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2nd JAPAN- INDIA MEDICAL PRODUTS REGULATION SYMPOSIUM

24th APRIL 2017

QUALITY STANDARDS AND GMP SYSTEM IN INDIA

Outline

- Drugs Regulation
- CDSCO and State offices
- Responsibilities under Drugs Regulatory System
- Quality standards
- GMP System and Inspections
- Types of inspection
- Inspection procedure
- Regulatory Action
- GMP Certification Scheme for Export
- GMP Practical Aspects - Common deficiencies identified

Drugs Regulation

- Drugs fall under the **Concurrent List** of the Constitution of India

- Drugs & Cosmetics Act is a **Central Act** enforced by both Central and State Government

CDSCO and State Offices

Zone	Sub Zones	Port Office
East Zone	Baddi	Delhi Airport
West Zone	Indore	Mumbai Airport
North Zone	Jammu	Mumbai Sea port
South Zone	Bengaluru	Chennai Airport
Ahmedabad Zone	Goa	Chennai Sea port
Hyderabad Zone		Kolkata Airport
		Kolkata Seaport
		Hyderabad
		Gandhinagar
		Vishakhapattanam

29 States
7 Union Territories

CDSCO

CDSCO and State Offices

CDSCO – Geographical Location Zonal /Sub Zonal Offices

- CDSCO North Zone (Ghaziabad)
- CDSCO West Zone (Mumbai)
- CDSCO South Zone (Chennai)
- CDSCO East Zone (Kolkata)
- CDSCO Zone (Ahmadabad)
- CDSCO Zone (Hyderabad)
- CDSCO Sub Zone (Bangaluru)
- CDSCO Sub Zone (Chandigarh)
- CDSCO Sub Zone (Jammu) and (Goa)

Port Offices/Airports : 11
Laboratories : 6

•Proposed Sub Zonal Offices (2) :
•Guwahati, Indore,

29 States
6 Union Territories

Responsibilities Under Drugs Regulatory System

Central Responsibilities:

- New Drug/Medical Devices Approvals
- Import of Drugs/Medical Devices/Cosmetics
- Clinical Trials
- Standards for Drugs
- Amendments to Act and Rules
- Pharmacovigillance

State Responsibilities:

- License for Manufacture, Sale and Distribution
- Monitoring quality of Drugs and Cosmetics
- Investigations and Prosecutions

Standards of Quality

- Indian Pharmacopoeia
- Non Pharmacopoeia standards as approved by Regulatory Authority.
- Bureau of Indian Standards (BIS)

GMP Standards & Inspection System

Standards for GMP:

- Schedule M of Drugs and Cosmetics Act and Rules
- WHO TRS guideline

Personnel Responsible for Inspection:

- Inspectors.
- Responsibilities of Inspectors Inspection of manufacturing/sale/clinical trials sites, sampling of drugs and cosmetics, search and seizures and launching of prosecutions
- Inspection team comprises of Drugs Inspectors from CDSCO, State Govt. and subject expert of biological, medical product, blood products, medical devices, diagnostics from Central Drugs Laboratory or other recognised institutions.

Tools of Inspection:

- Rules, Checklists, SOPs, and CDSCO guidance document for zonal office

Types of Inspection

- Inspections of Manufacturing Premises (Drugs/Biologicals/Medical Devices/Cosmetics etc.)
- Pre inspection prior to marketing authorization of the product during product development and clinical study (Form 29 - license to manufacture drugs for the purpose of Examination, Testing and Analysis)
- Routine inspection
  - Pre approval of the site (facility inspection for grant of license)
  - Inspection for renewal of license (facility inspection)
  - Periodic inspection (annual) as per Drugs & Cosmetics Act and Rules

Types of Inspection

- For issuance of Certificate of Pharmaceutical Products (CPP) for the purpose of export
- Inspection subsequent to post approval changes
- Risk based inspection
- For cause inspection incase of complaint investigation (may be announced or unannounced)
- Routine Inspection of vaccine manufacturing unit is carried out jointly by Central and State Drugs Inspectors along with one representative from National Control Laboratory

Inspection Procedure

- On site evaluation for newly introduced product involving reviewer in inspection
- Inspection for compliance to Post approval change submission
- Introduction of Risk Based Inspection approach for all inspections
- Taking samples for testing during inspection
- Follow up of inspection
  - Based on the inspection report, license is granted or renewed or suspended incase the deficiencies are critical in nature
  - Regulatory actions are initiated incase of non-compliances
  - Prosecution and action as per law is also initiated against manufacturers of substandard drugs

Inspection Procedure

- Application
- Assessment
  - Completeness of application
  - Technical Review (Site Master File, DMF, complaints, changes in facility, technical staff etc.)
  - Planning for inspection
- Notification of inspection date to firm
- Inspection duration – 3 to 5 days

Inspection Procedure

- Inspection 3-5 days focusing all critical areas
  - Opening Meeting
  - Documentation – Change Control, CAPA, Validation, OOS / OOT, deviations control, Product/process characterization, annual product quality review, consistency, SOPs, training, etc.
  - processing
  - Personnel
  - System
  - Facility
  - Including service and ancillary areas
  - Exit meeting
- Inspection Report
- Review
- Letter for Compliance
- Review of compliance
- Final action

