2nd Japan - India Medical Products Regulation Symposium

1. GMP/Quality issues

Report back from the discussion in last year's symposium

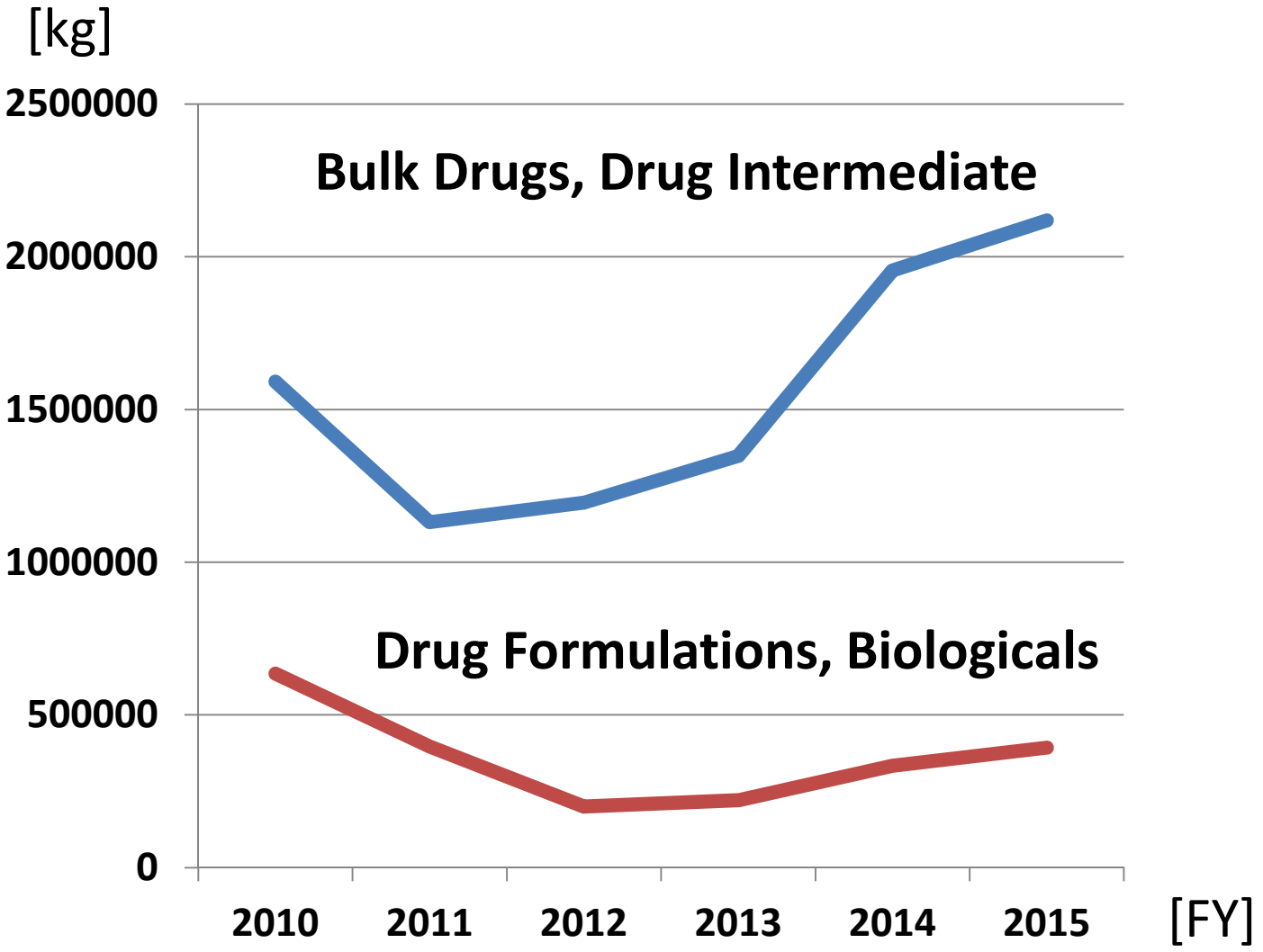
Mr. Fumihito Takanashi,

Office of International Regulatory Affairs

Ministry of Health, Labour and Welfare (MHLW)

April 24th, 2017

Drug Export from India to Japan (weight)



Source: Directorate General of Commercial Intelligence and Statistics, India

GMP Session at the 1st Symposium (May, 2016)

Major points at the 1st Symposium

Mr. Kudo (MHLW)/Mr. Morisue (PMDA)

- Risk-based approach (on-site/desktop inspection)
- International harmonization (ICH, PIC/S)

Dr. Somani (CDSCO)

- Regulation/Inspection procedure/Regulatory Actions
- Practical Aspects: Common deficiencies

Dr. Sanjit Singh Lamba (Eisai-India)

- Quality control in the manufacturing site
- Distinction between the regulatory requirements and business customary requirements

Slides available at: http://www.mhlw.go.jp/stf/houdou/0000125437.html

Cooperation started after the 1st Symposium

Agreement at the 1st symposium:

When PMDA conducts GMP on-site inspection for a pharmaceutical manufacturing site in India, based on the coordination with CDSCO in advance, PMDA accepts CDSCO to accompany the inspection as an observer.

On-site learning of GMP inspection methodology

PMDA-Asia Training Center
GMP Inspection Seminar in Toyama (Dec. 2016)

PMDA-ATC GMP Inspection Seminar 2016

Offered by Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC)

with the support of PIC/S

Around 20 inspectors from the world took the GMP course.

FY2017 Plan:
July 31 to August 4
@Yamaguchi prefecture
Registration by May 10

2nd India-Japan Medical Products Regulation Symposium

24th April 2017

Pharmaceutical GMP system of Japan

Toshiaki KUDO

Compliance & Narcotics Division

Pharmaceutical Safety and Environmental Health Bureau, MHLW Japan

Key Elements of Pharmaceutical 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 Drugs (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.**

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."

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

- 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
  - Japanese translation of ICH Q9 document (PFSB/ELD (Yakushoku-shinsa) notification No.0901004 and PFSB/CND (Yakushoku-kanma) notification No.0901005) issued on 1st September 2006.

Quality Risk Management

- The concept of **Quality Risk Management** has been implemented on manufacturing drugs (including APIs) under GMP Ordinance.
- 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.
  - For creating and disseminating mock models for good practice of Quality Risk Management, **The Federation of Pharmaceutical Manufacturer's Associations of Japan (FPMAJ)** have been collaborating with PMDA, supported under a MHLW regulatory science project.

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.

