1st India-Japan Medical Products Regulation Symposium
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GMP system of Japan

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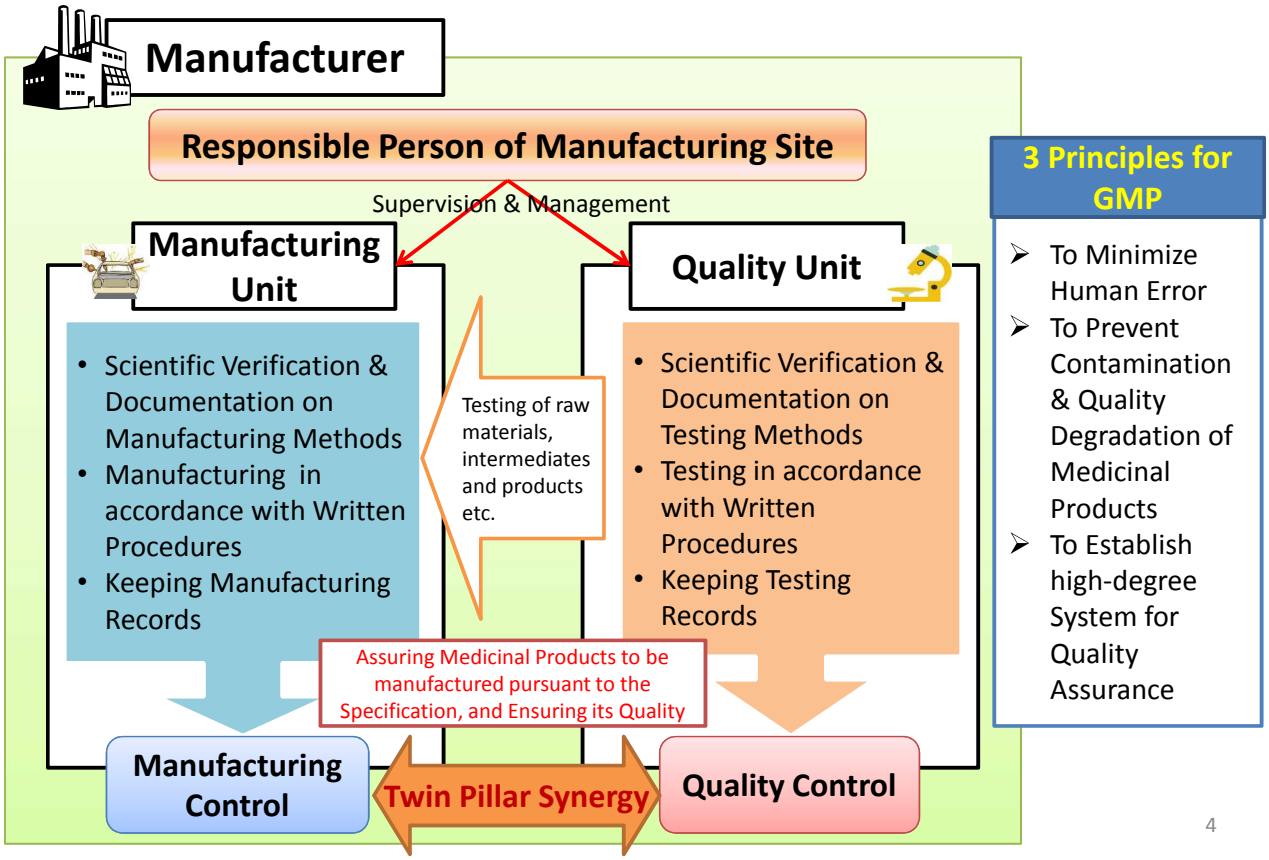
Key Elements of GMP System

- Manufacturing Control & Quality Control by Manufacturer
- Quality Assurance by Marketing Authorization Holder
- GMP Inspection by Competent Authority

Manufacturing Control & Quality Control by Manufacturer

- Manufacturing of Medicinal Products (including APIs) is basically subject to **the GMP Ordinance** (MHLW Ministerial Ordinance No. 179, 2004).
  - ➢ Applies to manufacturing sites in Japan, but also **to foreign manufacturing sites of the products to be exported to Japan**
- The current GMP Ordinance has resulted from comprehensive amendment to the former GMP Ordinance (MHLW Ministerial Ordinance No. 16, 1999), having **harmonized with ICH Quality Guidelines.**

Concept of Manufacturing Control & Quality Control, Prescribed in the GMP Ordinance



Manufacturing Control & Quality Control by Manufacturer

◆ PIC/S GMP Guides

provide various methods to ensure product quality, as useful references for implementing GMP.

➢ If applicable, each manufacturer is expected to utilize relevant PIC/S GMP guides as references, **on its initiative**.

PIC/S

Pharmaceutical Inspection Convention and
Pharmaceutical Inspection Co-operation Scheme

◆ An International Framework for Cooperation among Competent Authorities responsible for Pharmaceutical Inspection

- ➢ 48 participating authorities from European countries and others (as of Jan. 2016)
- ➢ Japan's competent authority (MHLW, PMDA and 47 prefectural inspectorates) has become one of PIC/S participating authorities, since Jul. 2014.

◆ Activities;

i. **International Harmonization on Pharmaceutical GMP**
ii. International Cooperation on Pharmaceutical Inspection, such as information sharing and training, etc.

Manufacturing Control & Quality Control for APIs

- **Stepwise Control,**
  in accordance with process advancing from early steps to final steps, purification and packaging,
- **Specified Control with Emphasis,**
  after the critical process for quality of the API product
  - To determine beforehand which step requiring specific control
  - **ICH Q7 guideline** is a good reference utilizable for manufacturers of APIs

Manufacturer's Responsibility

- Besides routine Manufacturing Control & Quality Control, **periodic duties for ensuring product quality** should be undertaken under **the manufacturer's system* for managing quality**.
  - **Product Quality Review**;
    Article 5 of the GMP Ordinance, ref. ICH Q7 2.5
  - **Periodic Review of Validated Systems**;
    Article 13 of the GMP Ordinance, ref. ICH Q7 12.6
  - **Internal Audits (Self Inspection)**;
    Article 18 of the GMP Ordinance, ref. ICH Q7 2.4
  - **Training**; Article 20 of the GMP Ordinance, ref. ICH Q7 3.1

*** ICH Q7 2.11**

"Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel."

Manufacturer's Responsibility

◆ Quality Risk Management

Manufacturer's Initiative to establish Scientific Evaluation and Management regarding the Manufacturing Process, as one of the components for good Manufacturing Control & Quality Control

- ➢ Each Manufacturer is expected to consider **Quality Risk Management** as effective evaluation methods for promoting continuous improvement of the validity of the manufacturing process & the product quality.

- ICH Q9; Quality Risk Management (2005)
  - ➢ Provides principles and examples of tools for **quality risk management** that can be applied to different aspects of pharmaceutical quality

■ Quality Assurance
by Marketing Authorization Holder

Quality Assurance
by Marketing Authorization Holder

◆ Under Japan's legislation, implementation of Manufacturing Control & Quality Control at the manufacturing site (including for APIs) is **one of the Requirements for Marketing Authorization (MA)** of the finished product, in principle.

- Implementation of Manufacturing Control & Quality Control at the manufacturing site, is undertaken by the manufacturer itself, but also **assured under the supervision by the MA holder** who entrusts its product manufacturing.

Quality Assurance
by Marketing Authorization Holder

◆ Product Recall **caused by GMP deficiencies at the Manufacturing Site** (including Foreign Manufacturing Site), has sometimes occurred.

- MA Holder of the Product should bear the Recall Cost, primarily.
  (due to the Responsibility for the Marketed Product)

Marketing Authorization Holder's Responsibility

- The Ordinance on Standards for Quality Assurance (**the GQP Ordinance**, Ministerial Ordinance No. 136, 2004) is enacted as **one of the requirements for Licensing of MA Holder**.

