



Current Status of Desk-top GMP inspection in Japan

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Today's Topics

1. Japanese Regulation
2. Method of GMP Inspection : On-site or Desk-top
3. Submission documents for Desk-top inspection for NDA
4. Key Performance Indicator

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PMDA Philosophy

PMDA continues to improve the public health and safety of our nation by reviewing applications for marketing approval of pharmaceuticals and medical devices, conducting safety measures, and providing relief to people who have suffered from adverse drug reactions.

We conduct our mission in accordance with the following principles:

- We pursue the development of medical science while performing our duty with greater transparency based on our mission to protect public health and the lives of our citizens.*
- We will be the bridge between the patients and their wishes for faster access to safer and more effective drugs and medical devices.*
- We make science-based judgments on quality, safety, and efficacy of medical products by training personnel to have the latest technical knowledge and wisdom in their field of expertise.*
- We play an active role within the international community by promoting international harmonization.*
- We conduct services in a way that is trusted by the public based on our experiences from the past.*



Responsibilities of MHLW and PMDA

[MHLW: Ministry of Health, Labour and Welfare]

Planning basic policy, enforcement of administrative measures, such as approval, administrative order, etc which are based on the law

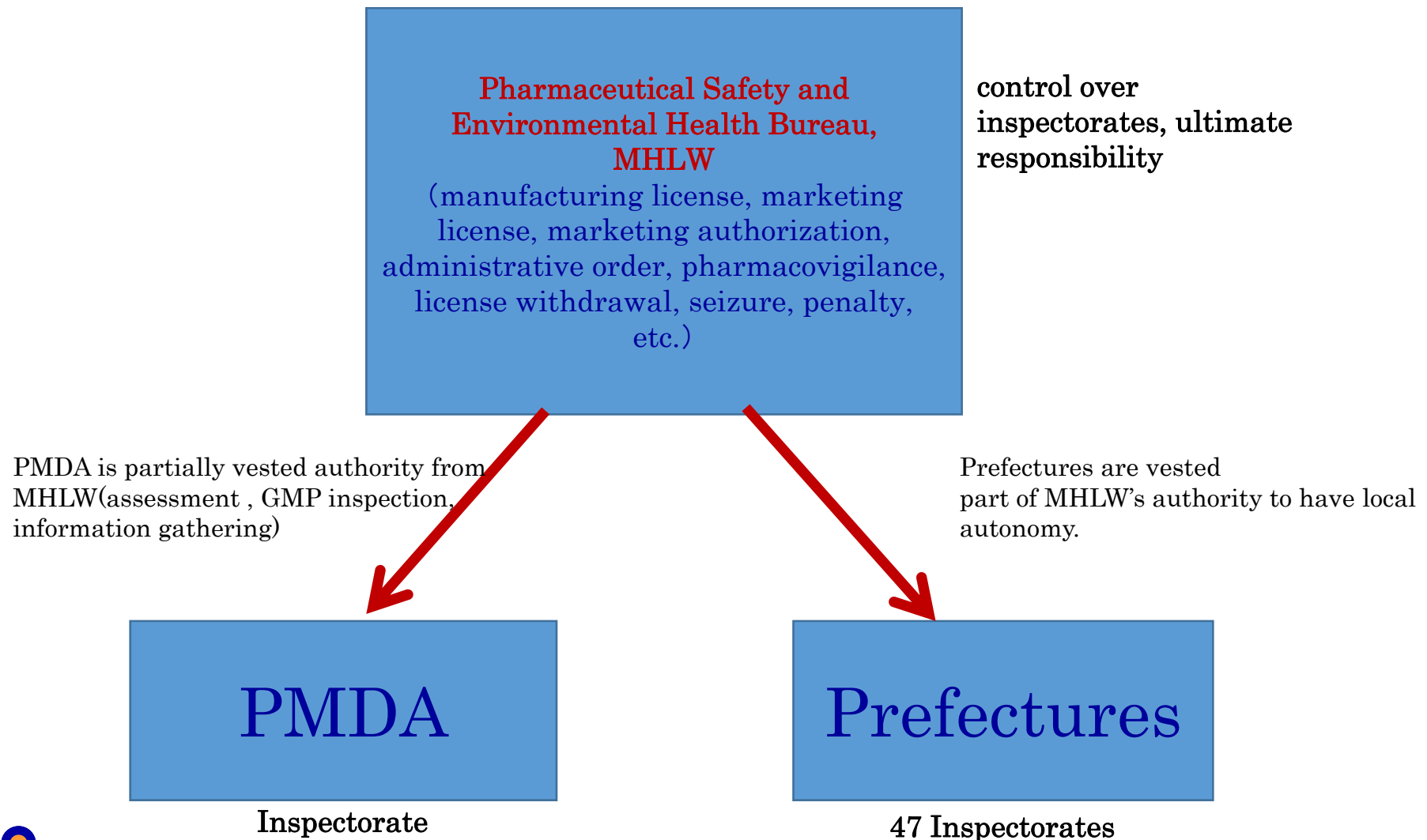
- ex.
- Final judgment on marketing authorisation
 - Withdrawal of the product from the market
 - Withdrawal of authorisation and license
 - Safety measures for emergent and significant cases

