for the return loop in February 2025, confirmed that the sampling frequency was daily. Test parameters included chemical analyses such as pH, conductivity, and TOC, along with microbiological tests for Total Aerobic Microbial Count (TAMC), E. coli, Salmonella spp., P. aeruginosa, and S. aureus. The microbial results for the year 2024, as reviewed during the Annual Product Quality Review for December 2024, were found to be satisfactory and in compliance with the required standards.

HVAC system
The HVAC system was reviewed during the inspection, with AHU 08 selected as an example. The system operated with recirculated air, supplemented by 10% fresh air, which was drawn from the service floor. The intake damper position was fixed.

The HVAC system was observed to be clean and well-maintained.

Environmental Monitoring Program
The facility had an SOP for microbiological environmental monitoring in production facilities. This procedure outlined the methodology for microbial evaluation of clean rooms and controlled environments, such as production lines. It detailed the procedures for sampling methods and frequencies, corrective actions, and the handling of deviations in accordance with the relevant SOPs. It also covered the handling and transport of samples, as well as data recording and reporting processes. Sampling locations were selected based on risk assessment, including areas near air handling units, inside pass boxes, around product contact areas (e.g., the tablet inspection machine), and near personnel entry points. The types of microbiological monitoring conducted included airborne microbial sampling and the use of the settle plate method. Settle plate and active air sampling were conducted monthly for the drug product facility, and the same frequency of sampling was followed for Warehouse I, II, and III. Trending for both settle plate and active air sampling was performed monthly. The facility had well-defined action levels and alert levels for microbiological contamination. For the settle plate method, with regard to TAMC, the alert and action levels were as follows:

- ISO 8: alert level – 50 cfu/plate/2 hrs; action level – 70 cfu/plate/2 hrs
- ISO 5: alert level – 2 cfu/plate/2 hrs; action level – 3 cfu/plate/2 hrs

Environmental monitoring results were recorded in the LIMS system, and the data were readily accessible for review. Any environmental deviations, along with root cause analysis and corrective and preventive actions, were managed according to the relevant procedures.

During the inspection, records of microbial counts for the Drug Product Facility were reviewed.

The equipment calibration and maintenance for the active air sampler followed the applicable SOP which described the operation and calibration of the microbial air sampler. Calibration was scheduled to be conducted once a year by an external agency. A review of the latest calibration records for the microbial air sampler, performed on 17/02/2025 by an external service provider was verified to adhere to the SOP.

The annual summary report of environmental monitoring using settle plates and active air sampling for the period January 2024 to December 2024 in the drug product facility was reviewed.

Compressed air system
The compressed air system was not visited during the inspection; however, a schematic drawing of the system was presented and discussed. The system consisted of an oil-free compressed air generator, followed by a dryer with a dew point of –40 °C, leading to a storage tank, then a receiver, and finally distributed to user points.

The filter cascade included stages of 50 µm → 10 µm → 1 µm → 0.2 µm hydrophobic filter at the user points. Integrity checks of the 0.2 µm filters were performed every six months.

Trend analysis of compressed air monitoring for Total Viable Count in the drug product facility for the year 2024 was reviewed. The non-viable count test was contracted out, and all results were within specified limits.

14.Materials
Incoming materials and finished products were quarantined immediately after receipt or processing until they were released for use or distribution. Materials and products were stored under the appropriate conditions in an orderly fashion to permit batch segregation and stock rotation by a first-expire / first-out rule. Water used in the manufacture of pharmaceutical products was suitable for its intended use.

Raw materials
The approved suppliers' list was available in the warehouse. Incoming materials were checked using a checklist to ensure that the consignment matched the corresponding purchase order. A dedusting tunnel was used for materials upon receipt, prior to transfer to the test area.

There were three sampling booths available—two for APIs and one for Excipients. Sampling was conducted by QC staff, with 100% sampling carried out for both APIs and Excipients. A sampling plan was generated based on the Goods Receipt Note (GRN) created in SAP. Sampling was performed under LAF, and a checklist was used to verify line clearance and cleaning. A separate area was designated for the sampling and dispensing of primary packaging materials.