Key Points of the GQP Ordinance

- Article 5: Quality Standard Code
- Article 7: **Contract with Manufacturers** (including Foreign Manufacturers)
- Article 9: Control of Market Release
- Article 10: **Ensuring Proper Manufacturing Control & Quality Control at the Manufacturing Site** (including Foreign Manufacturing Site)
- Article 11: Handling Information on Quality, etc. and Quality Defects, etc.
- Article 12: Handling Product Recall
- Article 13: Self Inspection
- Article 14: Training

Marketing Authorization Holder's Responsibility

- Article 7 of the GQP Ordinance;

Key items to conclude a contract with manufacturers (including foreign manufacturers)

- The nature and extent of **the periodical verification**, by the MA holder, **of the manufacturing duties** that they are **conducted under the proper and efficient manufacturing control & quality control**,
- **The procedures and the responsible persons to communicate**, in advance, any change in the manufacturing procedure, testing procedure, etc. to the MA holder, in case where such a change could affect the quality of the products,

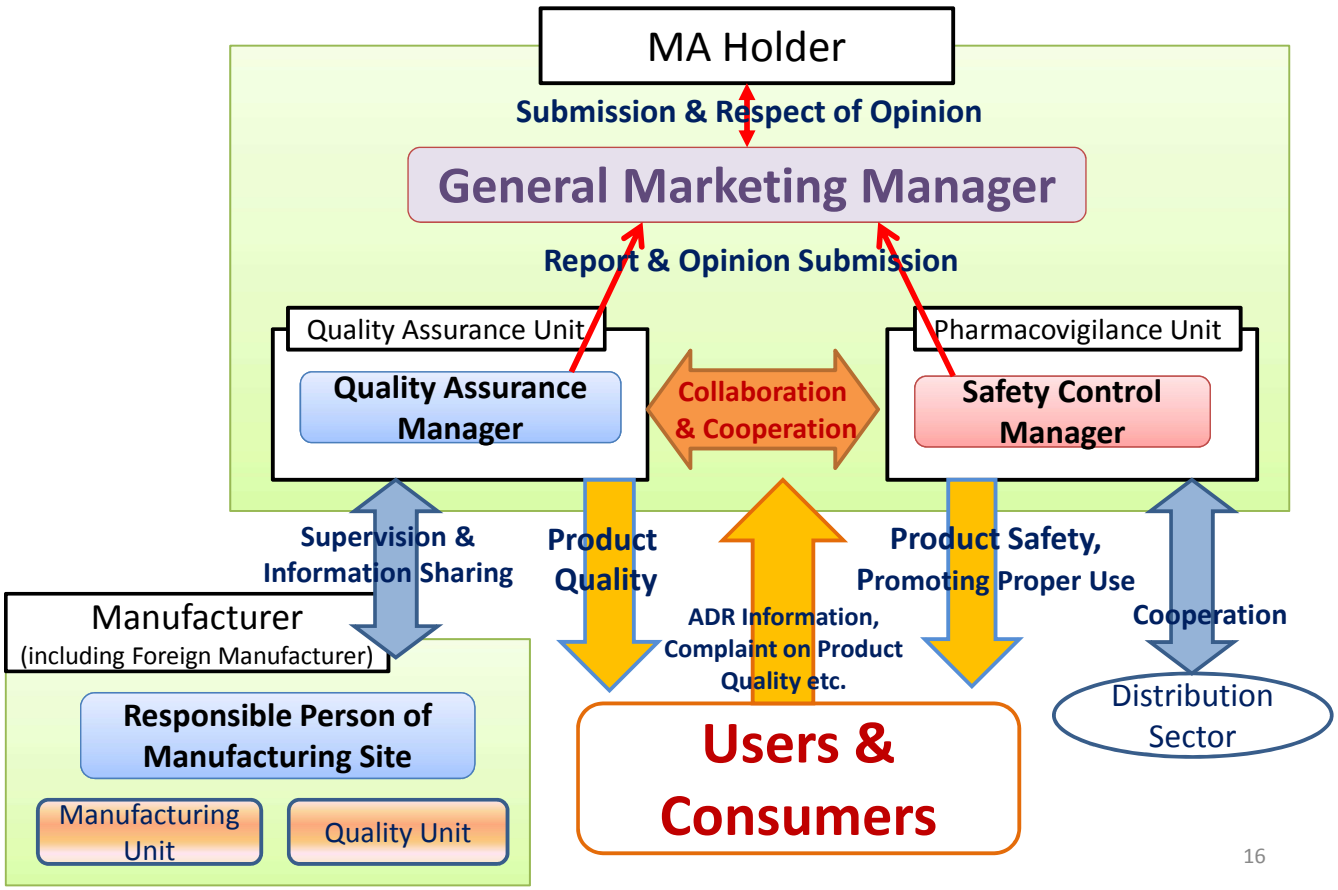
Marketing Authorization Holder's Responsibility

◆ Article 10 of the GQP Ordinance;

Ensuring Proper Manufacturing Control & Quality Control at the Manufacturing Site (including foreign manufacturing site)

- **Obtaining relevant information** from the Manufacturer (including Foreign Manufacturer),
- **Periodical verification (on-site, if necessary)** that the Manufacturing Control & Quality Control is conducted properly by the Manufacturer (including Foreign Manufacturer)

The Functions of Marketing Authorization Holder



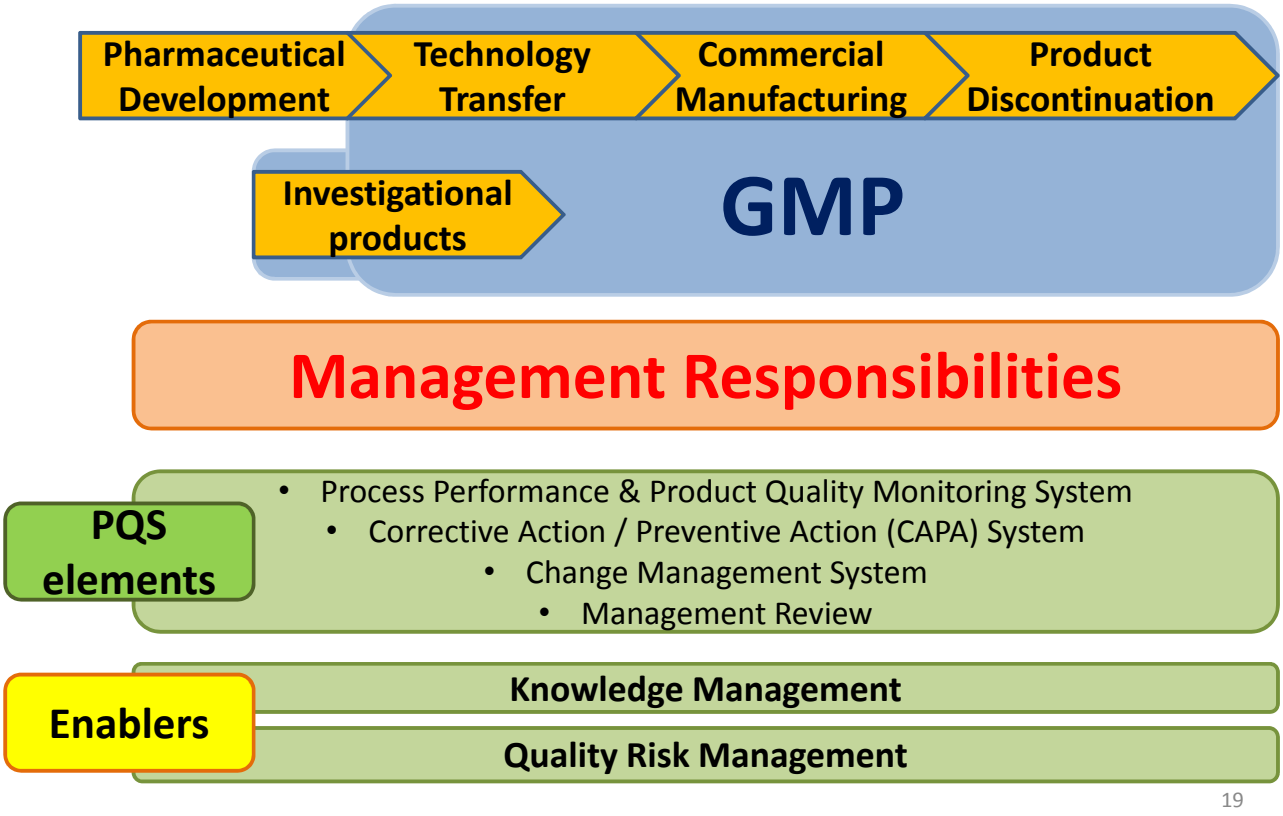
ICH Q10
(Pharmaceutical Quality System)

- Applies to the systems supporting the development and **manufacture of pharmaceutical drug substances (i.e., API) and drug products**, throughout the product lifecycle
- Describes one comprehensive model for an effective Pharmaceutical Quality System that is based on ISO quality concepts, **includes applicable GMP regulations and complements ICH Q8 and Q9**

ICH Q10
(Pharmaceutical Quality System)

- **Three main Objectives**
  - Achieve Product Realization
  - Establish and Maintain a State of Control
  - Facilitate Continual Improvement
- **Management Responsibility**
  - **Management Commitment**
  - Quality Policy
  - Quality Planning
  - Resource Management
  - Internal Communication
  - Management Review
  - **Management of Outsourced Activities and Purchased Materials**
  - Management of Change in Product Ownership

ICH Q10
Pharmaceutical Quality System Model



■ GMP Inspection
by Competent Authority

GMP Inspection
by Competent Authority

◆ Japan's Competent Authorities

- Office of Manufacturing/Quality and Compliance, Pharmaceuticals and Medical Devices Agency (PMDA)
- 47 Prefectural Inspectorates

Demarcation between Japan's Inspectorates

◆ PMDA conducts GMP Inspections

- On **Foreign Manufacturing Sites**, or
- Regarding **the drugs** (including APIs) **requiring special attention in terms of Manufacturing Control & Quality Control**, such as
  - ✓ New Drugs
  - ✓ Biological Products
  - ✓ Products utilizing Genetical Recombination Technology
  - ✓ Products utilizing Cell Culture Technology
  - ✓ Radio Pharmaceuticals, etc.

◆ **Prefectural Inspectorates** conduct GMP Inspections on Local Manufacturing Sites in Japan, regarding the products other than above, as of generic drugs, OTC drugs, etc.