MA 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: **Agreement with Manufacturers** (including Foreign Manufacturers)
- Article 9: Control of Market Release
- Article 10: **Ensuring appropriate 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: Internal Audit
- Article 14: Training/Education of Personnel

MA Holder's Responsibility

- Article 7 of the GQP Ordinance;

Key items to conclude an agreement with manufacturers (including foreign manufacturers)

- The nature and extent of **the periodic audits** by the MA holder, **on the manufacturer's duties** which are conducted under the appropriate and efficient manufacturing control & quality control,
- **The procedures and the responsible persons to communicate** with the MA holder in advance, regarding any change in the production process, testing procedure, etc., in case where such a change may affect the product quality,

MA 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),
  - **Periodic audits (on-site, if necessary)** that the Manufacturing Control & Quality Control is conducted appropriately by the Manufacturer (including Foreign Manufacturer)

Pharmaceutical Quality System (ICH Q10)

- 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**

Pharmaceutical Quality System
(ICH Q10)

- **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

- GMP Inspection
  by Competent Authority

Japan's Competent Authorities

- Compliance & Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW
- Office of Manufacturing/Quality and Compliance, Pharmaceuticals and Medical Devices Agency (PMDA),
  as National Inspectorate, pursuant to the provision in Article 13-2 paragraph 1 of the PMD Act.
- 47 Prefectural Inspectorates

Respective Duties among Japan's Inspectorates

- **PMDA conducts GMP Inspections**
  - At **Foreign Manufacturing Sites**, or
  - At Domestic Manufacturing Sites, concerning **the drugs** (including APIs) **requiring special attention in terms of Manufacturing Control & Quality Control**, such as
    - ✓ New Drugs
    - ✓ Biological Products (Vaccines, Blood products, etc.)
    - ✓ Products utilizing Genetical Recombination Technology
    - ✓ Products utilizing Cell Culture Technology
    - ✓ Radio Pharmaceuticals, etc.
- **Prefectural Inspectorates** conduct GMP Inspections at Local Manufacturing Sites in Japan, concering the products (including APIs) other than above, as of generic drugs, OTC drugs, etc.

Types of GMP Inspection (1)

● Pre- & Post- Marketing GMP review

Conformity Assessment, for which **the Marketing Authorization (MA) Holder or the manufacturer make an application** regarding their products, pursuant to the provision in Article 14 paragraph 6 or 9 of the PMD Act.

- ➢ **Pre-Marketing GMP Review** for MA
  (including partial change of existing MA)
- ➢ **Periodical GMP Review** after MA
  as **a Requirement for Maintaining the MA**, **at least Once every Five years** after MA of the product

◆ **GMP Conformity Assessment on domestic manufacturing sites concerning of the products to be exported from Japan**

where a GMP certificate being requested by foreign government and/or International Organization, for which **the manufacturer make an application** regarding their products , pursuant to the provision in Article 80 paragraph 1 of the PMD Act.

Types of GMP Inspection (1) (cont.)

◆ Pre- & post- Marketing GMP Review

categorized by method

➢ On-site Assessment

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

➢ Dossier Assessment (Desk-top Assessment)

may be substituted for the on-site assessment, 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.

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**, at 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)

Types of GMP Inspection (1) + (2)

- Each inspectorate may conduct **a GMP surveillance without notice**, regarding the matters which the manufacturer does not anticipate, **in the course of the notified GMP Review** for which the MA Holder/Manufacturer made an application.

PIC/S

Pharmaceutical Inspection Co-operation Scheme

- An International Framework for Cooperation among Competent Authorities responsible for Pharmaceutical Inspection
  - 49 participating authorities from 46 countries/regions (as of January 2017)
- Activities;
  i. **International Harmonization on Pharmaceutical GMP**
  ii. **International Cooperation on Pharmaceutical Inspection, such as information sharing and training, etc.**

PIC/S

Pharmaceutical Inspection Co-operation Scheme

- Japan's competent authority (MHLW, PMDA and 47 prefectural inspectorates) has become one of PIC/S participating authorities, since July 2014.
  - **As preparatory efforts for accession to PIC/S, Japan's competent authority upgraded its GMP System**, including training/qualification of inspectors of PMDA and 47 prefectural inspectorates, GMP inspection manual, and regular meetings among GMP inspectorates, etc.
  - **At Pharmaceutical Industries**
    - **Promoting Quality Risk Management**
    - Implementation of Revised Standard on Validation
    - **Application of PIC/s GMP Guide**, etc.

PIC/S

Pharmaceutical Inspection Co-operation Scheme

◆ **International Harmonization on Pharmaceutical GMP**

➢ PIC/S GMP Guides

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

✓Recent Updates; Revised Chapters 1, 2, 6 & 7 of Part I of PIC/S GMP Guide, entered into force on 1st January 2017

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

➢ Pharmaceutical Industry GMP Standards

- on **Crude Drugs and KANPO Preparations**, ref. PIC/S GMP Guide **Annex 7**
- on **Medicinal Gases**, ref. PIC/S GMP Guide **Annex 6**

PIC/S

Pharmaceutical Inspection Co-operation Scheme

- **International Cooperation on Pharmaceutical Inspection**
  - **Procedure to inform Foreign Regulatory Agencies of Foreign Inspections to be conducted in their Jurisdiction**
    - came into effect since Nov. 2015
    - **from Inspectorate(s) of the visited country/region**
      - ✓ 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

Other International Cooperation
on Pharmaceutical GMP Inspection

- Programme to rationalize international GMP inspections of API manufacturers
  - Participants;
    Regulatory authorities conducting routine GMP inspections of API manufacturers in foreign countries/regions
    - Authorities in Europe, including **EMA** and **EDQM**
    - Authorities in North America; **US-FDA** and **Health Canada**
    - Australian **TGA**
    - **WHO**, and
    - **PMDA Japan** (joined since November 2016)

- **Sharing information on GMP inspections, including planning and reports of API manufacturers located outside the participating countries.**

Thank You for Listening

GMP Inspection by PMDA

Kentaro Hara, Ph.D.
Principal GMP Inspector
Office of Manufacturing/Quality and Compliance

Agenda

1. **Risk-based approach**
   (On-site inspection or Desk-top inspection)
2. **On-site Inspection**
3. **Observations categorized major deficiencies**
4. **International Cooperation**