SOP No. INS –QA-002 GMP inspection and report writing

SOP No. INS –QA-007 Procedure for Planning and Preparation of Gmp Inspection

Inspection Procedures

Requirements under Schedule M

- General Requirements
  - Location and surroundings
  - Building and premises
  - Water System
  - Disposal of waste
  - Warehousing Area
  - Ancillary Areas
  - Quality Control Area
  - Personnel
  - Health, clothing and sanitation of workers
  - Manufacturing Operations and Controls
  - Sanitation in the Manufacturing Premises
  - Raw Materials
  - Equipment
  - Documentation and Records

Inspection Procedures

Requirements under Schedule M

- General Requirements
  - Labels and other Printed Materials
  - Quality Assurance
  - Self Inspection and Quality audit
  - Quality Control System
  - Specification
  - Master Formula Records
  - Packing Records
  - Batch Packaging Records
  - Batch Processing Records
  - Standard Operating Procedures (SOPs) and Records, regarding
  - Reference Samples
  - Reprocessing and Recoveries
  - Distribution records
  - Validation and process validation

Requirements under Schedule M

- General Requirements
  - Product Recalls
  - Complaints and Adverse Reactions
  - Site Master File

Inspection Procedures

Requirements under Schedule M

- Specific Requirements For Manufacture Of Sterile Products
  - General Requirements
  - Building and Civil Works
  - Air Handling System (Central Air-Conditioning)
  - Environmental Monitoring
  - Garments
  - Sanitation
  - Equipment
  - Water and Steam Systems
  - Manufacturing Process
  - Form-Fill-Seal Technology or Blow, Fill-Seal Technology
  - Product Containers and Closures
  - Documentation

Inspection Procedures

- The inspections of medicines and biologicals should be conducted using risk-based approach and should specifically focus on product development, stability study conducted to establish shelf life in Indian climatic conditions, process validation, complaint/recalls, handling of out of specification, deviations and change control procedures

Inspection Procedures

The inspectors are required to verify the following.

- Whether the firm has established proper shelf life for their products and whether firm has carried out stability study of the products in Indian climatic conditions.
- Whether the firm has established the process of manufacturing and testing on the basis of validation studies prior to introduction of the products in Indian market

Inspection Procedures

- Whether requisite trial manufacturing batches were taken at reasonable scale prior to marketing of the product
- Whether the firm is conducting prompt and effective recall up to the retailers level
- Whether the firm is initiating impact analysis and product recall whenever out of specification results are obtained during the stability study of the product which is already in the market

Inspection Procedures

- The zonal officers to verify all inspection/investigation reports critically and forward the reports with clear comments and recommendation
- All the zonal /sub-zonal officers and the State Drugs Control Authorities shall ensure that inspections are conducted for 3-5 days depending on the size of unit, the number of products handled, complexity of product and procedures

Inspection Procedures

- Inspections team shall prepare inspection plan, conduct opening meeting and exit meeting on the final day to summarize and discuss the observations with the manufacturers.
- The final report for inspection may be finalized within 1 week, critically reviewed by Zonal officers and forwarded to SLA for necessary action along with copy to CDSCO (HQ) and manufacturers for compliance

Regulatory Actions

- In case of critical observations which have direct impact on the quality, safety and efficacy of the products and where regulatory action has to be initiated immediately, reports are to be finalized at the end of inspection without delay

Regulatory Actions

- Regulatory actions are being taken against manufacturers for non compliances as per Rule-85 of Drug and Cosmetics Rules
- Regulatory actions include
  - Warning Letters
  - Suspension
  - Cancellation
  - Prosecution

Regulatory Actions

- The SOP number QA-INS-003 prescribes criteria for follow up action and the procedure for follow up activities
- Follow up actions are taken regularly on the basis of inspection report

Regulatory Actions

- SOP No. QA-INS-009-- procedure for qualifying lead inspector
- SOP No. QA-INS-010-- procedure for central oversight of inspection plan, procedures and practices
- SOP No. QA-GNL-014– criteria for follow-up action following inspection

GMP Certification Scheme for Export

- For grant of GMP certificate as per WHO TRS guidelines and issue of CPP.
- Joint inspection of the manufacturing facilities by the State and Central Drugs Inspectors
- CPP is issued by State Licensing Authorities (SLA) and valid for the period of 2 years

GMP Certification Scheme for Export

- For grant of Written Confirmation Certificate (WC) for export of APIs to EU, Inspection of facilities as per EU guidelines by CDSCO Inspectorate
- Written Confirmation certificate is issued by CDSCO

GMP Practical Aspects - Common deficiencies

- Lack of QA concept, Poor understanding of quality system with lack of procedures for
- Change control, Handling of out-of-specification(OOS) results, Handling of deviations, Complaint investigation,
- Corrective action of deviations, Product quality review, Failure of Quality unit to release , reject product, Failure to evaluate the potential impact of changes on quality of the product

GMP Practical Aspects - Common deficiencies identified

- Batch manufacturing record –not comprehensive
  - To ensure consistency in manufacturing ,
  - To facilitate recording of batch history
  - To facilitate investigation of complaint , handling of deviations and change control
- Not adequate documentation, justification, control for
  - Blending of batches
  - Reprocessing and reworking
  - Use of recovered materials and solvent
- Improper selection of supply chain and material control without risk assessment.
- Poor understanding of quality risk management principle

Thank You !