GMP Inspection by Competent Authority

◆ Types of GMP Inspection (1)

● GMP Audit

for which the Marketing Authorization (MA) Holder or the manufacture submitted an application regarding their products

➢ **Pre-Marketing GMP Audit** for MA
(including partial change of existing MA)

➢ **Periodical GMP Audit** after MA
as **a Requirement for Maintaining the MA**, **at least Once every Five years** after MA of the product

➢ **GMP Audit regarding manufacture of the products to be exported from Japan**
where a GMP certificate being requested by foreign government and/or International Organization, regarding the domestic manufacturing site

GMP Inspection by Competent Authority

◆ Types of GMP Inspection (1)

● GMP Audit categorized by method

➢ **On-site Audit**

to be conducted **at least Once every Two years approximately** in principle, to each manufacturing site

➢ **Dossier Audit (Desk-top Audit)**

may be substituted for the on-site audit, taking into account of

- ✓ The type of the product to be audited
- ✓ The manufacturing process of the product to be audited
- ✓ The changing history of the manufacturing facilities
- ✓ The results of previous GMP inspections to the site
- ✓ Previous product recall caused by the site, etc.

GMP Inspection by Competent Authority

◆ Types of GMP Inspection (2)

● **GMP Surveillance**

to be conducted **if needed by relevant Competent Authority, even though not requested by the MA Holder/the Manufacturer**, to the manufacturing site, pursuant to the provision in Article 69 or Article 75-4 paragraph 2 of the PMD Act.

➢ **Usual Surveillance**

may be conducted without notice, taking into account of the previous GMP deficiencies and/or the degree of requiring Manufacturing Control & Quality Control

➢ **Special Surveillance**

to be **conducted without notice, in principle, regarding pernicious non-compliances** e.g. fraud etc. (including suspicious cases)

GMP Inspection by Competent Authority

◆ Types of GMP Inspection (1) + (2)

➢ Competent Authorities may conduct **a surveillance without notice**, concerning the matters which the manufacturer does not anticipate, **during the notified GMP Audit** which have been requested by the MA Holder/the Manufacturer.

GMP Inspection by Competent Authority

- Competent authorities carry out GMP Inspections by **sampling of certain products / manufacturing processes in a certain period**.
  - As a matter of fact, Inspectors would be able just to confirm practically some parts of Manufacturing Control & Quality Control at the site, without staying there long term.
- **Relevant Companies** (the manufacturer(s) and the MA Holder of the product) are expected **to achieve the necessary and appropriate product quality, by themselves**.

GMP Inspection by Competent Authority

- However, only through the efforts of relevant companies, it would not be sufficient **to be trusted by users/consumers of the product and foreign authorities, etc**.
  - GMP Inspection by Competent Authority would **support the companies engaged in ensuring product quality earnestly**.
  - **Taking appropriate administrative action** to the companies not complying with the rules which have been internationally consented, e.g. ICH Quality Guidelines, would **lead to improve the confidence to the entire of pharmaceutical industry**.

International Cooperation on GMP Inspection

◆ PIC/S

Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

➢ to provide the framework for all necessary exchange of information and experience in the field of GMP

- **Procedure to inform Foreign Regulatory Agencies of Foreign Inspections to be conducted in their Jurisdiction**

  – came into effect since Nov. 2015

  ✓ the date of the last inspection

  ✓ the possibility to share available inspection reports (in the language in which the inspection report was written)

  ✓ where appropriate, request for opportunities to participate as an observer in the inspection or explore options for that of a joint inspection

Japan's Participation in PIC/S

- **Mar. 2012**;
  MHLW submitted the application form to the PIC/S office.
- **May 2012**;
  Japan's application was accepted at the PIC/S Committee.
- **Sep. 2013**;
  Local assessment was conducted in Japan.
  - ➢ **As preparatory efforts for participation in PIC/S, Japan upgraded its GMP System in each inspectorate**, including training of inspectors of PMDA and 47 prefectural inspectorates, revision of GMP inspection manual etc.
- **May 2014**;
  Japan's application for participation in PIC/S was approved at the PIC/S Committee.
- **Jul. 2014**;
  Japan's Competent Authority (MHLW, PMDA and 47 prefectural inspectorates) officially became **the 45th PIC/S participating authority**.

- **Participation in PIC/S** proves that the participating authority possess GMP Inspection system on a certain international level, however, does **not ensure the equivalence of GMP requirements and their implementation** among participating authorities.

Bilateral Cooperation on GMP Inspection

- Exchange of Letters for the establishment of a mechanism for facilitating **the mutual exchange of GMP inspection information**, between competent authorities of **Australia and Japan**, in Apr. 1993
  - **Recognizing the equivalence of GMP inspection system between Australia and Japan**, PMDA ascertains GMP conformity of the products manufactured in Australia, in principle, through the GMP certificate issued by the Australian competent authority, TGA.

Bilateral Cooperation on GMP Inspection

◆ Mutual Recognition Agreement **(MRA)** between **Japan and the European Community**, including GMP for medicinal products, since May 2004

- The Scope of MRA are currently limited to **chemical pharmaceuticals** (*excluding* **APIs and sterile products**).
- European competent authorities which are **confirmed the equivalence of GMP requirements and their implementation** were **expanded** from previous 15 countries **to 28 countries** (**All EU members**), in Apr. 2016.

Business Counterparts for GMP System

■ Manufacturing Control & Quality Control

➢ **Indian Manufacturer**

■ Quality Assurance

➢ **Japanese Pharmaceutical Company as MA Holder**

■ GMP Inspection

➢ **MHFW/CDSCO** (India)

➢ **MHLW/PMDA** (Japan)

Thank You for Listening

GMP Inspection by PMDA

Masatoshi Morisue

Office of Manufacturing/Quality and Compliance

PMDA

Today's Contents

- GMP inspection procedures and on-site inspection status
- Inspection under the global harmonization
- Examples of findings at manufacturing sites in India
- What PMDA see from Case Studies
- Issues prior to the GMP Compliance

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GMP Inspection by PMDA
Number of the sites (as of April 2014)

- Overseas manufacturing sites: About 3100
  - ”Accredited” sites : 2872
    - Asia, Middle East: 1220
    - Europe : 1091
    - North America and others : 561
  - No “Accredited”-required sites (API intermediates, etc) : About 200
- Domestic manufacturing sites: About 440
  - Inspected by PMDA: 81
    - Biological products, etc.: 62
    - Radio-pharmaceutical product : 19
  - Sites involved in new drugs: About 350

Inspection Procedure

- **Summary on products subject to inspection at manufacturing facilities in question : Form No 1**
- **Summary on pharmaceutical manufacturing facilities (for overseas facilities) : Form No 3**

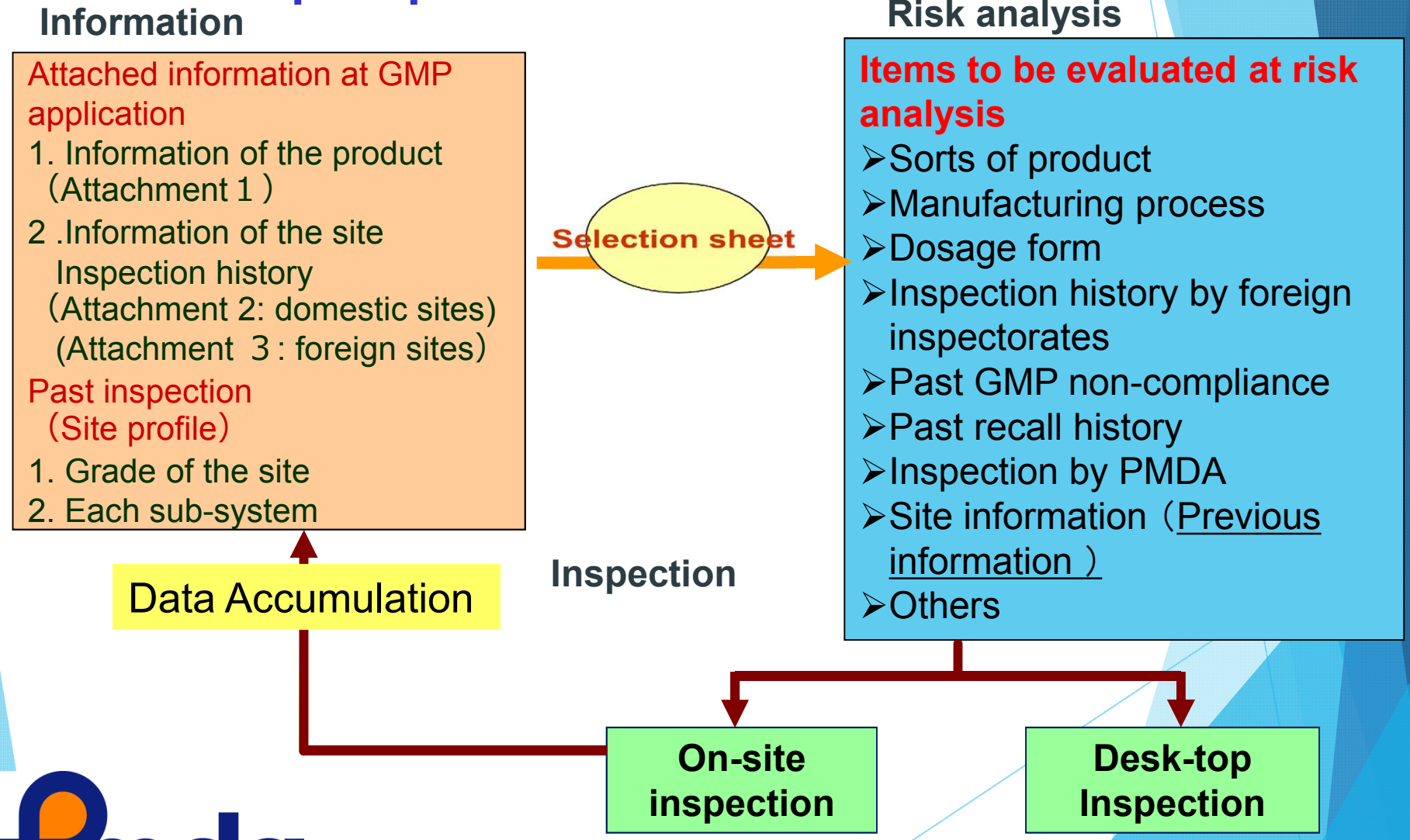
- **Risk based approach**
- **Decide inspection methods**