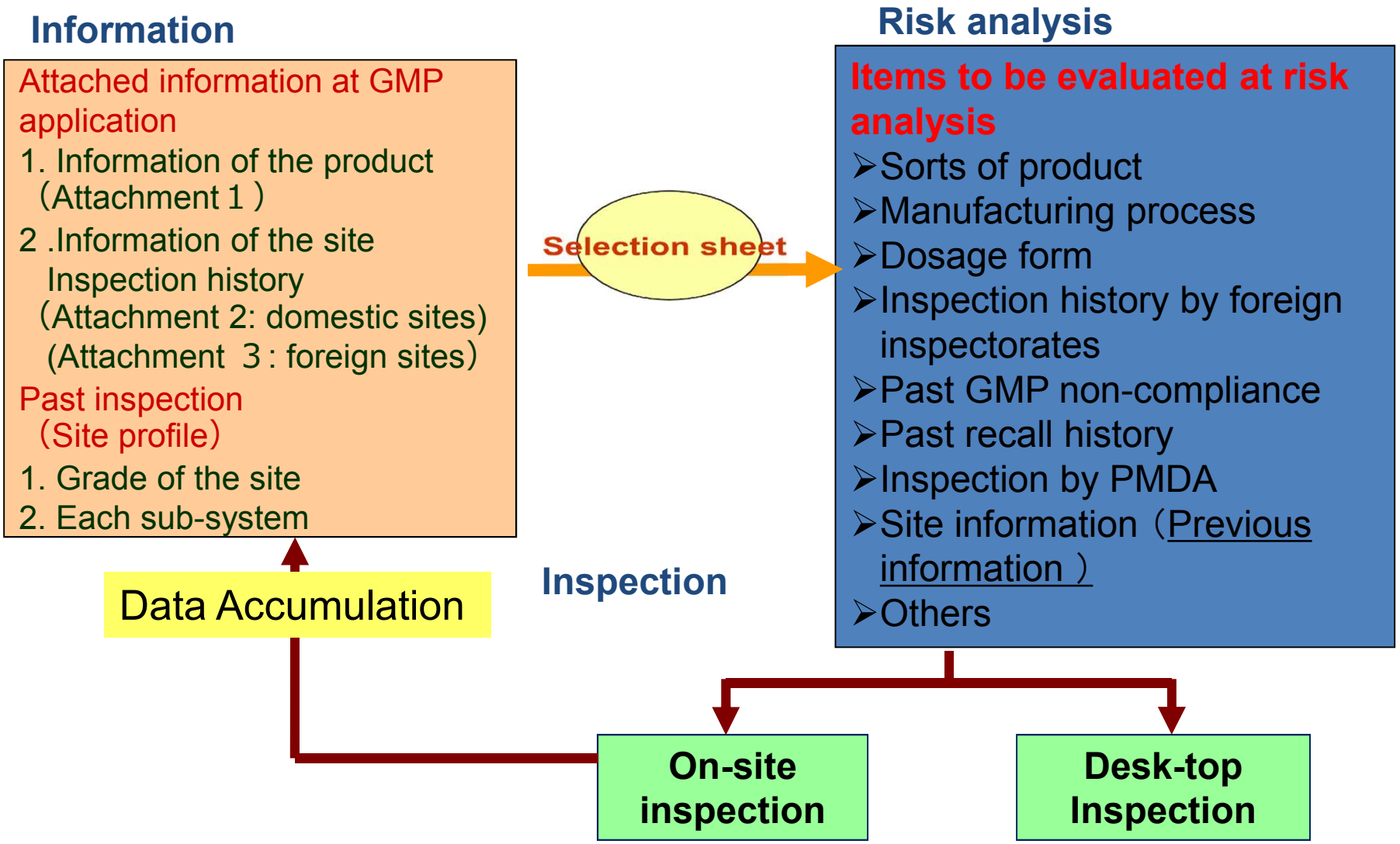
- **API Program**
- **Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC)**

Agenda

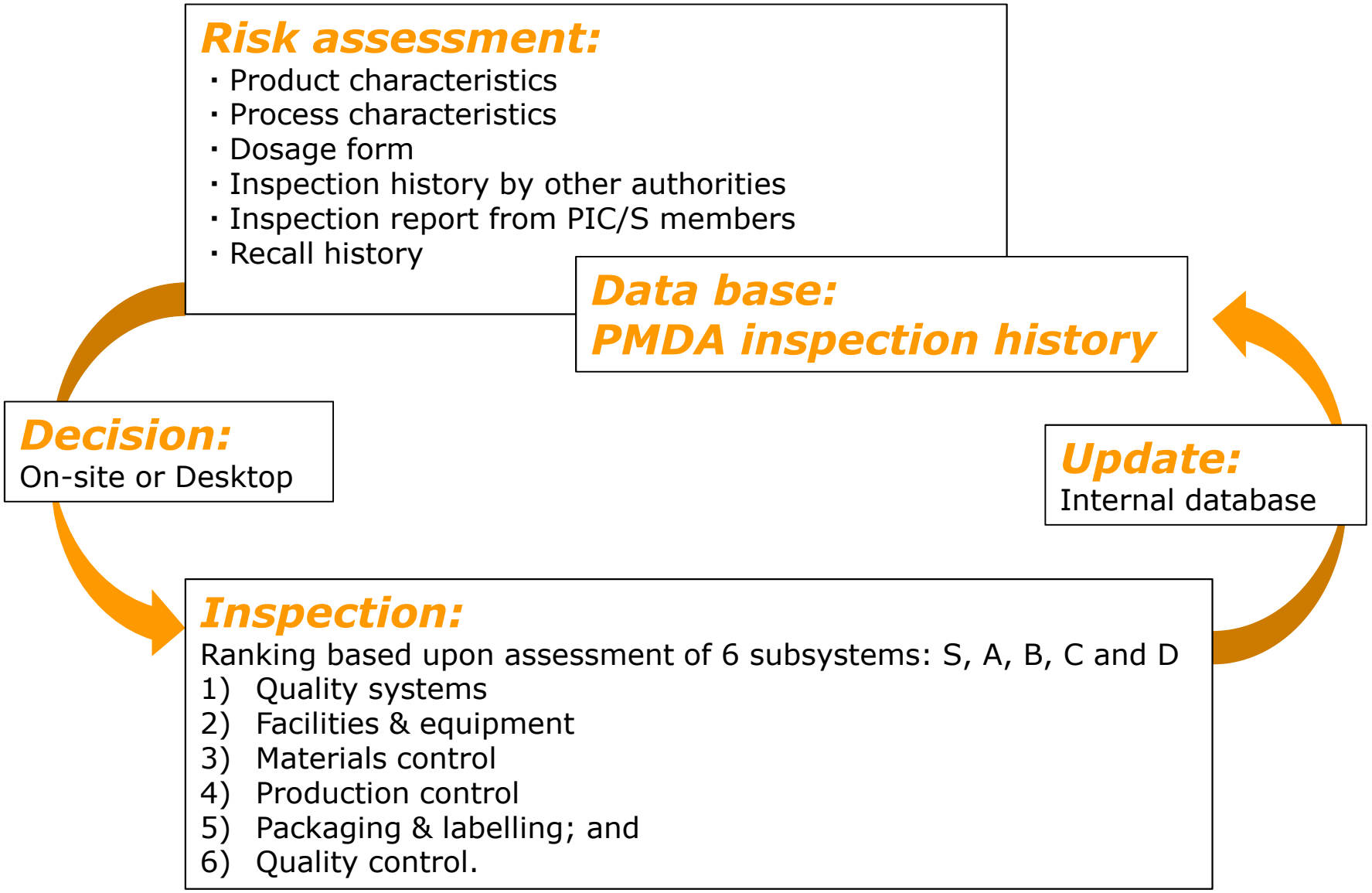
1. **Risk-based approach**
   (On-site inspection or Desk-top inspection)
2. **On-site Inspection**
3. **Observations categorized major deficiencies**
4. **International Cooperation**