SOP for “Performance re-qualification of AFU, LAF unit and dynamic pass box” was discussed.

Finished goods
Finished Goods from the secondary packaging line were quarantined under lock and key. QA was responsible for the release of approved Finished Products. Distribution was managed through SAP.

Packaging materials
Labels were stored under lock and key by warehouse staff. Excess labels from production were checked by production staff, then QA staff, and finally warehouse staff before being returned to the labelling store, to ensure no printed labels were mistakenly returned.

Rejected, recovered, reprocessed, and reworked materials
The facility had a defined procedure for handling returned and rejected batches, as outlined in the respective SOP. According to the SOP, all returned and recalled products were segregated and securely stored under lock and key until a thorough investigation was completed to determine the appropriate course of action.

The review and verification process included checking the accuracy of the documentation associated with the returned batches and assessing the physical condition of the products. A comprehensive risk assessment was performed for all returned products, considering factors such as the nature of the product, any special storage conditions required, and the overall condition and history of the product.

In line with the facility's policy, re-processing of drug products was not permitted under any circumstances, ensuring that returned or rejected batches are not reintroduced into production. This approach maintained the integrity of the manufacturing process and ensured compliance with GMP standards.

15.Documentation
Good documentation practices were maintained as part of the quality assurance system, ensuring compliance with GMP requirements. Documentation defined specifications, procedures, and controls for all materials and manufacturing processes, ensuring traceability, batch release decisions, and audit trails for investigation and validation. Documents were designed, reviewed, approved, and distributed according to regulatory requirements. They were clear, legible, and systematically organized to prevent errors. Regular reviews and updates were conducted, with measures in place to prevent the unintended use of superseded versions. Data entries were legible, indelible, and appropriately spaced, with any alterations signed, dated, and traceable. Records were completed in real-time and retained for at least one year after product expiry. Electronic documentation systems had controlled access, audit trails, and data integrity safeguards, with backup storage to ensure data availability during the retention period.

The facility followed an SOP for the preparation, review, approval, issuance, storage, retention, and control of documents, as outlined in the standard procedures. The SOP applied to all master and executed documents related to manufacturing, testing, holding, and distribution of products, ensuring the security, traceability, and integrity of all records. The user department was responsible for the preparation, review, and updating of documentation, with approval granted by the Head of Quality Assurance. Document issuance and control were managed through the electronic Quality Management System, specifically the one that was used for controlling various documents, including SOPs, Specifications, Standard Test Procedures (STP), General Test Procedures, and batch records.

The revision history of documents was found to be accurate and easily traceable. All changes made to documents were appropriately tracked, and the revision history was well-documented in the documents reviewed during the inspection. Superseded documents were retained by the QA department for reference, and obsolete versions were archived or marked as obsolete. Retrieval of all obsolete copies was performed, and they were properly destroyed, except for archived master copies, which were maintained.

Document storage and access control were managed by QA personnel. Master and executed documents were securely stored, with access restricted to authorized personnel only. The SOP specified retention periods for key documents: SMF and VMP hard copies were stored permanently, executed batch and analytical records were retained for 8 years from the release date as hard copies, obsolete master documents were stored for 5 years, and logbooks (e.g., calibration logs) were kept for 10 years from completion of use. Documents were stored in various formats, including active storage (hard copies), passive storage (scanned copies), and electronic storage (soft copies). Archived records were accessible solely to authorized personnel for audits or inspections and could only be accessed with the approval of the Head of QA or their designee, following the document issuance request approval.

The laboratory used a LIMS for managing analytical workflows, sample tracking, and electronic data capture.

In the production area, SAP was used for material management, batch processing, and related operations. Both systems were interfaced to enable seamless data exchange between laboratory and production functions, supporting end-to-end traceability and process integration. Samples were received at the QC Laboratory and stored in designated cabinets segregated by category. Leftover samples were reconciled in the respective LIMS and disposed of in accordance with applicable procedures. Sample analysis was assigned to qualified analysts based on the competency matrix maintained in the LIMS, with the laboratory manager responsible for ensuring appropriate assignment.