- **On-site inspection : Schedule adjustments → Prewritten (draft) documents**
- **Document-based inspection : Inspection documents**

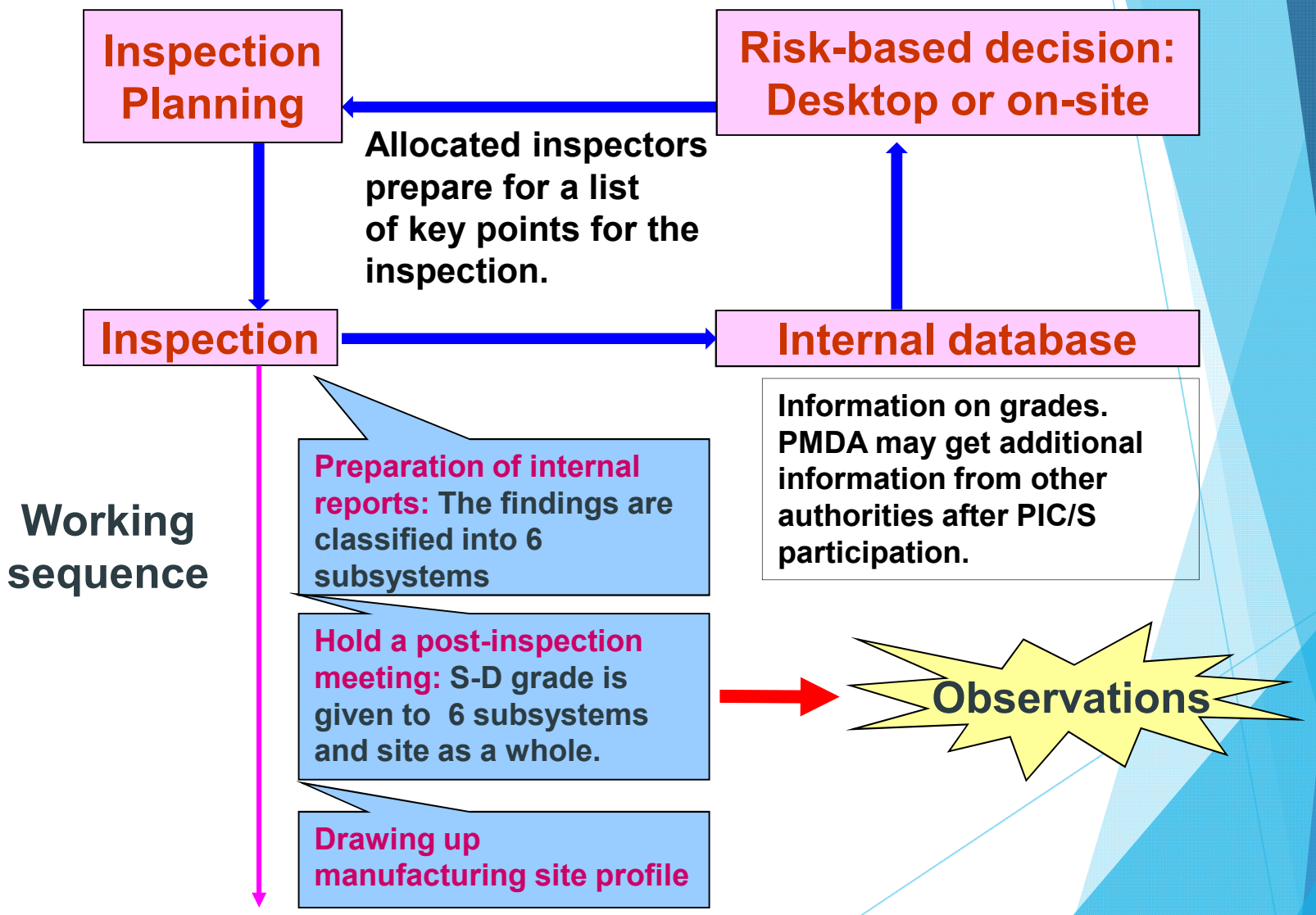
- **Discrepancy between actual and applied manufacturing methods**
- **Reconfirm compliance to GMP**

- **On-site inspection : Findings, grading manufacturing sites**
- **Document-based inspection : Reconfirming by referral documents**
- **Check discrepancies**

PMDA:
Risk-based approach in selecting on-site inspection or desk-top inspection

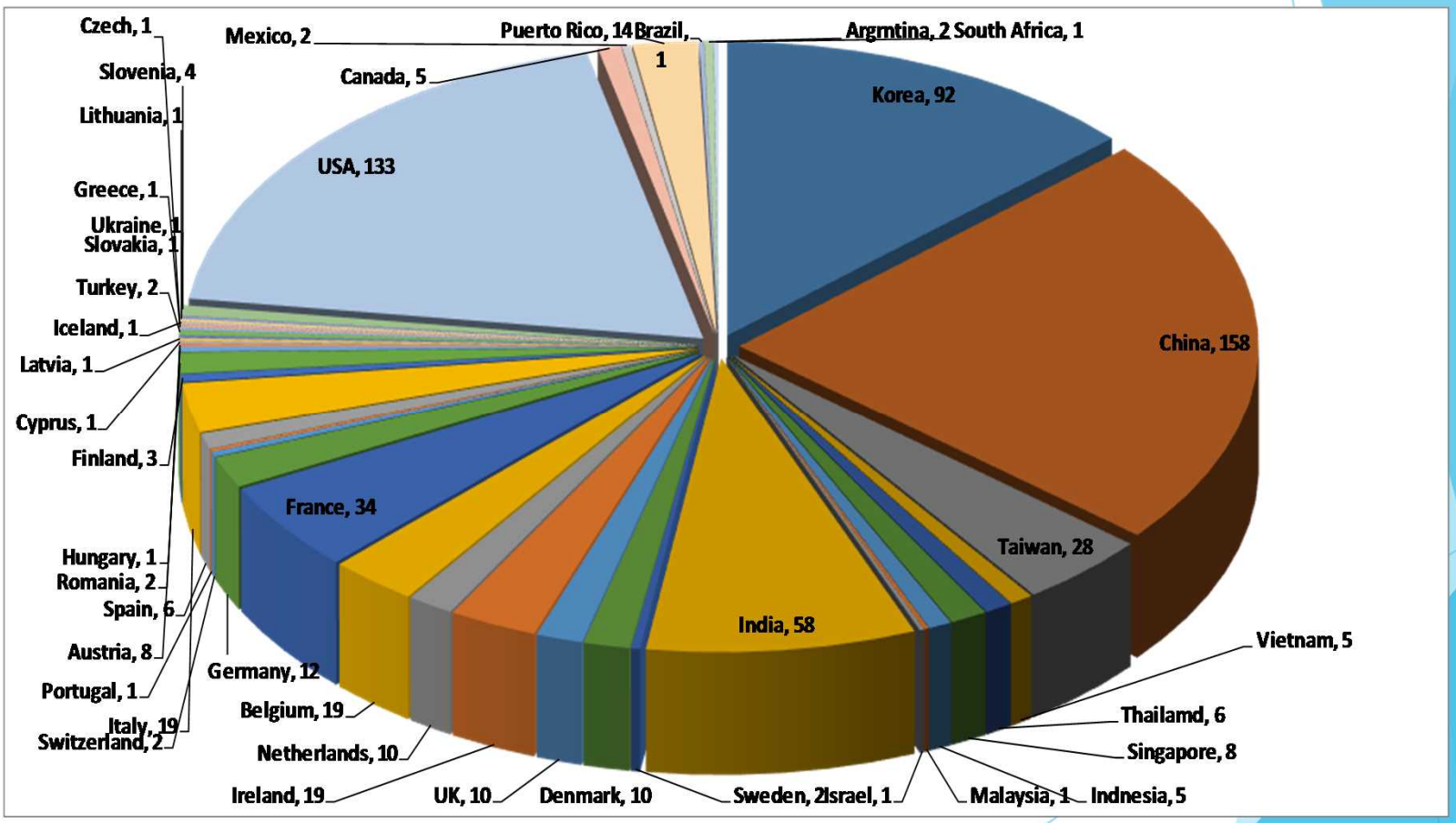


PMDA's on-site GMP inspection cycle



Overseas on-site GMP inspections by PMDA

2005.4～2015.12（684sites, 43 countries）



Summary of PMDA Inspections in India

PMDA's Overseas On-Site Inspection / On-Site Inspection to Manufacturing Sites in India