[PMDA]

Implementation of work, such as review, examination, data analysis, etc before administrative measures

- ex.
- Scientific review of Pharmaceuticals and Medical Devices
GLP/GCP/GMP/QMS/GCTP inspections, Clinical trial consultation
 - Collection, examination, analysis, assessment and provision of ADR information

GMP Inspection System



Delegation of MHLW's authority of GMP inspection to PMDA and prefectural government

	Domestic Site	Foreign Site
New Drugs, Biological Products, Radio Pharmaceuticals	MHLW Delegated to PMDA	MHLW Delegated to PMDA
Other Drugs	Pref. Gov.	MHLW Delegated to PMDA

GMP inspection and product marketing authorization

- GMP requirement is realigned to be product authorization requirement (Art.14.6 of PMD Act.)
- GMP inspection before product authorization (Art.14.6 of PMD Act.)

PMD Act. : Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics

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On-site inspection or desk-top inspection

- Article 14.6 of PMD Act. provide that GMP inspection is to be done either by on-site inspection or desk-top inspection

Article 14-6.

A person intending to obtain the approval specified in Paragraph 1 or a person obtaining the approval specified the same paragraph, with respect to the drugs, quasi-drugs (abbreviated) specified by Cabinet Order, shall be subjected to a desktop inspection or an on-site inspection performed by the Minister as to whether a method of manufacturing control or quality control of it in the manufacturing establishment complies with the standards specified by MHLW Ministerial Ordinance specified by Paragraph 2, Item 4, when intending to obtain the approval concerned, and at an interval of not less than 3 years as specified by Cabinet Order after obtaining the approval concerned.



Product
Approval



GMP
Compliance

On-site inspection or desk-top inspection

- The competent inspectorate has responsibility to select on-site or desk-top inspection at each inspection, based on risk based assessment. This is regulated in the “Procedure for conducting GMP inspection(February 16,2014, Yakushokukanmahatsu 0216-7)” and is unifying Procedure thorough out Japan.

Section 2.4.Selection of onsite inspection or desk top inspection

Upon receipt of application for GMP inspection, each inspectorate should decide which of the inspection method, onsite inspection or desktop inspection, is employed taking the items in the above Table 1 into consideration, and inform it to the applicant. Onsite inspection should be selected in principle, if the site does not receive on site inspection in the previous 2 years. Onsite inspection may be selected even the site is inspected within 2 years, taking the compliance status or GMP control status into consideration.

- Section 2.2 of the Procedure for conducting GMP inspection provides procedure for both onsite and desk-top inspection.