Furthermore, the LIMS was interfaced with key laboratory equipment in the Quality Control Laboratory, including analytical balances, the chromatography data system, and systems used for AQL calculations. Data generated by these instruments was automatically transferred into LIMS without manual transcription, either for further calculation or for direct documentation, thereby minimizing transcription errors and enhancing data reliability.

The electronic documentation systems had features aligned with data integrity requirements, including controlled access based on user roles, complete audit trails capturing all actions and changes, and safeguards to prevent unauthorized data manipulation. Backup mechanisms were in place to ensure long-term data availability throughout the defined retention period. Access rights were assigned to the employees based on their roles and the respective requests to the IT administrators, and the activity was managed using the respective application.

BMR/BPR

It was noted that the batch manufacturing records were thoroughly reviewed by both the production and QA departments in accordance with the relevant checklists. Key areas reviewed included line clearance, environmental monitoring, in-process control checks, and yield reconciliation. An SOP governed the preparation, review, approval, issuance, and retrieval of batch records, as well as the allotment of batch numbers. Batch records were requested through the DMS system, ensuring proper tracking, and preventing duplication. The assigned batch numbers were unique, incorporating the manufacturing date, product code,

and BMR version for traceability. The procedure also detailed the management of canceled batches, including retrieval, documentation of cancellation reasons, and destruction after QA verification. The process adhered to WHO GMP standards for batch traceability and documentation control.

16.Good practices in production

The manufacturing process for Diethylcarbamazine Citrate Tablets 100 mg USP started with the dispensing of active and excipient materials (Lactose monohydrate NF (200) and corn starch NF. Each batch was divided into four individual lots, which were processed separately through the initial stages. These included dry mixing, and wet granulation, followed by drying of the granules. Post-drying, the granules were milled to achieve uniform particle size. All four lots were then pooled and subjected to a final blending step along with magnesium stearate and talc. The blending was performed, and, in this process, pre-lubrication was performed to improve uniformity and distribution. This was followed by the lubrication step, where magnesium stearate and talc were added and blended to enhance flow properties and prevent sticking during compression. In-process checks for blending included description, assay, and LOD.

The blended material was compressed into tablets under defined compression parameters, including weight, hardness, and thickness. Tablets were subjected to disintegration and uniformity testing. Finally, the compressed tablets were packed, and finished product samples were collected for analysis as per FP specifications.

For visited areas, refer to the Section for Premises.

17.Good practices in quality control

The Quality Control Department, including the Microbiology laboratory, was responsible for the sampling and testing of raw materials, packaging materials, in-process samples, and finished products. The department also handled environmental monitoring, and water system sampling. Stability studies and the storage of Quality control samples were supervised by the QA department.

All sampling activities were conducted in designated controlled areas under appropriate environmental conditions to prevent cross-contamination. QC laboratories were equipped for chemical, instrumental, and microbiological testing and were maintained under controlled temperature and humidity conditions.

Applicable SOPs described all QC activities, including sampling, testing, release, and retention of samples. Stability chambers were maintained to conduct stability studies as per regulatory requirements. The stability chambers provided different storage conditions as per the applicable stability protocols. Temperature and humidity were continuously monitored and controlled by the digital temperature monitoring system, which ensured that the chambers operated within the defined limits. The associated software was reviewed to verify the system's temperature and humidity recording, as well as the alarm log system.

SOP for “Handling of Out-of-Specification (OOS)” defined the procedure for managing OOS results obtained from all physical and chemical tests conducted in internal or external laboratories. The scope of the SOP included raw materials (RM), packaging materials (PM), finished products (FP), intermediates, in-process samples, stability samples, working standard qualifications, drug products, and drug substances at Eisai-India, Vishakhapatnam.

OOS results related to microbiological samples were excluded from this SOP and were handled according to a separate procedure, SOP for Handling of Out-of-Specification (OOS) in Microbiological Laboratory.

The OOS procedure did not apply to in-process tests and environmental monitoring results intended solely to support manufacturing process endpoints. It also did not apply to studies conducted under variable parameters, such as process evaluations and evaluations under drift conditions, or to samples related to method transfer and vendor evaluation. Additionally, OOS procedures were not required for tests where pharmacopeia provisions allowed for additional analysis, such as dissolution testing (stages S1, S2, and S3) and uniformity of dosage units (levels L1 and L2).