- **API Program**
- **Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC)**

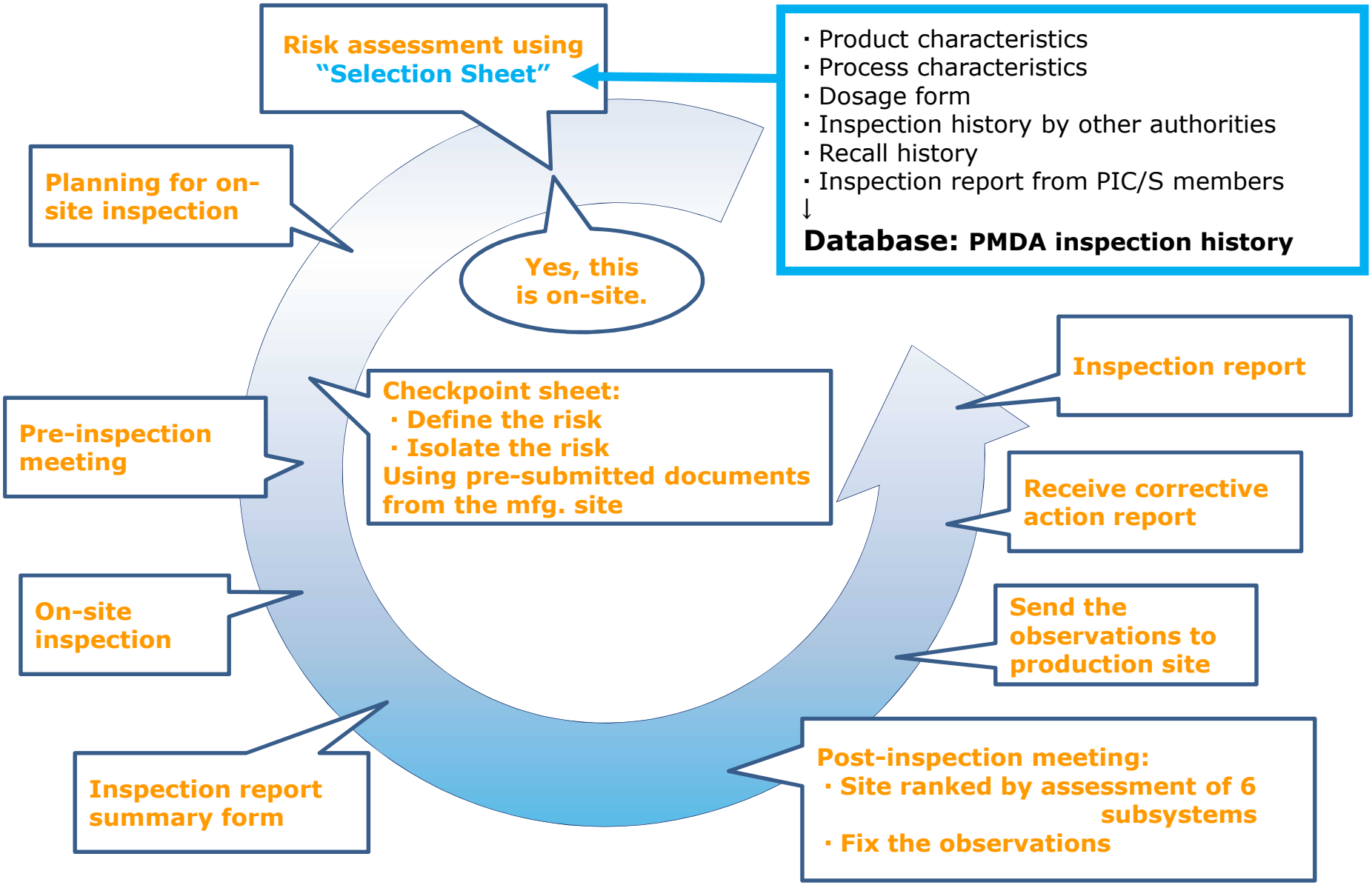
Risk-based approach
(On-site inspection or Desk-top inspection)