* SOPs for risk based selection of onsite or desk-top inspection are to be in place at each inspectorate

Selection of inspection sites according to risks

Prior information

Attached documents at application, etc.

- (1) Information about the drug (Form 1)
- (2) Information on manufacturing site and history of inspection (Form 2 [domestic], Form 3 [foreign])

Previous on-site inspections (Profile of manufacturing site)

- (1) Grade of the manufacturing site
- (2) Checking each subsystem
S, A, B, C or D ranking based upon assessment of 6 subsystems:
 - 1) Quality systems; 2) facilities & equipment;
 - 3) materials control; 4) production control, 5) packaging & labelling; and
 - 6) quality control.

Risk assessment

Risk assessment items

- Classification of the product (the drug)
- Manufacturing process
- Dosage form
- History of inspection by foreign regulatory authorities
- Previous GMP non-compliance
- Previous recalls
- Previous inspection by the PMDA
- Information about the manufacturing site (results of the last inspection)
- Others

Preparation of selection sheet

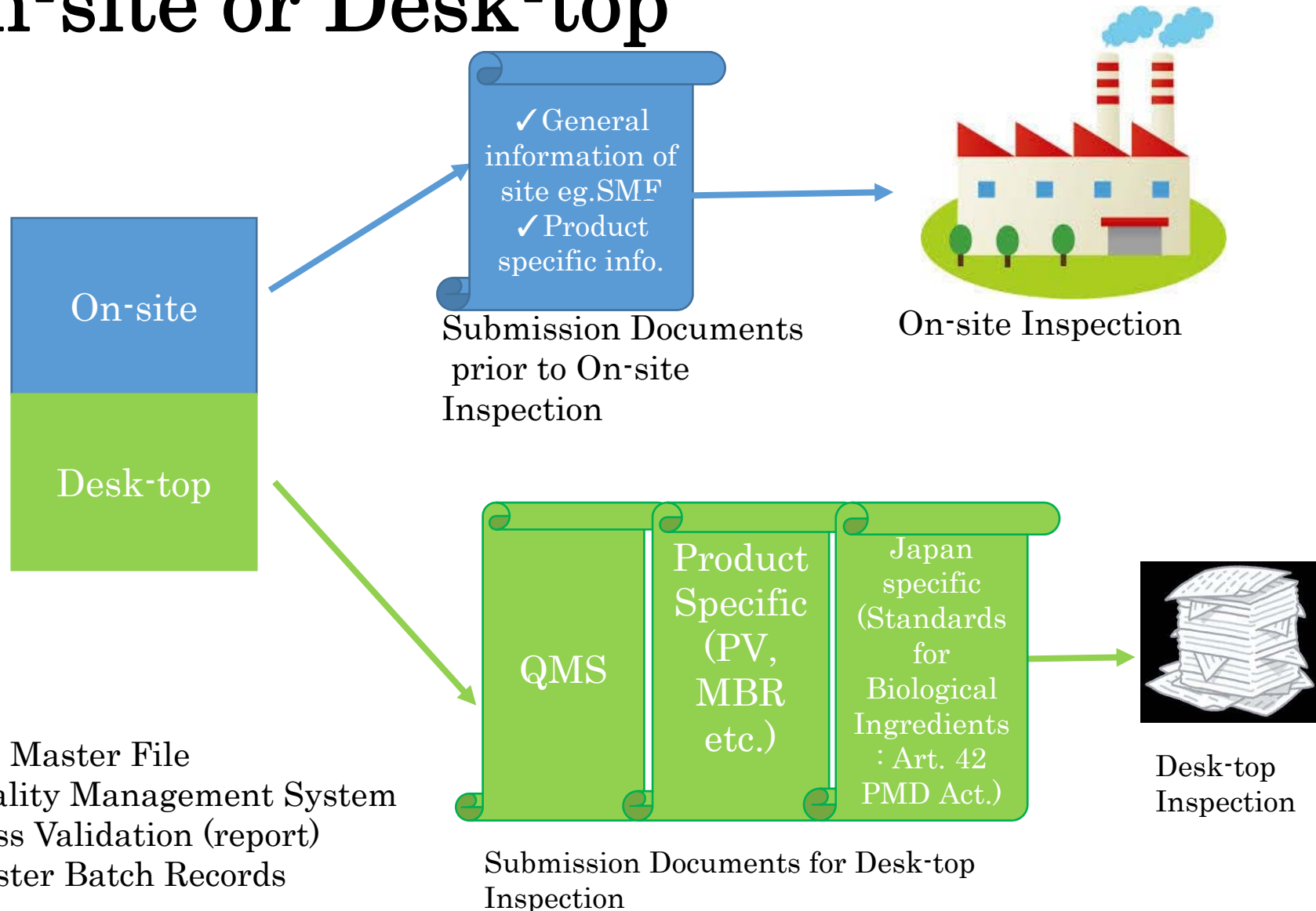
Internal database

Implementation of inspection

On-site inspection

Desk-top inspection

Method of GMP Inspection (PMDA) : On-site or Desk-top

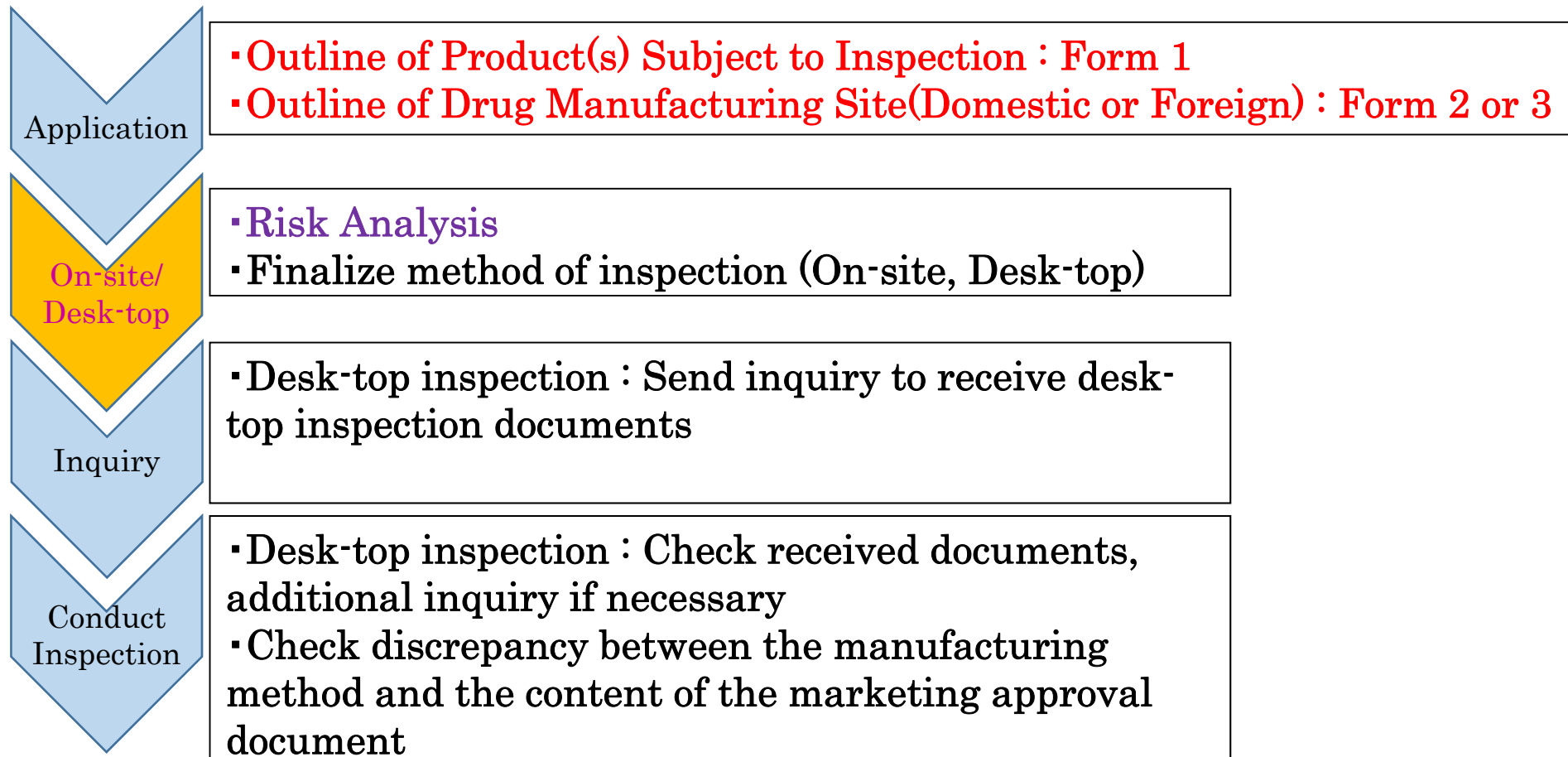


SMF: Site Master File
 QMS: Quality Management System
 PV: Process Validation (report)
 MBR: Master Batch Records

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Flow of Desk-top inspection for NDA



Submission documents(NDA)

- Outline of Product(s) Subject to Inspection : Form 1
- Outline of Drug Manufacturing Site(Domestic or Foreign) : Form2 or 3
- Copy of Marketing approval document
- Copy of results or reports of GMP inspection which conducted past 2 years

Those information will be used for risk assessment to decide method of inspection either on-site or desk-top.

General Submission Documents : NDA

(If those documents are included in the SMF, submission of the SMF is acceptable)

To confirm function of quality management system

- Documents for quality assurance system
- SOP of deviation and record for past 2 years
- SOP of change control and record for past 2 years
- Usage of CSV

To confirm compliance of the regulations

- GMP documentation
- GMP organization chart

Red: QMS (General) items
Blue: Specific to products

General Submission Documents : NDA

(If those documents are included in the SMF, submission of the SMF is acceptable)

To confirm the consistency between practical operations at the site and the marketing authorization application

- Documents relates to the manufacturing process (eg. Master Batch records)
- Specification and SOP for analytical tests
- Documents on the management status of Standards for Biological Ingredients
- Documents on the status of validation
 - Process validation reports