	2011	2012	2013	2014	2015
Number of PMDA's Overseas On-Site Inspection	61	65	66	71	65
Number of On-Site Inspection in India ◆ (Site Evaluation：C/D)	4 (0/0)	4＊ (0/2)	2 (0/1)	2 (0/0)	20 (1/0)
Percentage to Total Number（%）	7	6	3	3	3 1

◆**Manufacturing Sites were graded as S,A,B,C,D according to PMDA's On-Site Inspection**

D*：*Manufacturers in non-compliance with GMP
C: Manufacturers in compliance with GMP but needed to be given continuous instructions

Breakdown on On-Site Inspection in India

	2011	2012	2013	2014	2015
Drug Substances/Intermediates of Active Pharmaceutical Ingredients (including sterile)	4	2＊	0	2	15
Over The Counter Products	0	1＊	2	0	1
Sterile Products	0	2＊	0	0	4
Percentage to Total Number of Drug Substances（%）	100	50	0	100	75

＊Inspection on Drug Substance, OTC Products and Sterile Products per one Manufacturing Site

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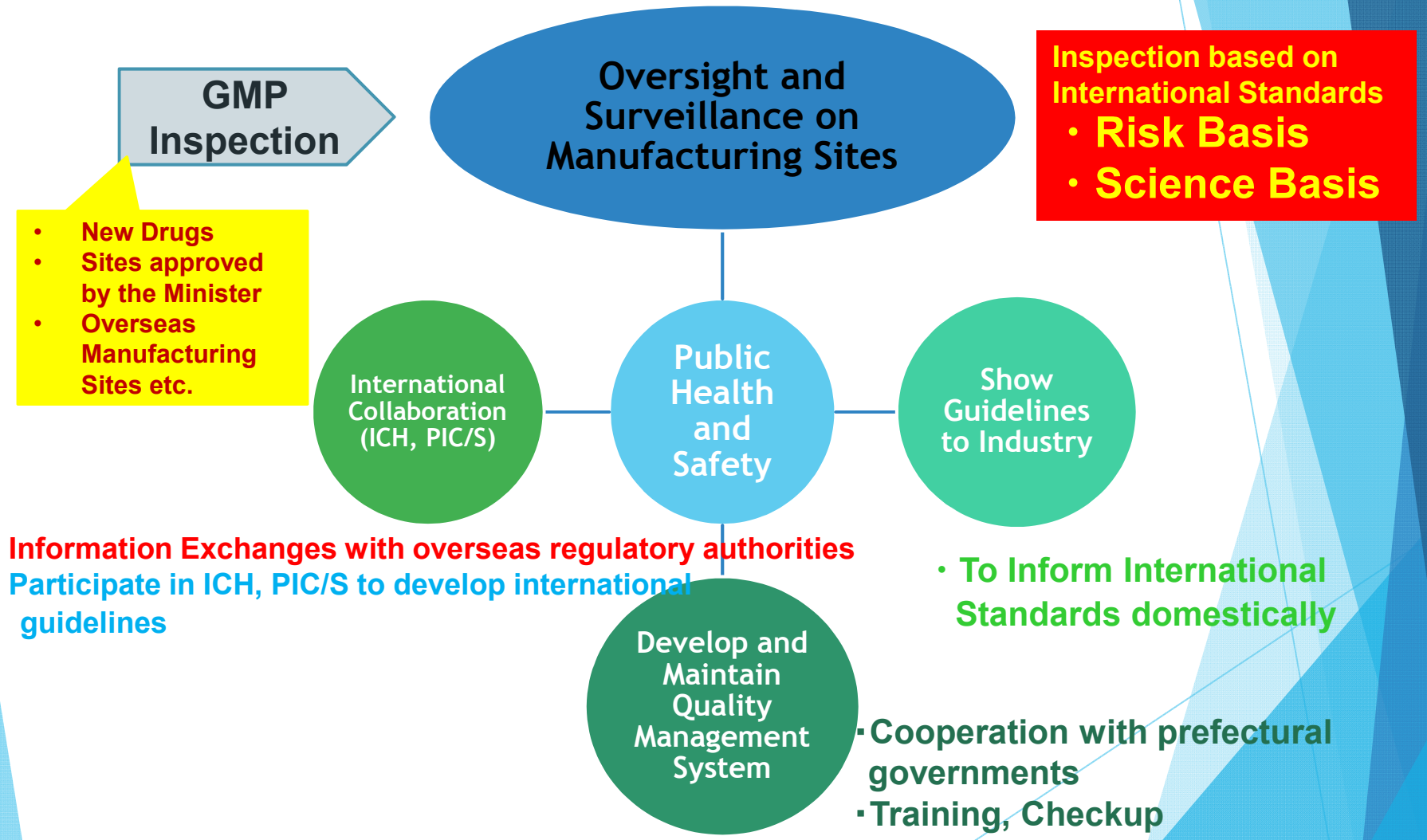
Oversight and Surveillance on Pharmaceutical Manufacturing Sites

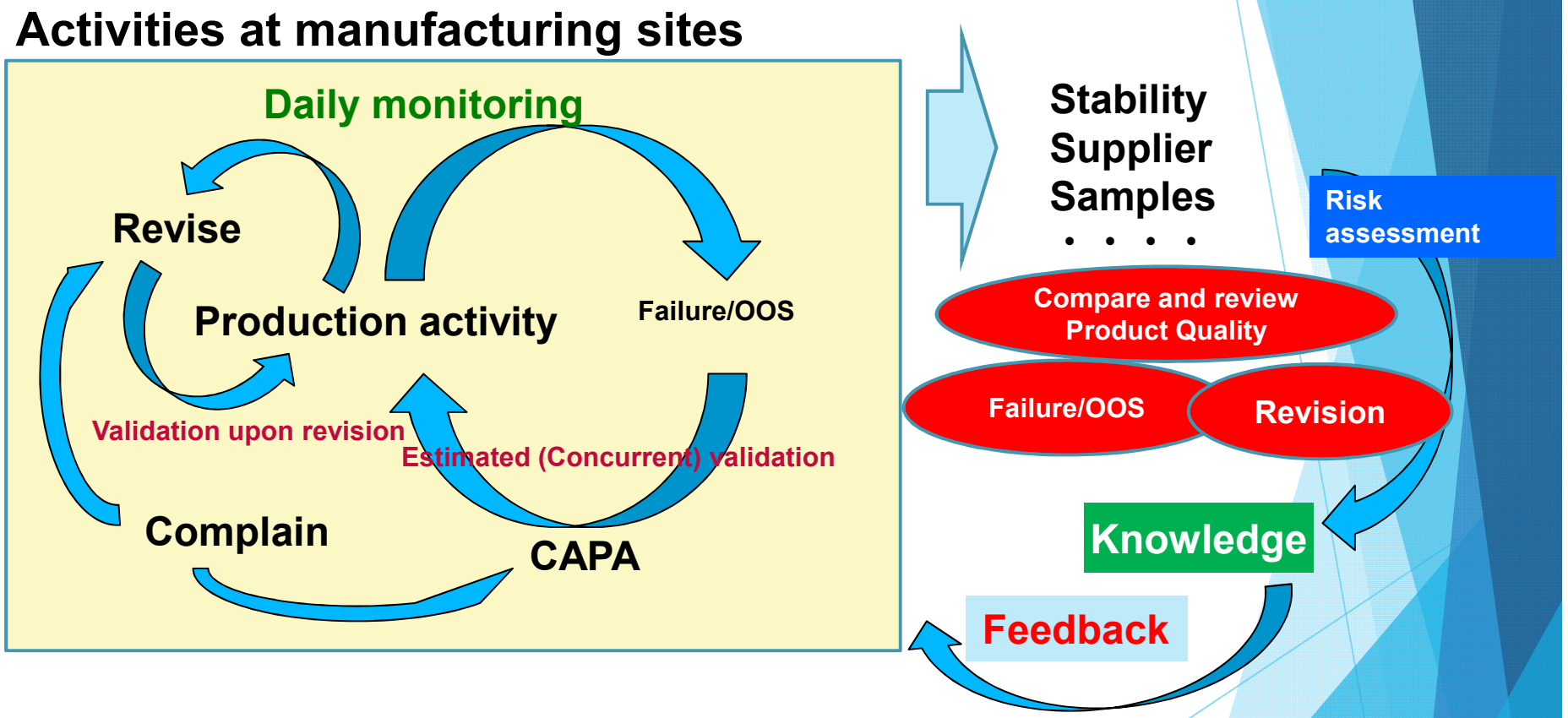


GMP Inspection (International Standards)

- **Risk based and science based**
  - ICH Q7/Q8/Q9/Q10/Q11
  - PIC/S guidelines

- **Life Cycle Management**
  - Risk management ideas reflected on overall notification
  - Compare and review product quality (annual review)
  - Oversight on manufacturer (supplier) for raw materials
  - Stability monitoring for products and raw materials

Quality System and Life Cycle Management



Manufacturing sites
(complied with GMP)

Manufacturing sites which are operated by risk based management under the scientific backgrounds

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Prevent Cross-Contamination

- Method on cleaning were not verified in advance
- Validation of cleaning were not applied
- No evaluation on the appropriateness of cleaning method at single-purpose facility
- No evaluation on the cross-contamination risk with multiple products at a common facility
- No evaluation on the appropriateness of an on-site visual confirmation after cleaning

Containment

- Single changing room was used
- Powder drifting workroom was positively pressurized
- Treatment of drug substance adhered to production record was not appropriate
- There was no specific procedure for air filters replacement
- Monitoring had never been performed to confirm the level of containment at the manufacturing building

Compare and Review Product Quality

* Product Quality is not compared and reviewed as to determine whether products are manufactured under proper condition or still have room for improvement.