2nd Japan-India Medical Product Regulatory Symposium

Challenges in Stable Supply of Pharmaceutical Products to Japan

24 April, 2017

Yoshio Urawa

Kashima Plant, Eisai Demand Chain Systems

Eisai Co., Ltd.

hhc
human health care

CONTENTS

Eisai Pharmaceuticals India Pvt. Ltd.

Introduction of Eisai Pharmaceuticals India

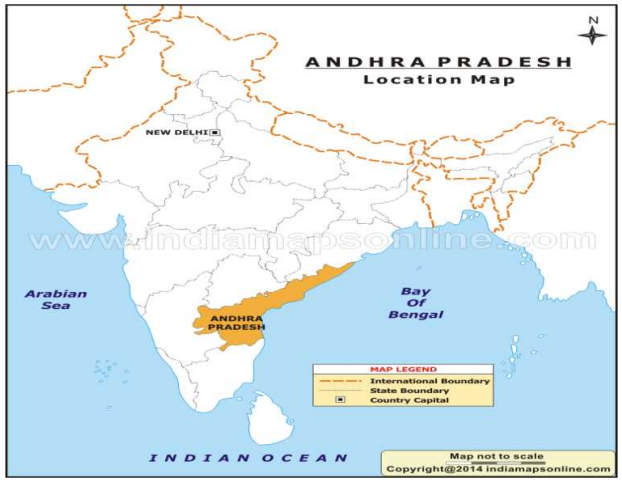
- Eisai is a research based human health care (*hhc)* company that discovers, develops and markets pharmaceutical products throughout the world.

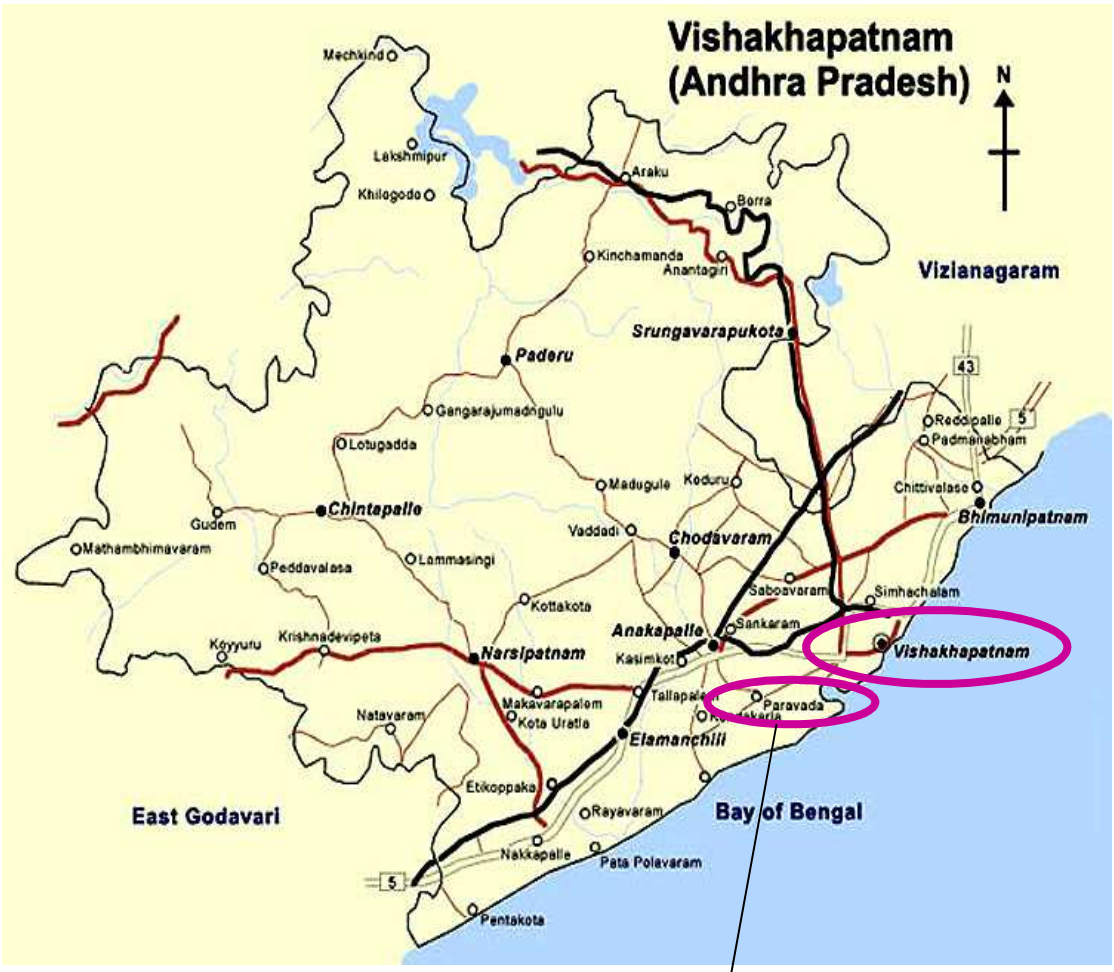
- Eisai India (EIL) is an affiliate of Eisai Company Limited (ECL) headquartered in Tokyo, Japan