Risk-based decision making cycle



Events for on-site inspection

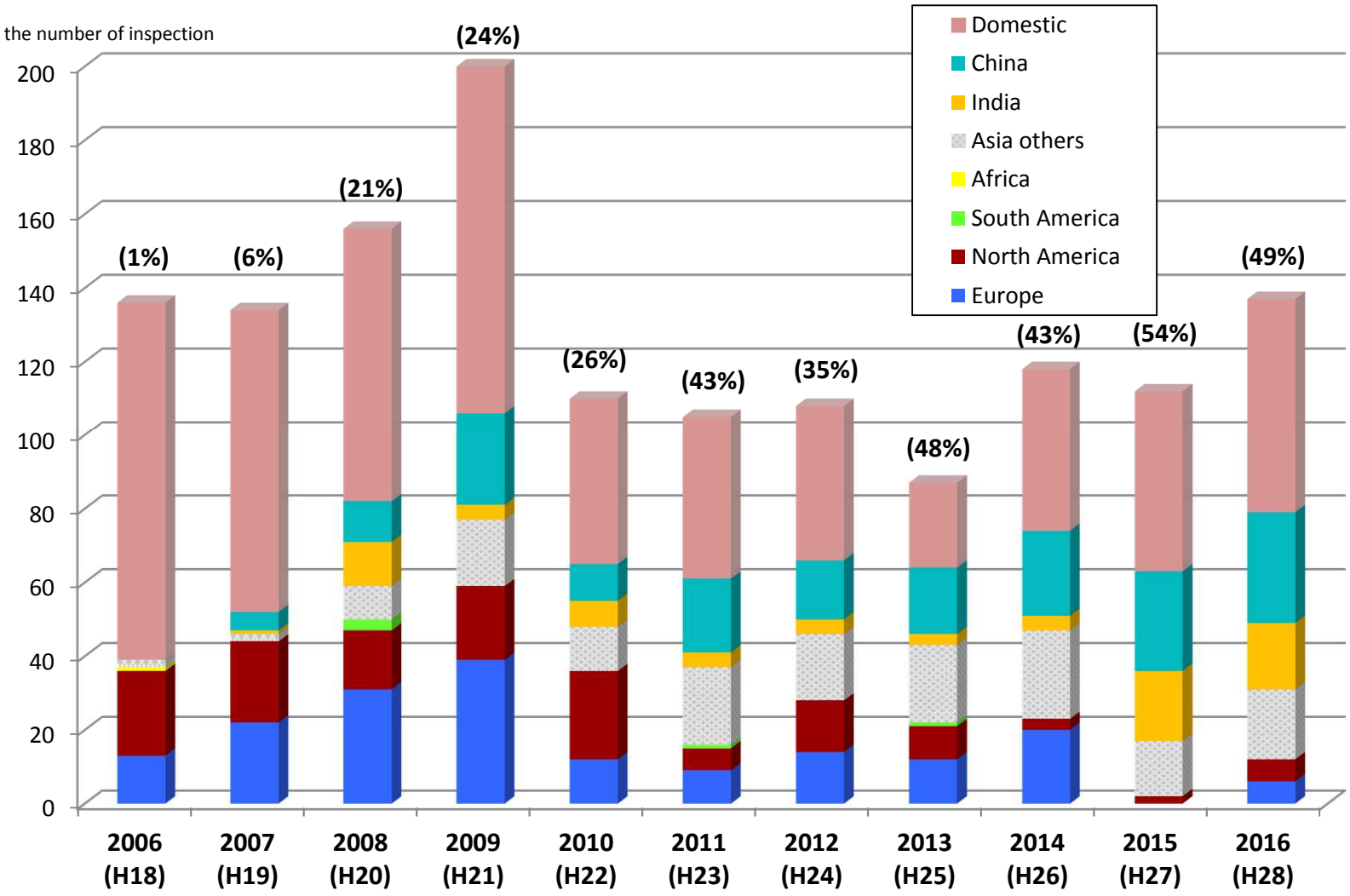


Agenda

1. Risk-based approach
   (On-site inspection or Desk-top inspection)
2. **On-site Inspection**
3. Observations categorized major deficiencies
4. International Cooperation

- API Program
- Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC)

On-site Inspection by PMDA (2006-2016)



% : Asia/Total

On-site Inspections in India by PMDA

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

	2011	2012	2013	2014	2015	2016
Total number of On-Site Inspection (Overseas)	61	65	66	71	65	79
Number of On-Site Inspection in India ◆ (Site Evaluation：C/D)	4 (0/0)	4＊ (0/2)	2 (0/1)	2 (0/0)	20 (5/0)	18 (3/0)
India / Total（%）	7%	6%	3%	3%	31%	23%

◆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

As of 12 Apr. 2017

Agenda

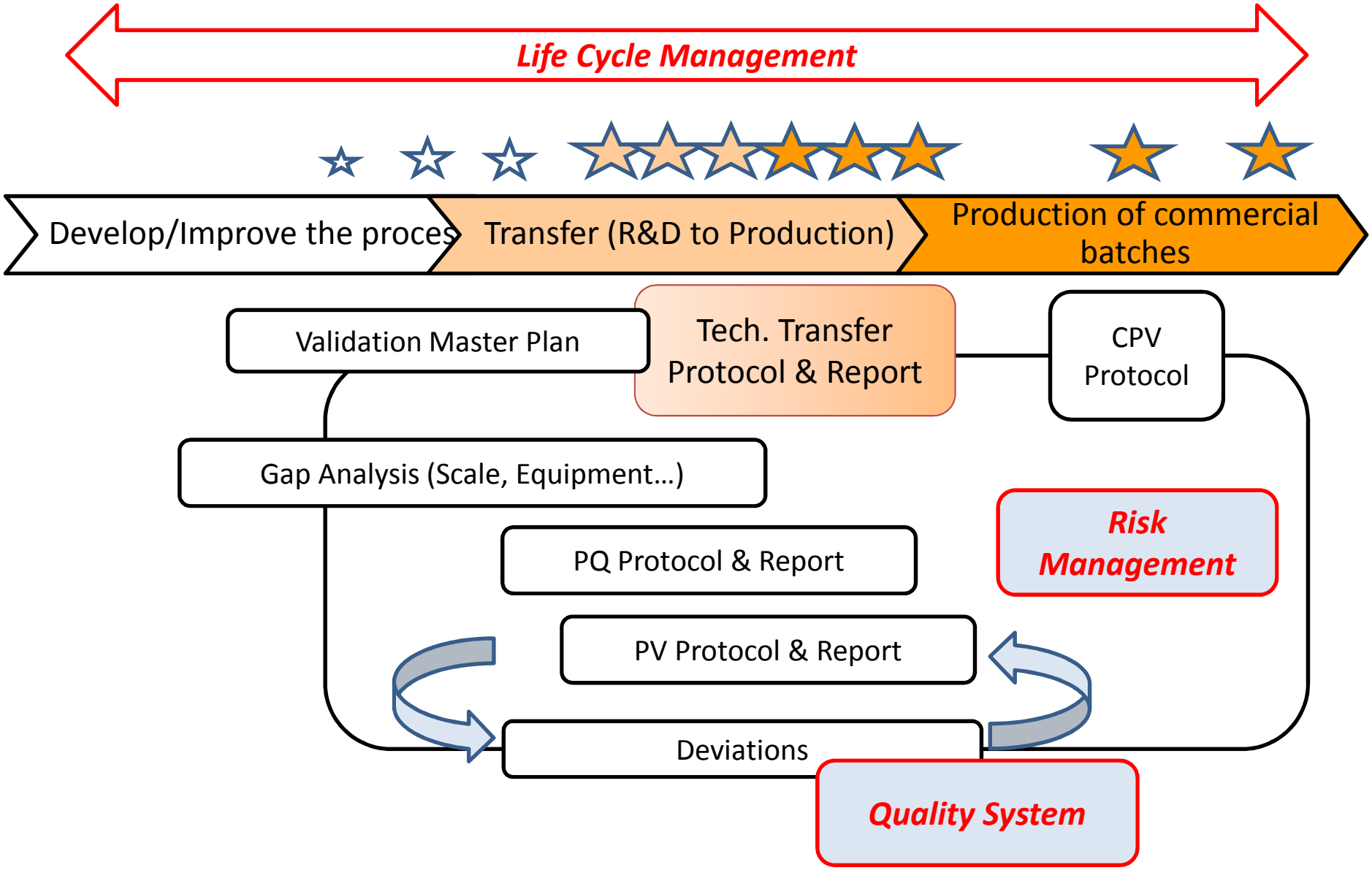
1. Risk-based approach
   (On-site inspection or Desk-top inspection)
2. On-site Inspection
3. **Observations categorized major deficiencies**
4. International Cooperation

- API Program
- Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC)