- Failure, revision, and complaints were not considered
- Although the percentage of impurities of a product is not normal, no specific actions were taken

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Consideration - Manufacturing Sites

- Condition of manufacturing equipment is Inappropriate
- No evaluation is made on cross-contamination risk
- Method on cleaning is inappropriate

…

Complied with the specified test of products

There’s no Problem

What is GMP ?

Passive Activities

Standard of methods for manufacturing management and quality control which is strictly required to comply by the Pharmaceutical and Medical Devices Act.

Positive Activities

Measures to guarantee the quality of manufactured products

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- **Issues prior to the GMP Compliance**
- Summary

Issues prior to the GMP compliance

- To recognize compliance at the company in total
- A full control of the company by its top leader
- Education to all workers in the company
- To share common responsibility with all staffs of their commitment to producing “Life-Related Products”.
- Powerful quality management system in place at the company.

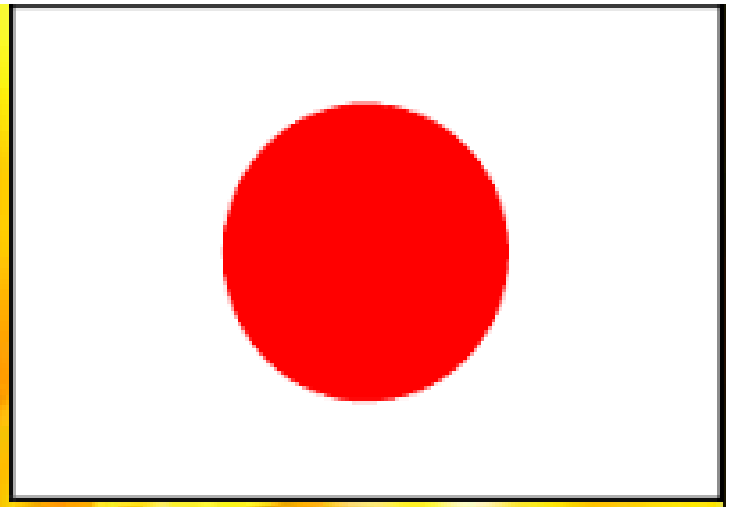
  Policy on quality → Target for quality → Management review

Administrative inspection is just “sampling”. Importance for companies Is to manufacture their products on its own responsibility.

Basis of GMP Activities

- Risk Based Ideas
  - Sort out risk for the worse case scenario
  - Require rationality on risk based ideas
  - Require predictability to keep up with shifting risks
  - Enable to explain in a logical manner
- Quality Assurance
  - Quality management system at the manufacturing site is the basis of quality assurance. A robust system increases the level of quality assurance.
- Education on Quality
  - People generate culture at manufacturing sites

Thank you very much!!



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Central Drugs Standard Control Organization (CDSCO), HQ
Ministry of Health & Family Welfare, Govt. of India
www.cdsco.nic.in

GMP INSPECTION SYSTEM IN INDIA / PRACTICAL ASPECTS OF GMP

OUTLINE

- Drugs Regulation
- CDSCO and State offices
- Responsibilities under Drugs Regulatory System
- Regulation on inspection
- 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 Governments.

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:

1. New Drug/Medical Devices Approvals
2. Import of Drugs/Medical Devices/Cosmetics
3. Clinical Trials
4. Standards for Drugs
5. Amendments to Act and Rules
6. Pharmacovigillance

State Responsibilities:

1. License for Manufacture, Sale and Distribution
2. Monitoring quality of Drugs and Cosmetics
3. Investigations and Prosecutions

REGULATION ON INSPECTION

- **Regulatory Provisions**
  - **Rule 68:** Manufacture on more than one of premises.
  - **Rule 68-A:** Grant or Renewal of Licences by the Central Licence Approving Authority.
  - **Rule 68-B:** Delegation of Powers by the Central Licence Approving Authority.

REGULATION ON INSPECTION

- **Regulatory Provisions**
  - **Rule 79:** Inspection before grant or renewal of licence
  - **Rule 80:** Report by Inspector
  - **Rule 81:** Procedure of licencing authority
  - **Rule 82:** Further application after rejection
  - **Rule 83:** Renewal inspection
  - **Rule 84-A:** Provisions for appeal to the State Government or Central Government by party whose licence has not been granted or renewed
  - **Rule 85:** Cancellation and suspension of licences

REGULATION ON INSPECTION

Standards for Inspection:

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

Personal Responsible for Inspection:

- Inspectors are appointed by the Central and the State Governments under section 21 of Drugs and Cosmetics Act.
- Roles and responsibilities of Inspectors are defined in section 23 of Drugs and Cosmetics Act which include 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.

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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 - licence 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 PROCEDURES

- 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

INSPECTION PROCEDURES

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

- 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

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India-Japan Medical Product Regulation Symposium

Challenges in Stable Supply of Pharmaceutical Products to Japan

Dr. Sanjit Singh Lamba

Managing Director

18th May, 2016



hhc
human health care

EISAI PHARMACEUTICALS,VIZAG

ACCREDITATION OF EISAI INDIA'S FACILITY OF GLOBAL REGULATORY AUTHORITIES

- **May 2010**
- Schedule "M" GMP Certification

Indian FDA

- **June 2011**
- Approval for Aricept Tablets (Donepezil Hydrochloride)

PMDA (JAPAN)

- **Nov 2011**
- Approval for Donepezil Hydrochloride & Aricept Tablets

US FDA (U.S.A.)

- **May 2012**
- Approval for Donepezil Hydrochloride

MHRA (UK)

- **Nov 2012**
- Approval for Donepezil Hydrochloride

KFDA (Korea)

- **Feb 2013**
- WHO Approval for Diethyl carbamazine (Citrate tablets)

WHO

KEY BUILDINGS



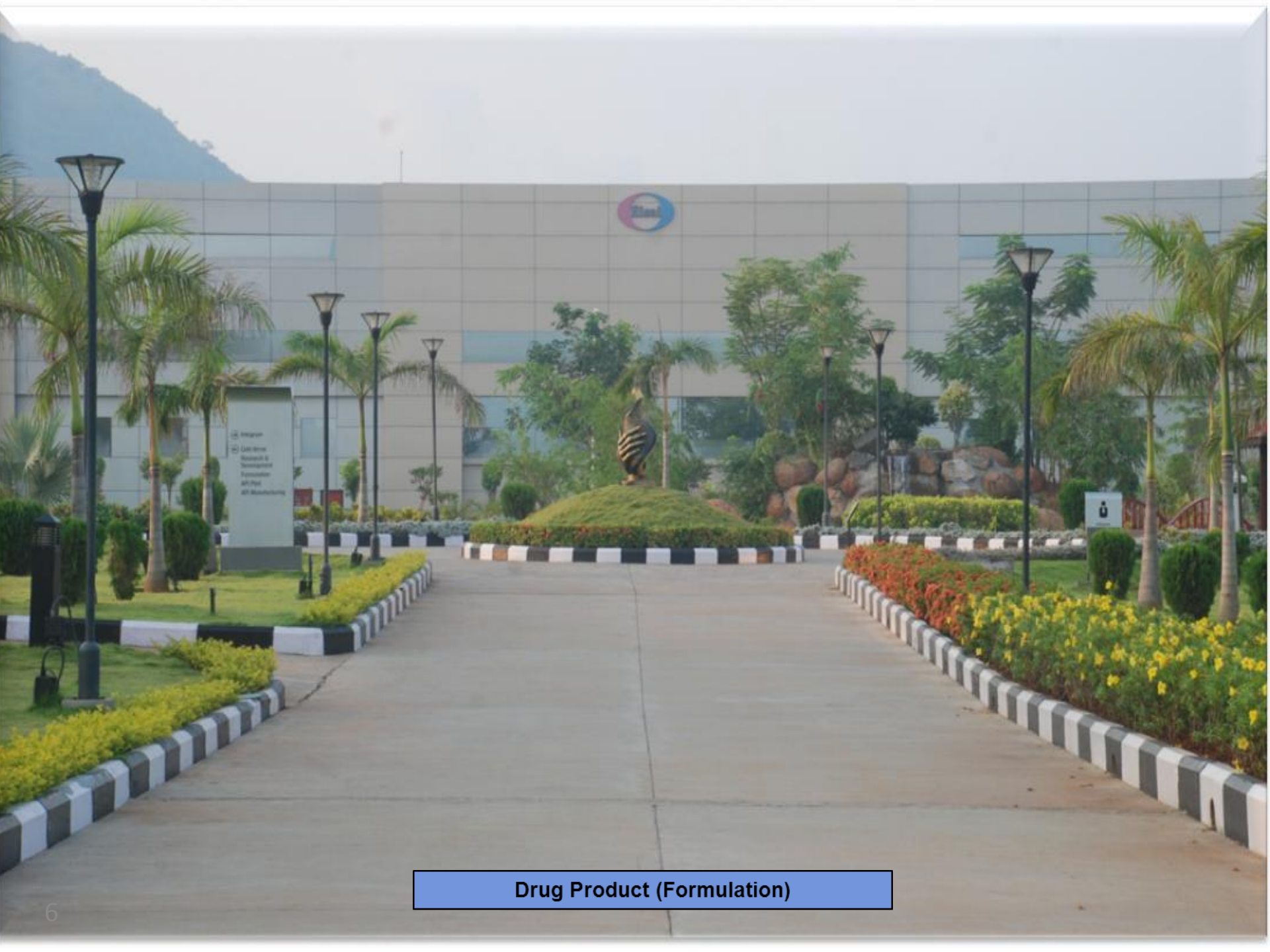









Drug Substance (API)