- EIL Vizag is Eisai's only manufacturing facility in India and is part of Eisai Demand Chain Systems (EDCS) organization (Global Manufacturing division of Eisai)

- EIL's domestic business's marketing and commercial operations are carried out from sales office in Mumbai.

Location of Eisai Pharmaceuticals India





Eisai Pharmaceuticals India Pvt. Ltd.

EIL Vizag **Site -** 17.3936° N, 83.555° E

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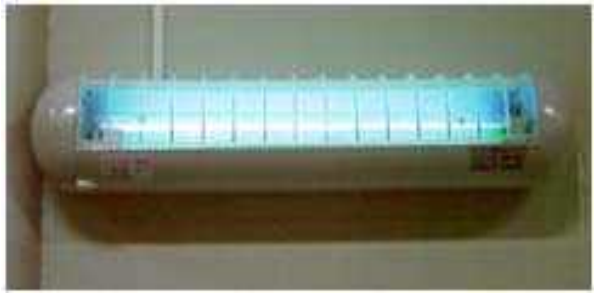
Differences between India and Japan

- Recommendation/Expectation for Regulations
- Analytical method: Unique method in JP
- Quality control at manufacturer: Foreign material
- Expectation of Customer: Variation

Differences in Pest Control

Measures for insect prevention

Electric insecticide kills big insects, but the insect's body would scatter



Adhesive trap
Prevents scattering of insect's body

Adhesive Trap
Trap for crawlinginsects

Trap and kill, Prevention of contamination risk from goods at Clean area in India

Monitoring and counting: trap at Clean area

Gathering information for effective measure to prevent invaders

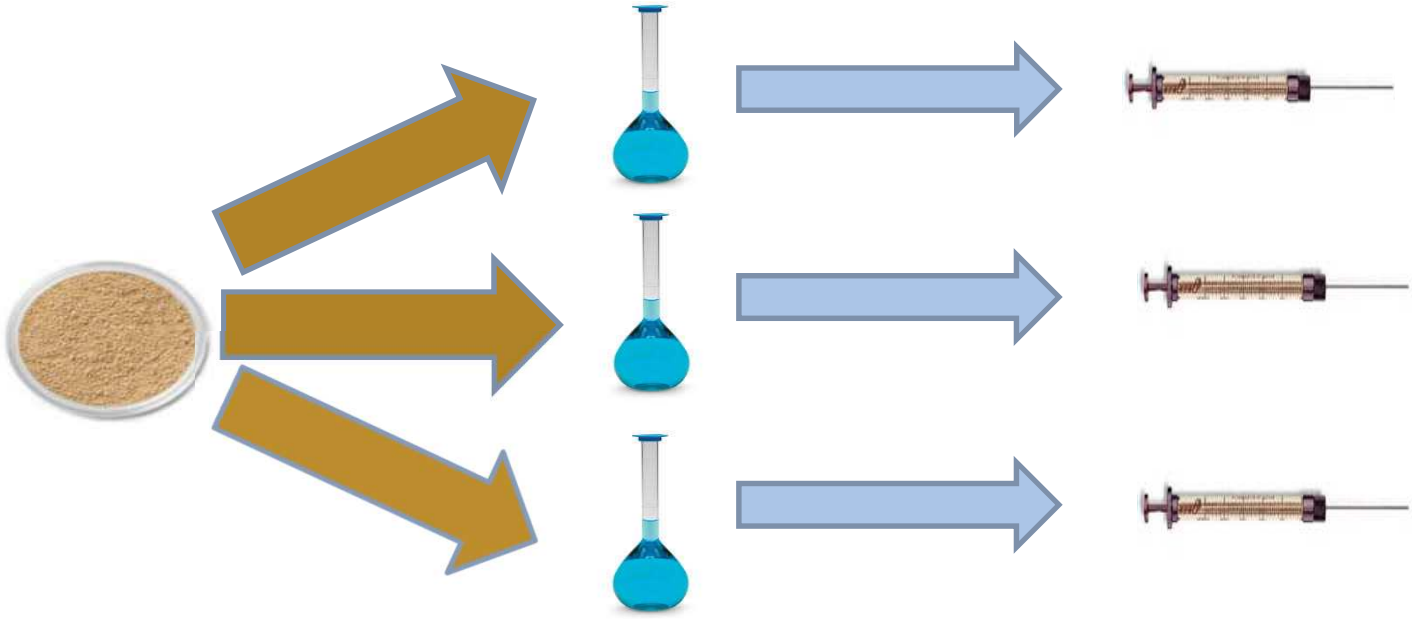
Analytical Testing in Triplicate for Generic submissions

Testing of stability samples needs to be carried out in triplicate in accordance with the *JP for the generic submissions* *(Handling of Data on Stability Testing Attached to Applications for Approval to Manufacture or import Drugs - PAB/PCD Notification No. 43 dated February 15, 1991)*

Composite sample from the batch

Three preparation from the sample

Single injection from each preparation



3 Lots x n=3 (= 9 data should be submitted for release test result, method validation and stability study for each time point for Generic drugs and OTC drugs.)