Observations categorized major deficiencies

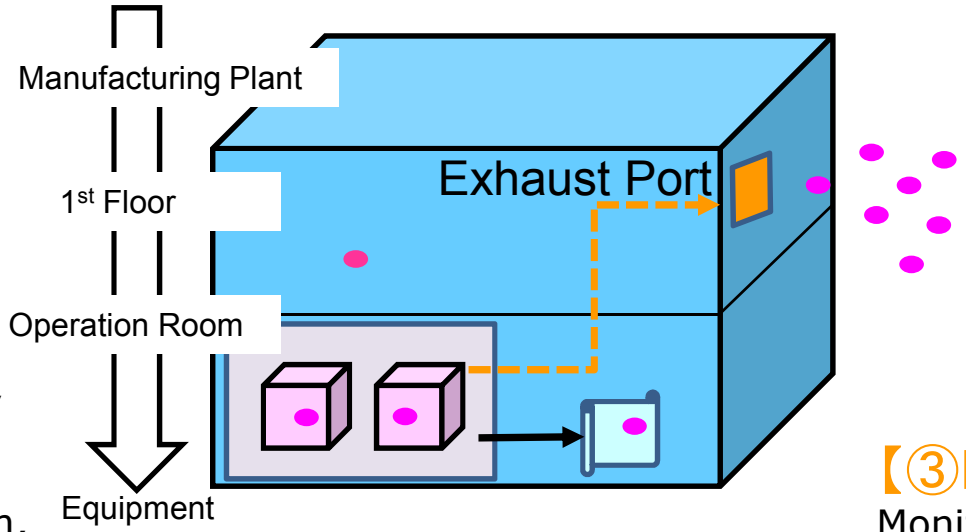
2014		2015	
Category	Number	Category	Number
Validation	35	Validation	33
Document Control	34	Document Control	25
Cross Contamination / Containment	24	Deviation Control	19
Deviation Control	18	Cross Contamination / Containment	13
Quality control of materials	10	Change Control	11
Quality Risk Management	9	Manufacturing Procedure	7
Equipment (IQ,OQ,PQ. Daily Check, Calibration)	7	Equipment (IQ,OQ,PQ. Daily Check, Calibration)	5
Training	5	Training	5
Release	5	Cleaning Validation	5

Which documents should we check?



Containment (Reference: ICH Q7 Q&As)

Appropriate containment measures and controls include but are not limited to the following:

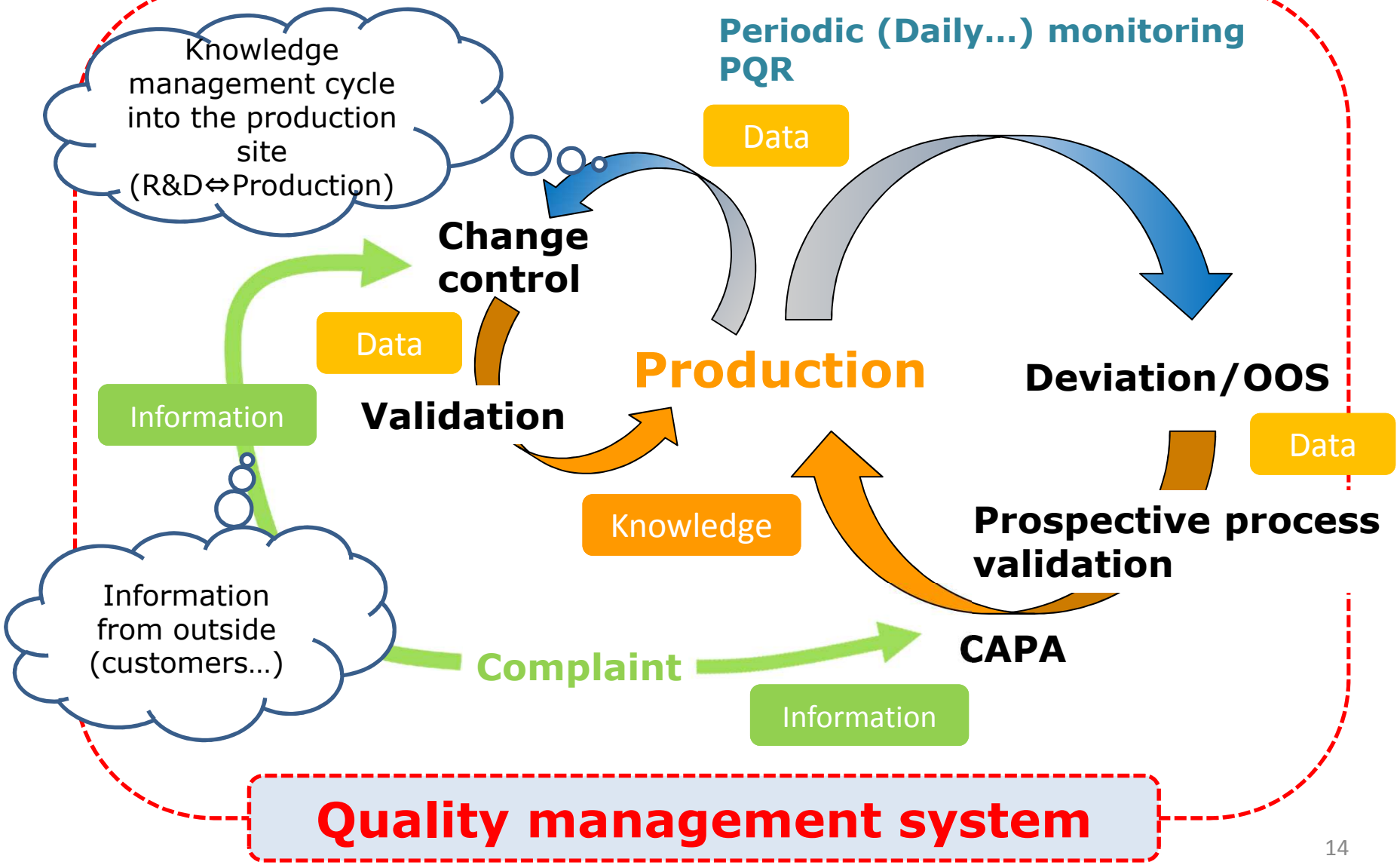


【①Hard】
Technical controls (e.g., dedicated production areas, closed/dedicated Heating Ventilation and Air Conditioning (HVAC) system, closed manufacturing systems, use of disposable technologies,
design of facility and equipment for containment and ease of cleaning)

【②SOPs】
Procedural (organisational) controls (e.g., cleaning, personnel flow, environmental monitoring and training)

【③Monitoring】
Monitoring systems are important to check the effectiveness of the containment controls.