Drug Product (Formulation)

Clean Corridor

Courtyard /Mezzanine

Process Research Lab

Awards and Recognition

FOYA – Category Winner by ISPE 02nd May, 2012 (Facility of the Year Award)

EHS Excellence Award 2012, 2013 and 2014 by CII

UBM Indian Pharma Awards 2013 - Winner for Excellence in Corporate Social Responsibility

OTHER ACCOMPLISHMENTS IN FY2015 – AWARDS & RECOGNITIONS

National Excellence Award 2015
The Best R&D in Pharmaceuticals

Global Awards for Excellence in Quality Management 2015

UBM India Pharma Awards 2015
Operational Excellence

* CII="Confederation of Indian Industry"

QUALITY CONTROL IN JAPAN

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

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

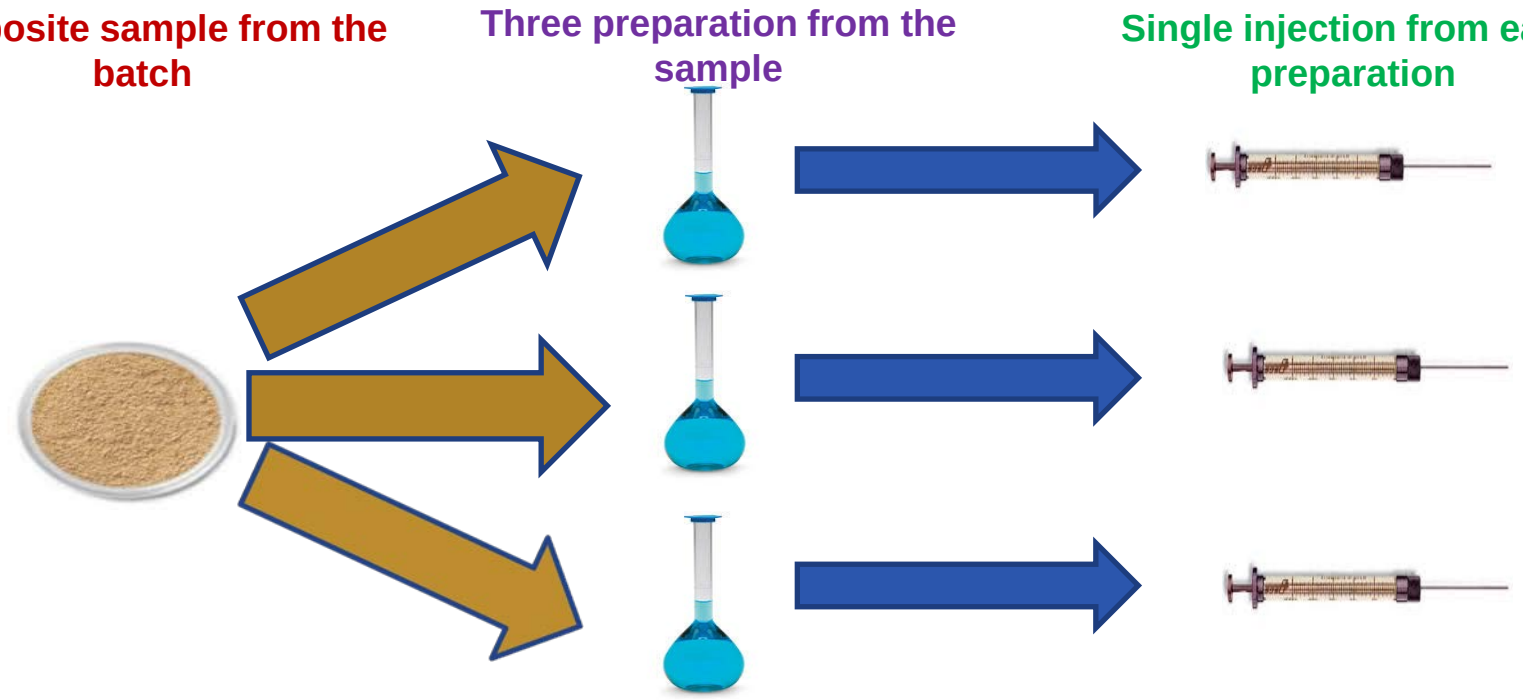
If consumers find small difference from regular products and even there is NO effect to their health, a lot of consumers start to worry

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

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

Analytical Testing in Triplicate for Generic submissions

Testing of stability samples and release testing sample 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)*



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 testing – Stringent limits

Residual solvents limits and Impurities limit for Japanese customer are very stringent

- *In most of the cases limits of the residual solvents are considered to be **1/10th of the ICH Limit***
- *The Impurity limit are set to be **1/10th of the specification (JP) limit***
- *Customer In-house specification requirements are very stringent*

Analytical testing – Stringent AQL limits

Japanese manufacturing company set up AQL as a part of the specification,. This AQL addresses detail specifications which correspond to the quality requirements received from the market.
Japanese AQL is severer than the most of other countries.

	USA	Germany	France	Japan
Critical	0.1	0.4	0.1-0.4	0-0.1
Major	0.25-1.0	1.0	1.0-4.0	0.15-0.25
Minor	2.5-4.0	NA	NA	1.0

Data source: JPMA

CONTAMINATION OF FOREIGN PARTICLE TO SOLID DOSAGE FORMS

Organism related:

- Hair, Bugs/insects → Voluntary recall
- Contamination of hair (human related)

Others:

- Voluntary recall depends on what kind of foreign particle / frequency in occurring
- A small piece of metal object;
- Spot / single matter

→ Complaint handling

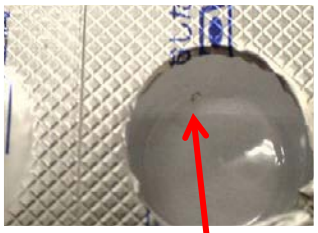

Black spot


Black spot


Black spot


Black spot


Unidentified Foreign particle


Paper powder

IDENTIFY THE PRIMARY FACTOR OF FOREIGN PARTICLES AND ITS IMPROVEMENT

Investigate the primary factor which is listed below and improve.

- API, Excipients
- Manufacturing processes
- Packaging materials
- Packing materials/Materials for transport
- Personnel

Need to prevent from contamination of Foreign Particle as much as possible!!!

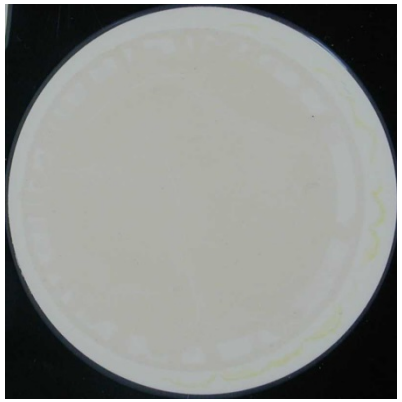
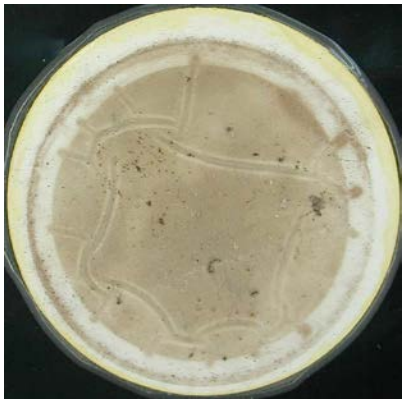
VISUAL INSPECTION

- At Visual inspection, it is too difficult to remove contaminated product
- It is very important to identify the primary factor of Foreign Particle and its improvement
- There is NO tolerance / allowance for contamination of Foreign Particle

→ **The target is ZERO!!!**

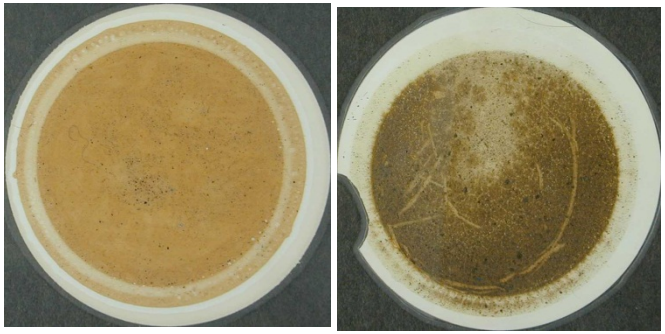
EXAMPLE OF FOREIGN MATTER (FILTER TEST)

Filtering a dissolved certain amount of API in suitable solvent.