Analytical Method in JP

- **Heavy Metals Limit Test, method 4 in JP19**

1.4. Method 4

Place an amount of the sample, directed in the monograph, in a platinum or porcelain crucible, mix with 10 mL of a solution of magnesium nitrate hexahydrate in ethanol (95) (1 in 10), fire the ethanol to burn, and carbonize by gradual heating. Cool, add 1 mL of sulfuric acid, heat carefully, and incinerate by ignition between 500°C and 600°C.

2.03 Thin-layer Chromatography

Not common method in India

Foreign matter – Analytical controls

Particulate matter analysis – Quality control lab must be equipped with analysis of foreign matter

- Each batch of the Drug substance and Drug Product should be analyzed to evaluate the contamination level of particulate matters.
- Rejects detected by Visual inspection machine shall be investigated.
- Metal, hair and Insect contamination is considered as critical.

It is difficult to measure amount of foreign matter in batch. So root cause of contamination/generation of foreign matter is important to evaluate impact.

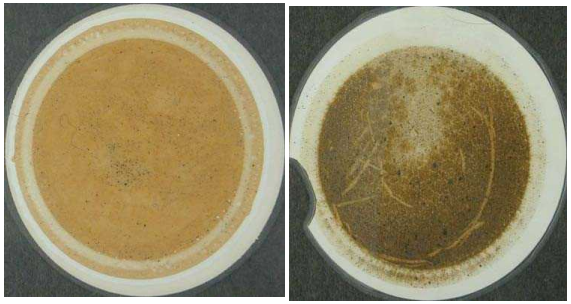
Example of Foreign Matter (Filter Test)

Filtering a dissolved certain amount of API in suitable solvent.

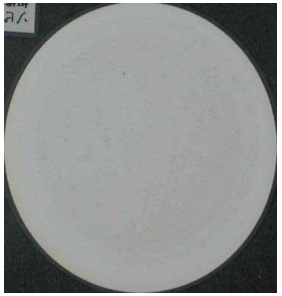


Samples from different suppliers

Filtering a dissolved certain amount of API in suitable solvent.



Samples from overseas supplier



Sample of Japanese Supplier

- Foreign matter also doesn't included in specification in many cases

Quality Concerns in Japan

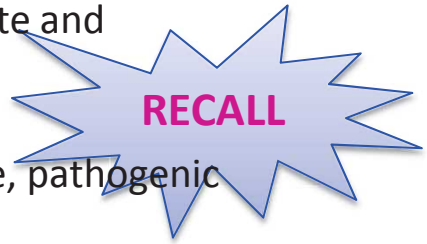
Japanese consumers have very strict and characteristic idea for quality of drugs.

- Effectiveness of drug, Safety and Stability of drugs.
- Appearances (such as color, form/shape, foreign particle), Taste etc.

If consumers find small difference from regular products and even there is NO effect to their health, a lot of consumers start to worry

Japanese Pharmaceutical Law No.56: Forbid to distribute and manufacture

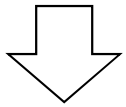
Section 4: If Drugs is contaminated with foreign particle, pathogenic bacteria / organism and virus



Background of Quality Concerns in Japan

If consumers find small difference not only in regular products but also in Process Validation and even though there is NO effect on their health and acceptance criteria, a lot of consumers start to worry

Why?



Could be an indication for future critical deviations

or

Something could be hidden and is a risk for future disaster

Japanese are concerned with even small deviations or inconsistency in delivery even if there is a compliance to specifications

Expected actions for small differences

- **Check and review of record and operation by cross functional team through interviewing operator and researcher to identify difference in operation/equipment status**
- **Periodic (and expanded) monitoring**
- **Make plan to manage small difference like broad/sensitive detection method**
- **Confirmation of effectiveness**

Usually investigation into small difference is more difficult than that of deviation due to lack of information.

Important items to meet expectations from Japanese customers are:

- Design and installation of operation/equipment to detect/prevent difference
- Review by cross functional team
- Knowledge accumulation and careful monitoring by operator during routine activity from initial stage.