Three OOS investigations were identified since 2021 when the company started to use LIMS for the registration of OOS and reviewed during the inspection, all related to the product in the scope of the inspection.

For a selected API batch, it was verified that the sampling was performed per the respective SOP and pooled as per the GRN. A sample ID was assigned. Testing was conducted using a USP monograph via an STP in use since 2013. No changes to the API supplier or analytical method were noted. The respective analyses were reviewed and verified in the applicable software system.

The HPLC instruments were interfaced with LIMS for automatic data transfer. HPLC calculations and injection sequence were reviewed. Column specs, reference standards, and reagents were verified. The analytical balance was LIMS-integrated, and usage was properly recorded.

QC personnel were qualified, and training was provided on GMP, safety, and analytical techniques. Reference standards (RS), working standards (WS), and reagents were also managed and controlled through the LIMS. The system maintained traceability of their receipt, qualification, usage, and expiry, ensuring compliance with applicable procedures.

The control sample process was managed electronically through SAP and LIMS. After batch posting in SAP, a lot was automatically created in the LIMS Retain Sample Module. IPQA collected, labelled, and packed the control samples and transferred them to the storage area. QA received the samples, entered them into LIMS, verified the details, and updated the storage location and retention period. Samples were reviewed by a second person and stored until the defined retention period. Annual verification was performed, and samples were destroyed as per the applicable procedures. If needed, samples were re-issued via LIMS. Retention periods varied depending on the material, with up to 6 years from the expiry date for APIs and excipients.

Safety measures were implemented in the laboratory, including the availability of a safety shower, eye-wash station, warning signs, proper storage of flammable reagents, fire extinguishers, fire blankets, and accessible Material Safety Data Sheets (MSDS) through the applicable software application.

Retention samples
Retention samples of each finished product batch were stored for at least one year beyond the expiry date, in final packaging under recommended conditions. Retention samples of each API were stored for up to 6 years from the expiry date. All retention samples were sufficient in quantity to allow at least two full re-examinations if required. Retention samples were checked annually, and checks were recorded in PQRs.

Stability studies
Walk-in chambers with the following conditions were used:
- T 25 °C ± 2°C, RH 60% ± 5%
- T 30 °C ± 2°C, RH 75% ± 5%
- T 30 °C ± 2°C, RH 65% ± 5%
- T 40 °C ± 2°C, RH 75% ± 5%
- T 2 - 8 °C

One stand-by chamber was available and was calibrated for all above-mentioned conditions, except T 2 - 8 °C. T and RH were monitored using the digital monitoring system. Data was recorded every hour and verified once per day. Chambers were equipped with an audible alarm system and text message alert.

In the Microbiology laboratory, two types of culture media were used:
- Ready-prepared media, purchased from outside suppliers
- Self-made media from dry powder

Upon receipt of both ready-made and dry media, pH was measured, and Growth Promotion Tests (GPT) were performed. The expiry of self-made media was validated as follows:
• 15 days for agar media
• 30 days for liquid media
• 21 days for R2A media in bottles

Handling of growth media was conducted in accordance with an SOP. Records for media preparation, sterilization, growth promotion, and inhibitory properties were spot-checked for R2A and SCDM (self-made). R2A media was purchased ready-made.

Miscellaneous	
Samples taken	N/A
Assessment of the site master file	The Site Master File (SMF) was submitted and reviewed.
Annexes attached	A list of change controls was submitted prior to the inspection.

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, **Eisai Pharmaceuticals India Pvt. Ltd**., located **at Plot No. 96, 97, 98, 124 & 126, Visakha Pharmacity Limited (SEZ), Parawada – 531019, Anakapalli District, Andhra Pradesh, India**, **Drug product facility, bottle packing line**, was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines.

The deficiencies observed during the inspection, as listed in the full report, were addressed by the manufacturer to a satisfactory level before 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***
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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

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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.
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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.
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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
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30. 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.
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31. 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
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