Other

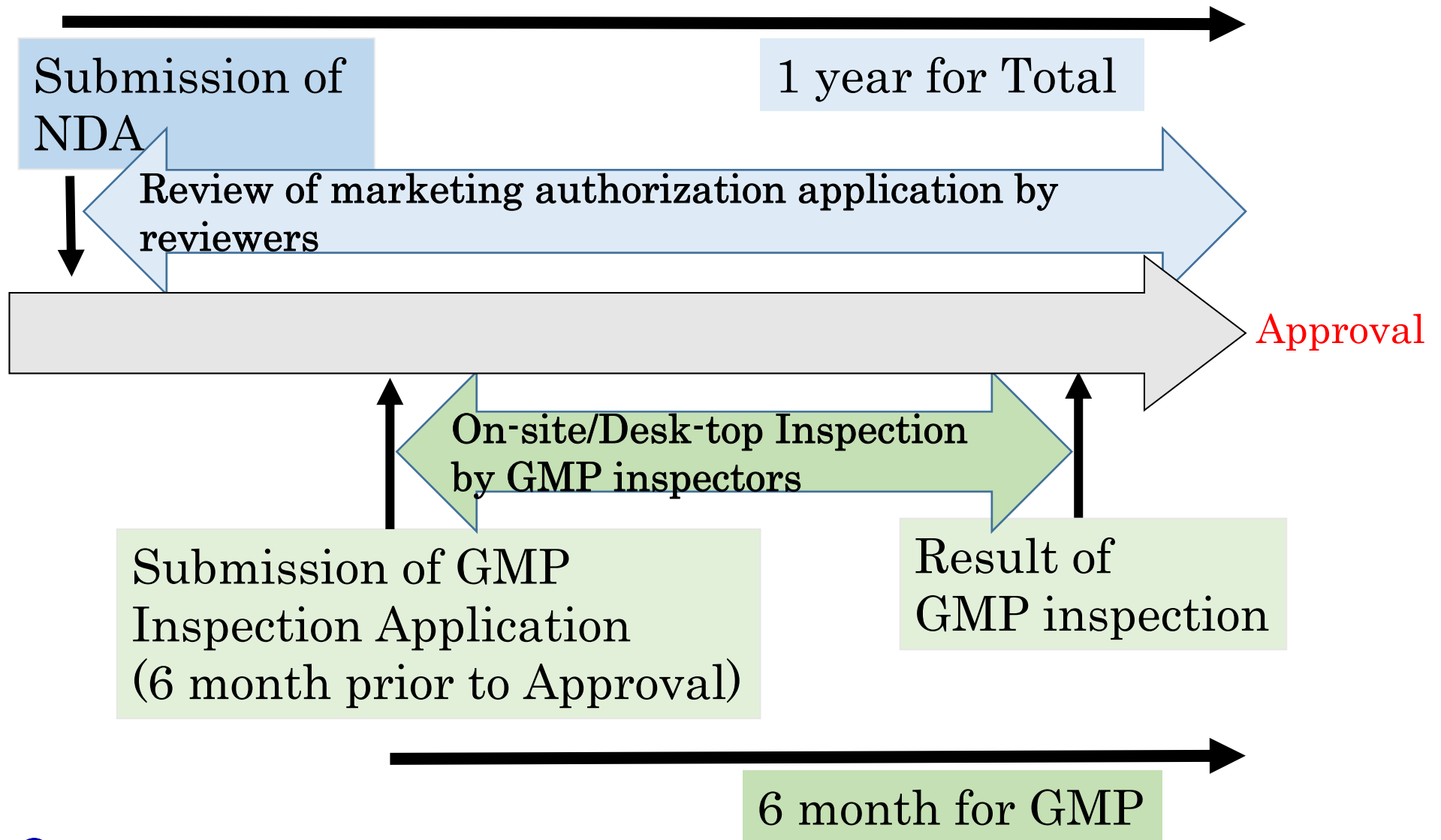
- Site map
- Floor map
- A list of the number of manufactured batches per year and the amount manufactured per year
- Documents on the status of validations
 - Process simulation tests reports for sterile products
 - Cleaning validation reports for shared equipments