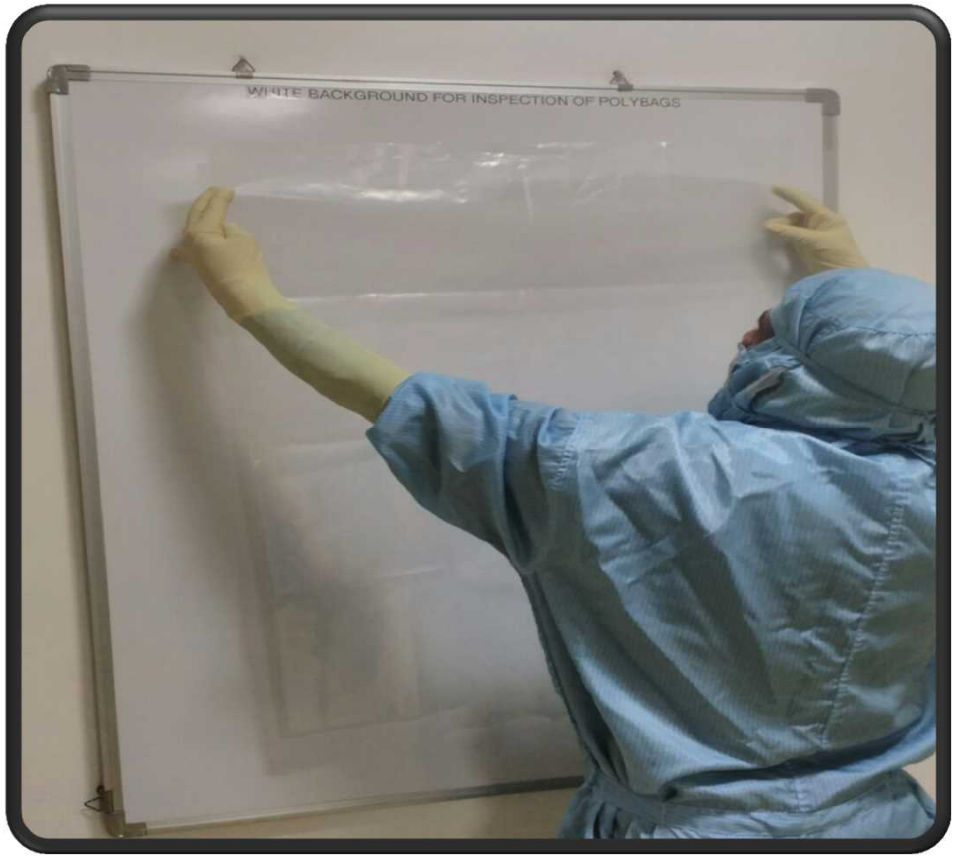
Our Initiatives

Facility & Manufacturing Controls – Stringent Gowning Practices

Personnel gown for manufacturing facility designed in such a way that it eliminates the risk of product contamination with hair or other contaminant.
Prior to the entry in the manufacturing area, personnel uses the tacky rollers to remove any hair or other contaminant adhered to the gown.

Facility & Manufacturing Controls – Input material controls

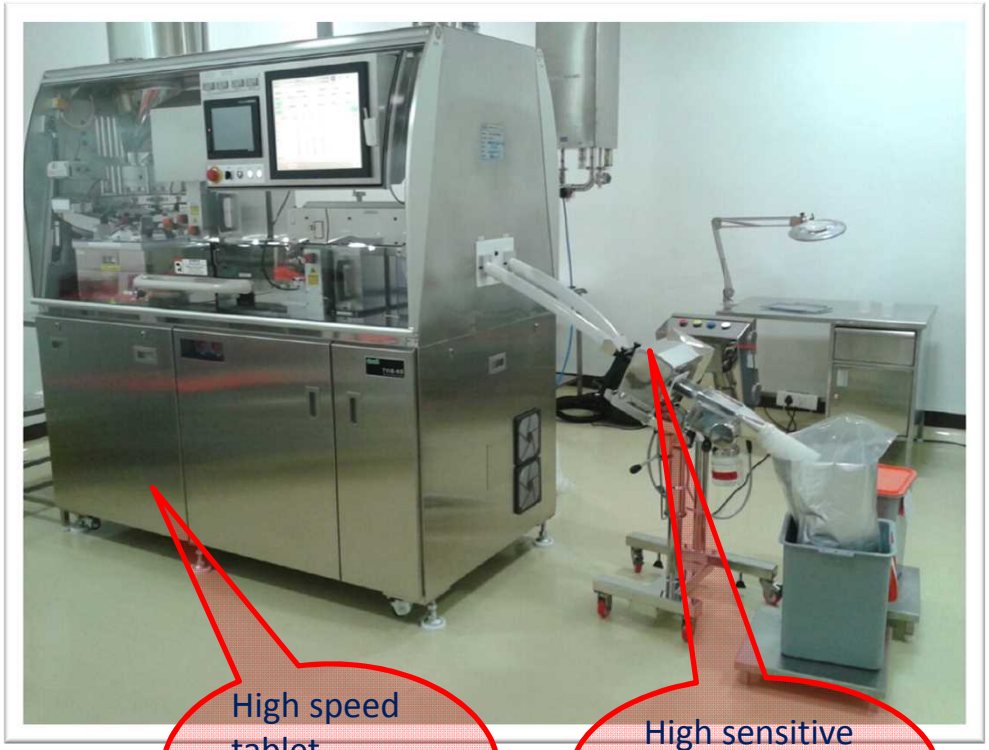
Each primary packaging polybag is inspected on the white background to confirm the absence of foreign matters.