Knowledge management cycle



Practical models and tools for Quality system and Quality Risk Management

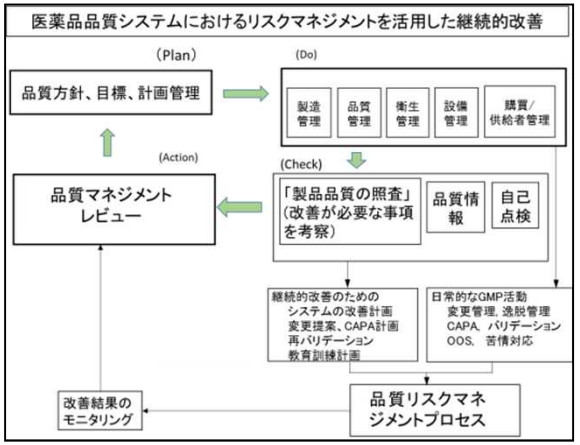
SOPs for Quality System

Quality Manual

SOP for QRM

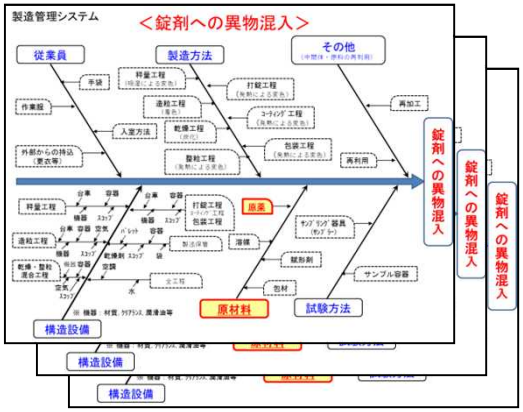
SOP for Quality Management Review

Conceptual Diagram for QRM



Example of QRM

Target of QRM

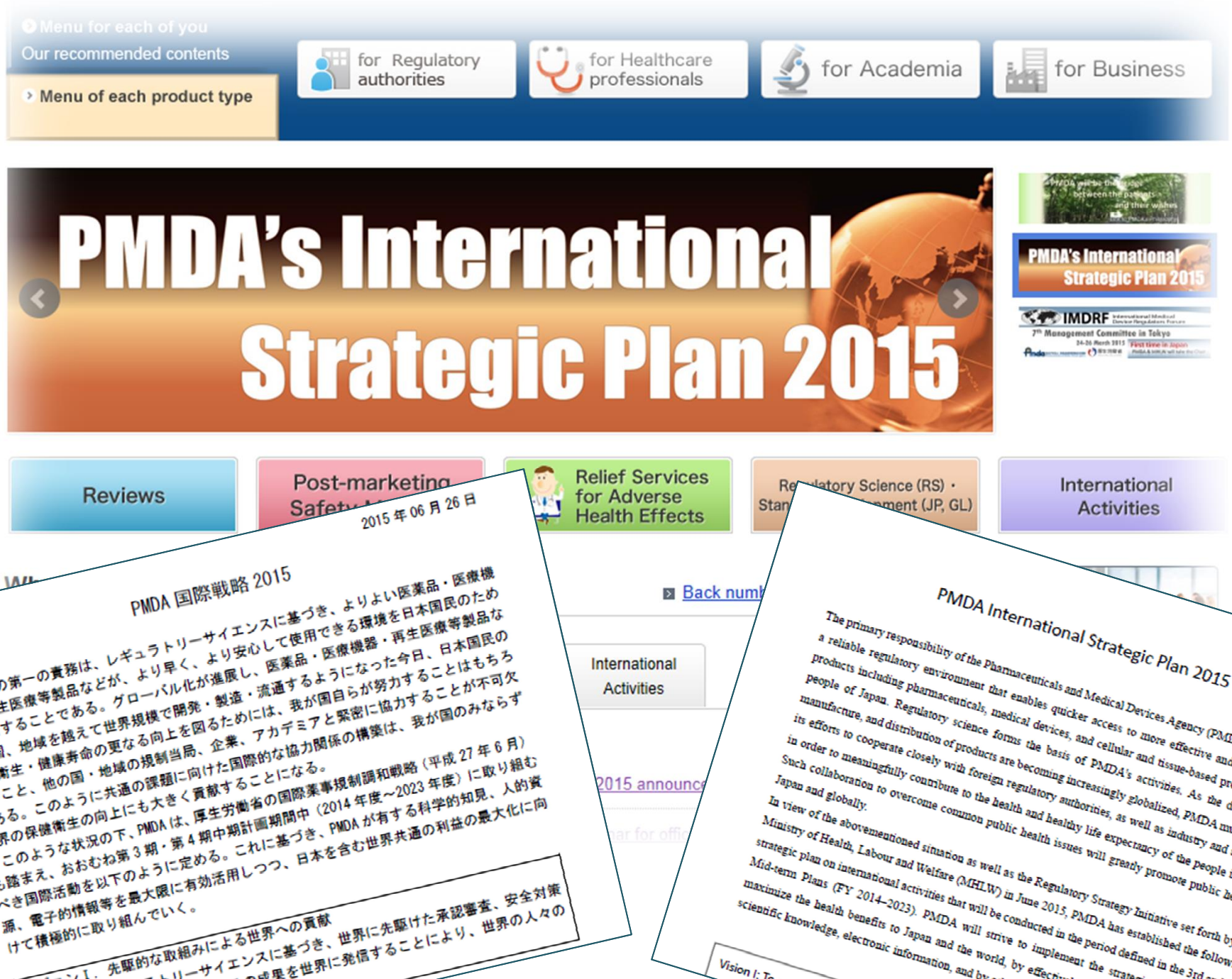


Example of QRM (Risk assessment Sheet)