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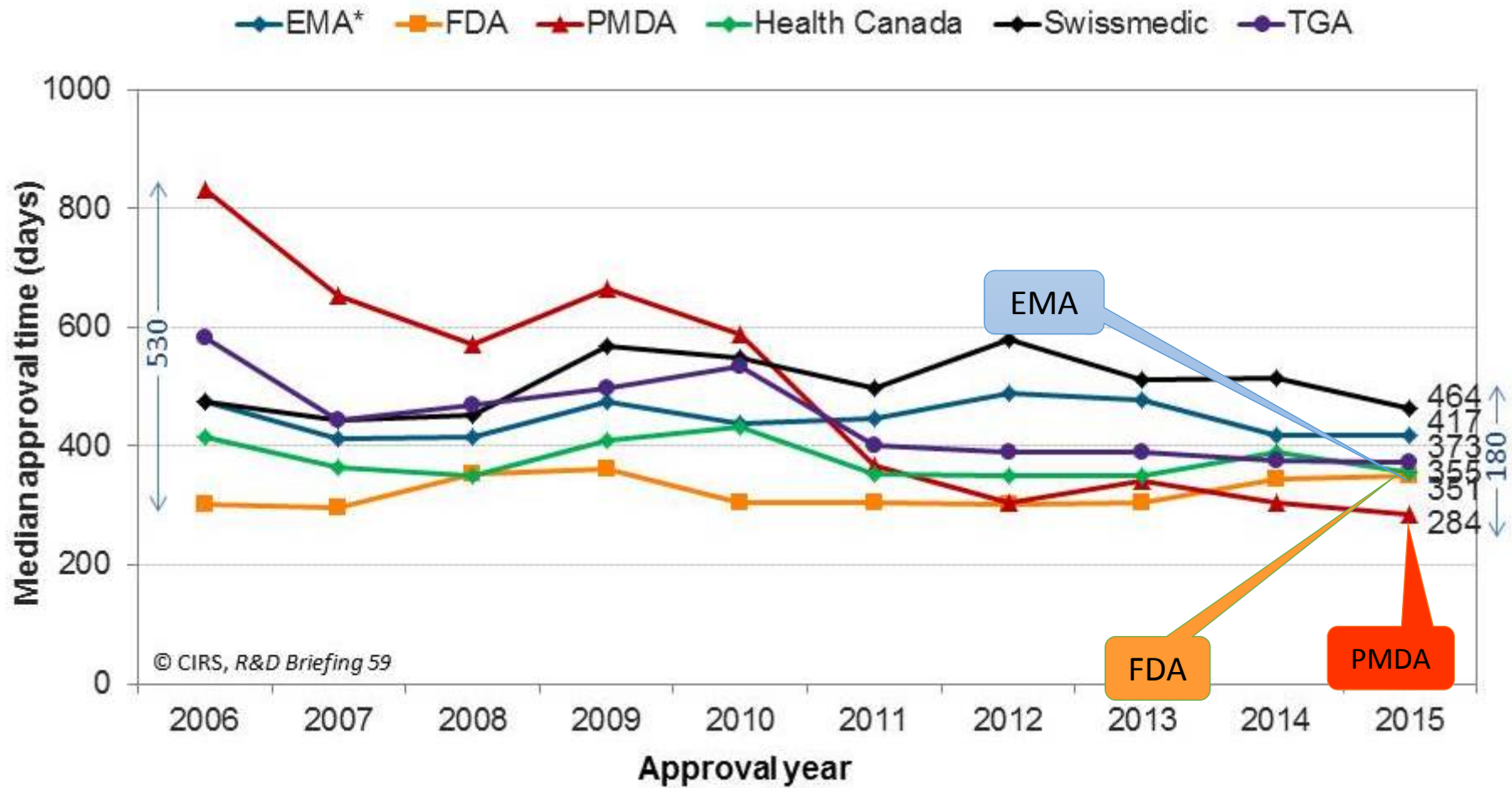
Timeline for NDA



Cooperation within PMDA



New active substance median approval time for six regulatory authorities in 2006-2015



“In 2015, PMDA was the agency with the shortest median approval time (284 days), followed by FDA (351), Health Canada (355), TGA (373), EMA (417), and Swissmedic (464).”

The Center for Innovation in Regulatory Science 2016

PMDA's Achievements

Time Clock at PMDA for Desk-top GMP Inspections

For Desk-top inspection, our KPI is 180 days.
Counts start from submission of GMP inspection application until issues of GMP inspection results.

Time clock at PMDA
Average: 79~90days

Summary

- PMDA put our much effort to resolve drug lag such as make a clear time line until approval for new drugs.
eg. Total 1 year from submission of NDA to approval. GMP for 6 month)
- For GMP group, we set KPI and every year we are reviewing our performance.
- Need to explain more clearly to the applicants what we are requesting to shorten more inspection period.