Filtration of all the solvents with 0.5 micron filters to avoid introduction of foreign matter into the process.

Facility & Manufacturing Controls – Highly sensitive equipment for FM detection

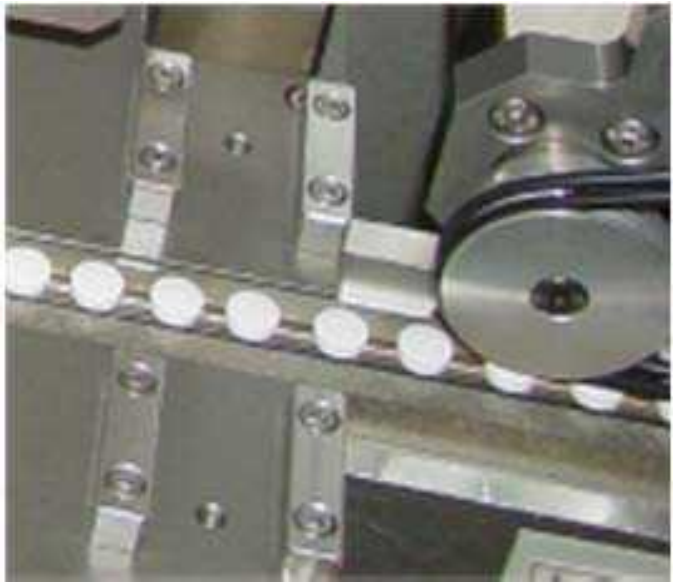
High sensitive inspection machine for detecting the foreign matter contamination with cameras to cover 360 degree angle of the tablets and highly sensitive metal detection and rejection system of APIs. 100% tablet inspection is an essential requirement.



human health care

Facility & Manufacturing Controls
–100% visual inspection: zero defect

100% visual inspection is necessary to provide the products to Japanese market.



Tablet Inspection Machine

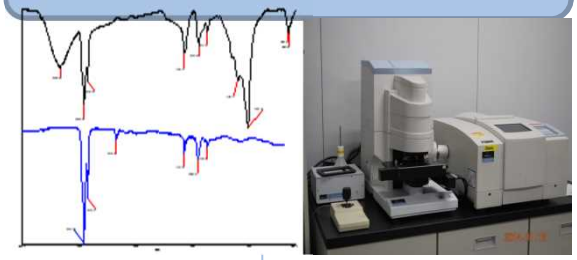
Foreign Matter identification by Quality control using advanced analytical techniques

Foreign matter detection

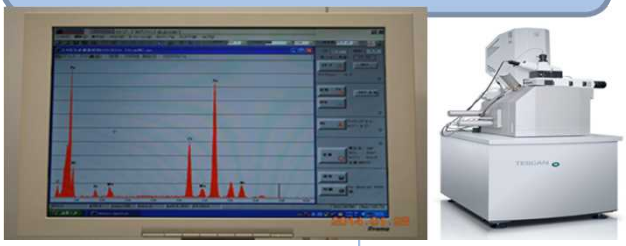
Visual Inspection by Microscope

Judge the Nature of the Particle

Microscope FT-IR



Scanning Electron Microscope & X-ray detector



JUDGEMENT & Identifying the root cause

human health care

Brief on Eisai Pharmaceuticals

Drug Product

API Pilot Plant

Drug Substance

R&D/Laboratories/QA

Administration

Energy Centre

Raw Material & Bulk

HazMat Storage

Cafeteria

Tank Farm

Pump House

Locker Room

Gate House 1

Gate House 2

New complex consists of 14 buildings, including labs, administration, warehousing, R&D and both small- and large-scale production.

Administration	12,147sf
Cafeteria	10,856sf
Locker Room	3,715sf
Gate House 1	3,152sf
Gate House 2	4,336sf
R&D/Laboratories/QA	37,641sf
Drug Substance (API)	48,543sf
API Pilot Plant	16,421sf
Drug Product (Formulation)	97,261sf
Energy Centre	9,296sf
Pump House	1,879sf
HazMat Storage	8,496sf
Bulk Product Storage	7,024sf
Drum Stores	602sf