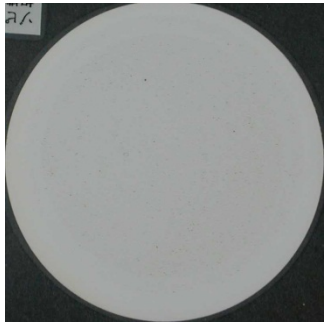




Samples from different supplier Their facilities meet GMP requirement and passed FDA audit）

Filtering a dissolved certain amount of API in suitable solvent.



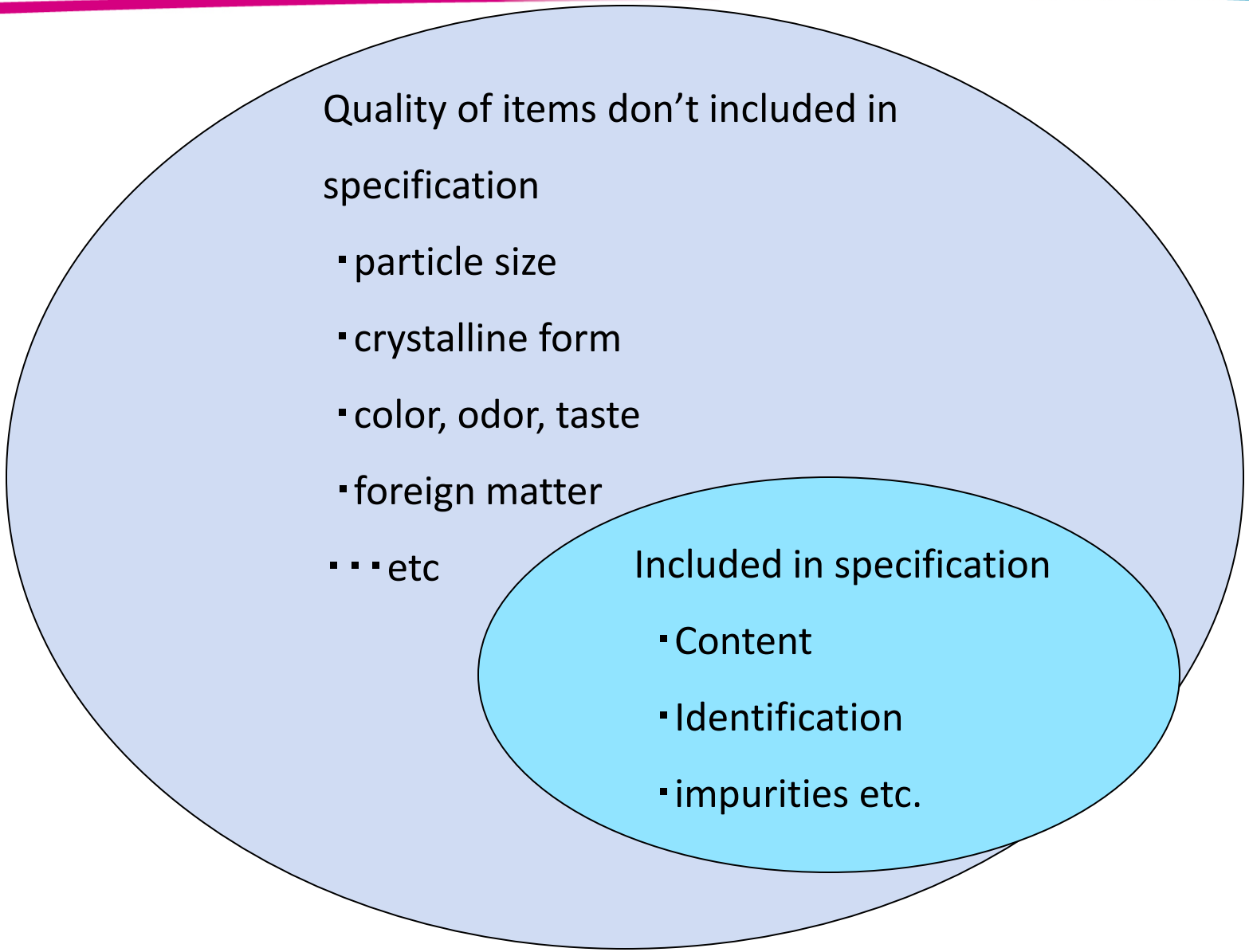
Samples from overseas supplier



Sample of Japanese Supplier

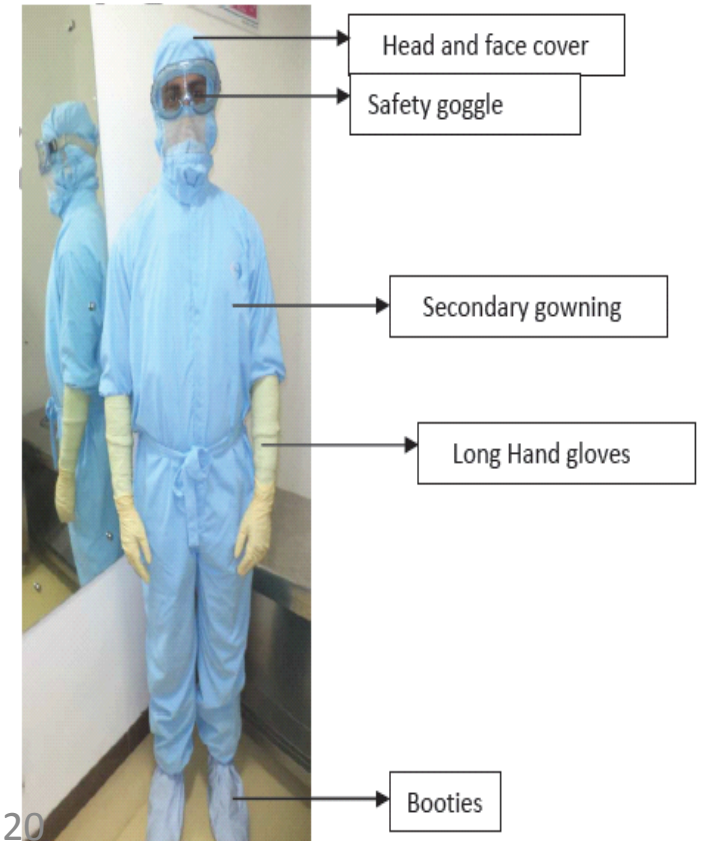
- Foreign matter also doesn't included in specification in many case
- We have to pay attention to these issues

QUALITY OF API



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 – Integrated Processing lines

Closed integrated processing line is an essential requirement to avoid human interventions as much as possible to avoid foreign matter and other contamination. *Approach - 2*

Integrated Granulation line

Integrated API Powder handling system

human health care

Facility & Manufacturing Controls – Highly sensitive equipment for foreign matter 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.

High speed tablet Inspection Machine

High sensitive metal Detector

API metal detection & Rejection M/c.

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

Foreign Matter identification by Quality control using advanced analytical techniques

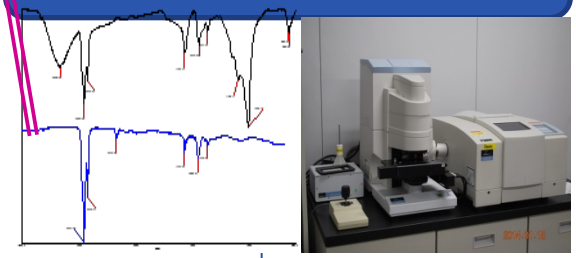
Foreign matter detection

Visual Inspection by Microscope

Judge the Nature of the Particle

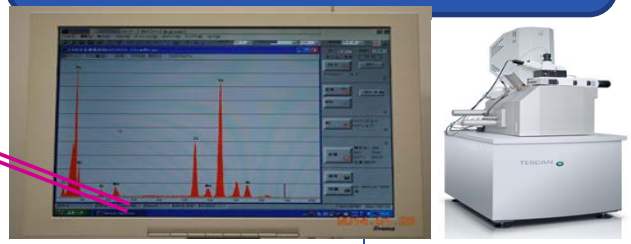
This characteristic peak shows as oil compound.

Microscope FT-IR



Scanning Electron Microscope & X-ray detector

Elemental analysis by X-ray detector



JUDGEMENT & Identifying the root cause

LESSONS -CONSIDER PATIENT AS GOD

- Japan is most stringent market for pharmaceuticals in terms of purity and cosmetic quality requirements
- Contamination control practices-Hair, Fibers, particles , insects etc
- Respecting the cultures of both the countries
- Past success with US/EU markets guarantees no success in Japan
- Kaizen for continuous improvements
- Tools for problem investigation and improvements like SQC
- Closed transfers in API and Formulation facility
- More focus on Critical process controls / CQAs
- Vestibules in each building including access control and pest management
- Communicate failures promptly to partners.

THANK YOU

ありがとうございました

बहुत बहुत धन्यवाद