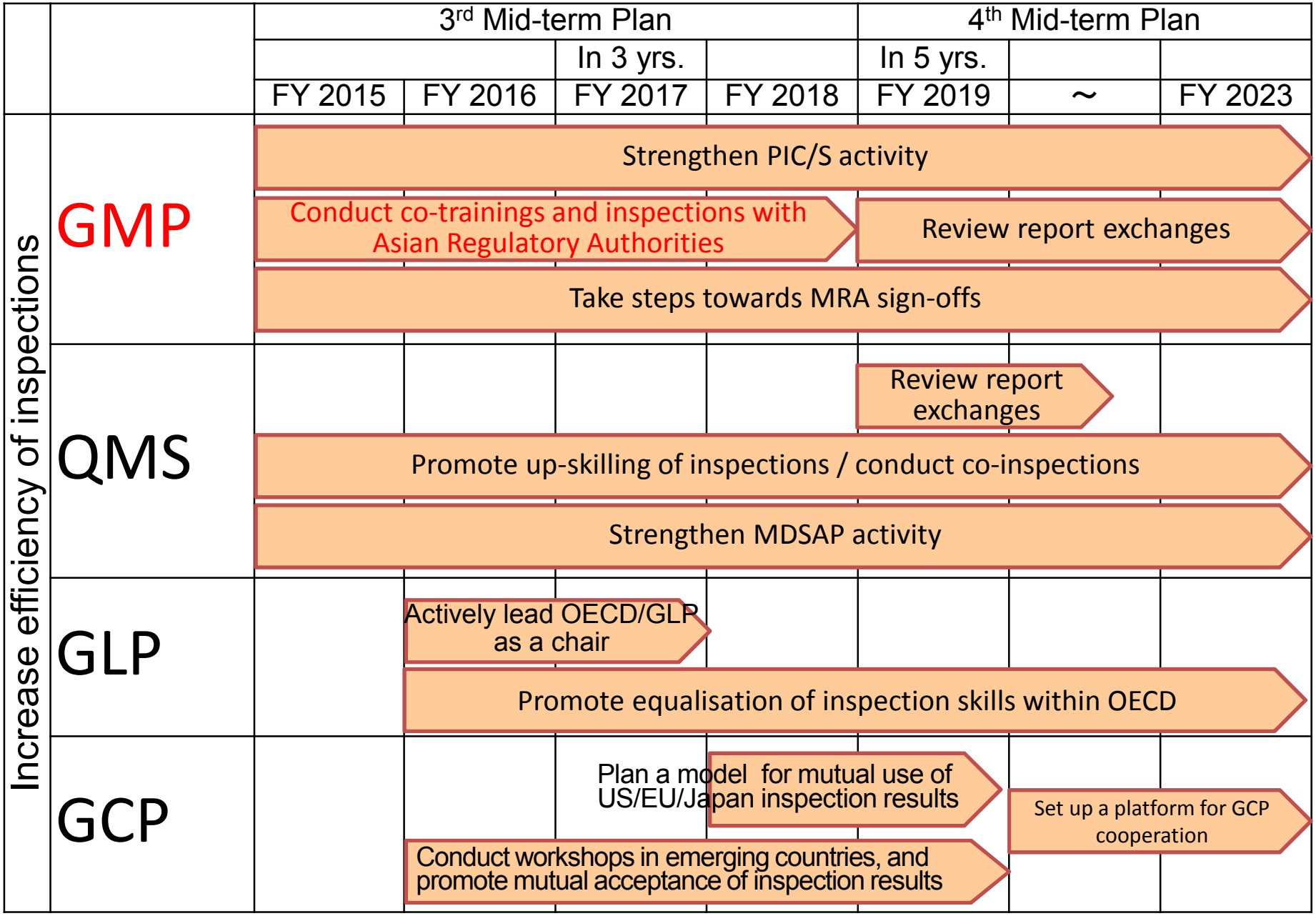
Agenda

1. Risk-based approach
   (On-site inspection or Desk-top inspection)
2. On-site Inspection
3. Observations categorized major deficiencies
4. **International Cooperation**

- **API Program**
- **Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC)**

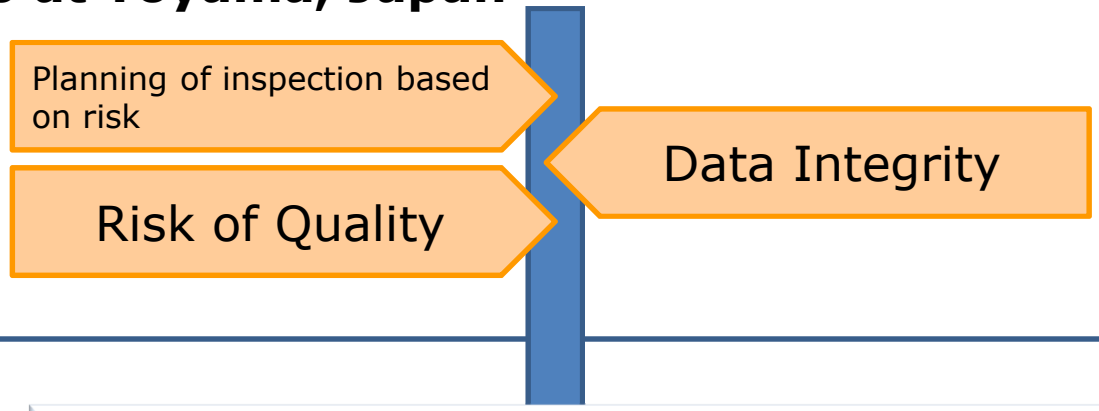

Menu for each of you
Our recommended contents
Menu of each product type
for Regulatory authorities
for Healthcare professionals
for Academia
for Business
PMDA's International Strategic Plan 2015
IMDRF
Reviews
Relief Services for Adverse Health Effects
International Activities
2015 年 06 月 26 日
PMDA 国際戦略 2015
PMDA の第一の責務は、レギュラトリーサイエンスに基づき、よりよい医薬品・医療機器・再生医療等製品などが、より早く、より安心して使用できる環境を日本国民のために創出することである。グローバル化が進展し、医薬品・医療機器・再生医療等製品などが国、地域を越えて世界規模で開発・製造・流通するようになった今日、日本国民の保健衛生・健康寿命の更なる向上を図るためには、我が国自らが努力することはもちろんのこと、他の国・地域の規制当局、企業、アカデミアと緊密に協力することが不可欠である。このように共通の課題に向けた国際的な協力関係の構築は、我が国のみならず世界の保健衛生の向上にも大きく貢献することになる。
このような状況の下、PMDA は、厚生労働省の国際薬事規制調和戦略（平成 27 年 6 月）も踏まえ、おおむね第 3 期・第 4 期中期計画期間中（2014 年度～2023 年度）に取り組むべき国際活動を以下のように定める。これに基づき、PMDA が有する科学的知見、人的資源、電子的情報等を最大限に有効活用しつつ、日本を含む世界共通の利益の最大化に向けて積極的に取り組んでいく。
PMDA International Strategic Plan 2015
June 26
The primary responsibility of the Pharmaceuticals and Medical Devices Agency (PMDA) is to provide a reliable regulatory environment that enables quicker access to more effective and safer medical products including pharmaceuticals, medical devices, and cellular and tissue-based products for the people of Japan. Regulatory science forms the basis of PMDA's activities. As the development, manufacture, and distribution of products are becoming increasingly globalized, PMDA must increase its efforts to cooperate closely with foreign regulatory authorities, as well as industry and academia, in order to meaningfully contribute to the health and healthy life expectancy of the people in Japan. Such collaboration to overcome common public health issues will greatly promote public health in Japan and globally.
In view of the abovementioned situation as well as the Regulatory Strategy Initiative set forth by the Ministry of Health, Labour and Welfare (MHLW) in June 2015, PMDA has established the following strategic plan on international activities that will be conducted in the period defined in the 3rd Mid-term Plans (FY 2014–2023). PMDA will strive to implement the strategies to maximize the health benefits to Japan and the world, by effectively utilizing its human resources, scientific knowledge, electronic information, and

Roadmaps to implement Strategy 3



Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC)

Practical training in the form of a mock inspection with the support of Japan Pharmaceutical Manufacturers Association (JPMA) and PIC/S.
Dec. 2016 at Toyama, Japan



- Upskilling of GMP inspectors in Asia
- Harmonize the procedure of GMP inspection

- Improvement of GMP level of manufacturing site in Asia

Programme to rationalize international GMP inspections of API manufacturers

- Participants; Regulatory authorities conducting routine GMP inspections of API manufacturers in foreign countries/regions
  - Authorities in Europe,
    such as European Medicines Agency (EMA), EU Member States, and European Directorate for Quality of Medicines & Healthcare (EDQM)
  - Authorities in North America; US-FDA and Health Canada,
  - Australian Therapeutic Goods Administration (TGA),
  - World Health Organization (WHO), and
  - **PMDA Japan** (joined since November 2016)

- **Sharing information on GMP inspections, including planning and reports of API manufacturers located outside the participating countries.**

"PMDA-ATC GMP Inspection Seminar 2017" for GMP inspectors from overseas regulatory authorities.

This Seminar will be held in Yamaguchi prefecture, Japan, from July 31 to August 4, 2017.

The primal object of this Seminar will be Risk-based Inspection and Data Integrity.

Registration will close on May 10, 2017

http://www.pmda.go.jp/english/symposia/0107.html

Thank you for your attention.

Pharmaceuticals and Medical Devices Agency