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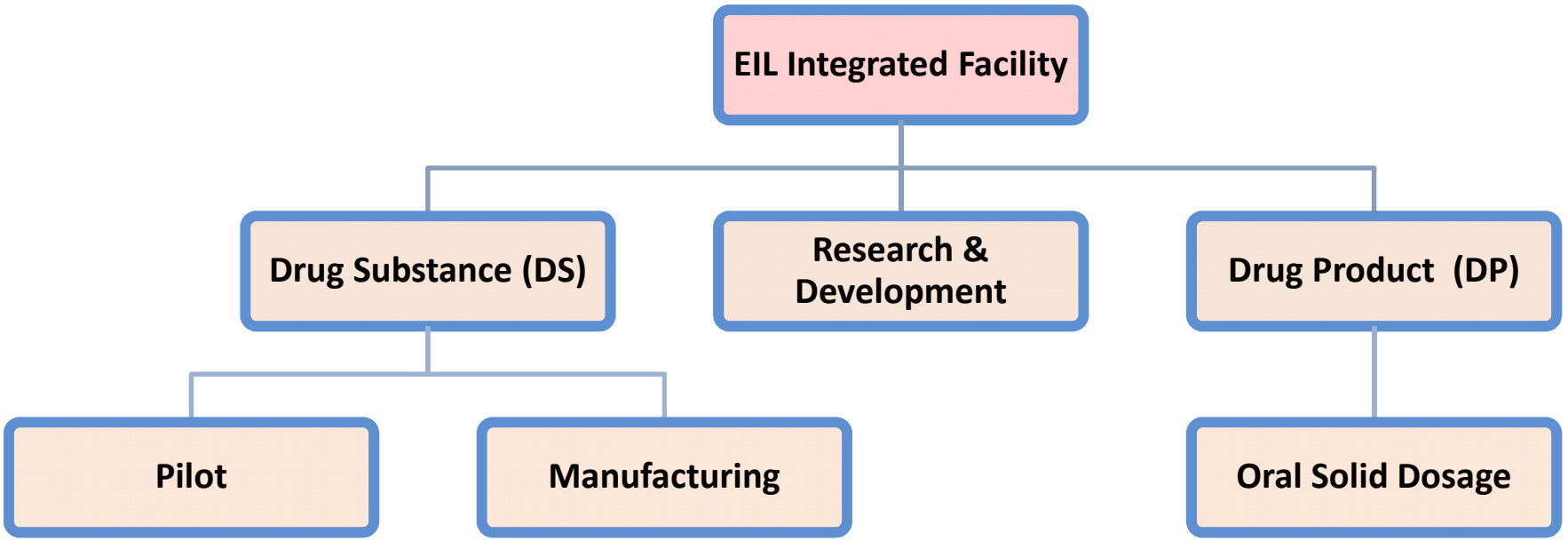
VIZAG- Integrated Facility



EIL – Bird's Eye View

human health care


Drug Substance (API)


Drug Product (Formulation)

Clean Corridor

Courtyard /Mezzanine

Process Research Lab

FACILITY OF THE YEAR AWARD – CATEGORY WINNER

Winner of Global Facility of the Year 2012 awarded by ISPE, Interphex & Pharmaceutical Processing at New York

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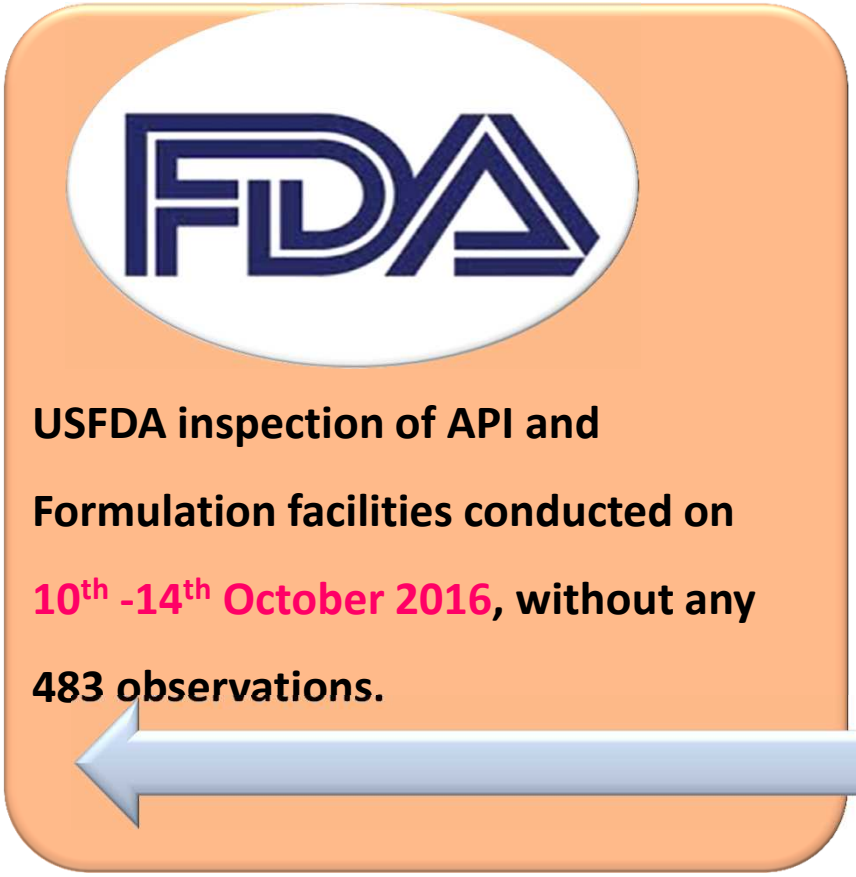
Recent major regulatory inspections

- **In FY 2016, Major regulatory inspections completed without any Critical or Major observations .**



human health care

ध्यान देना के लिए बहुत बहुत धन्यवाद

Thank you for your kind attention.

ご清聴ありがとうございました。