What we can do to Ensure the Quality

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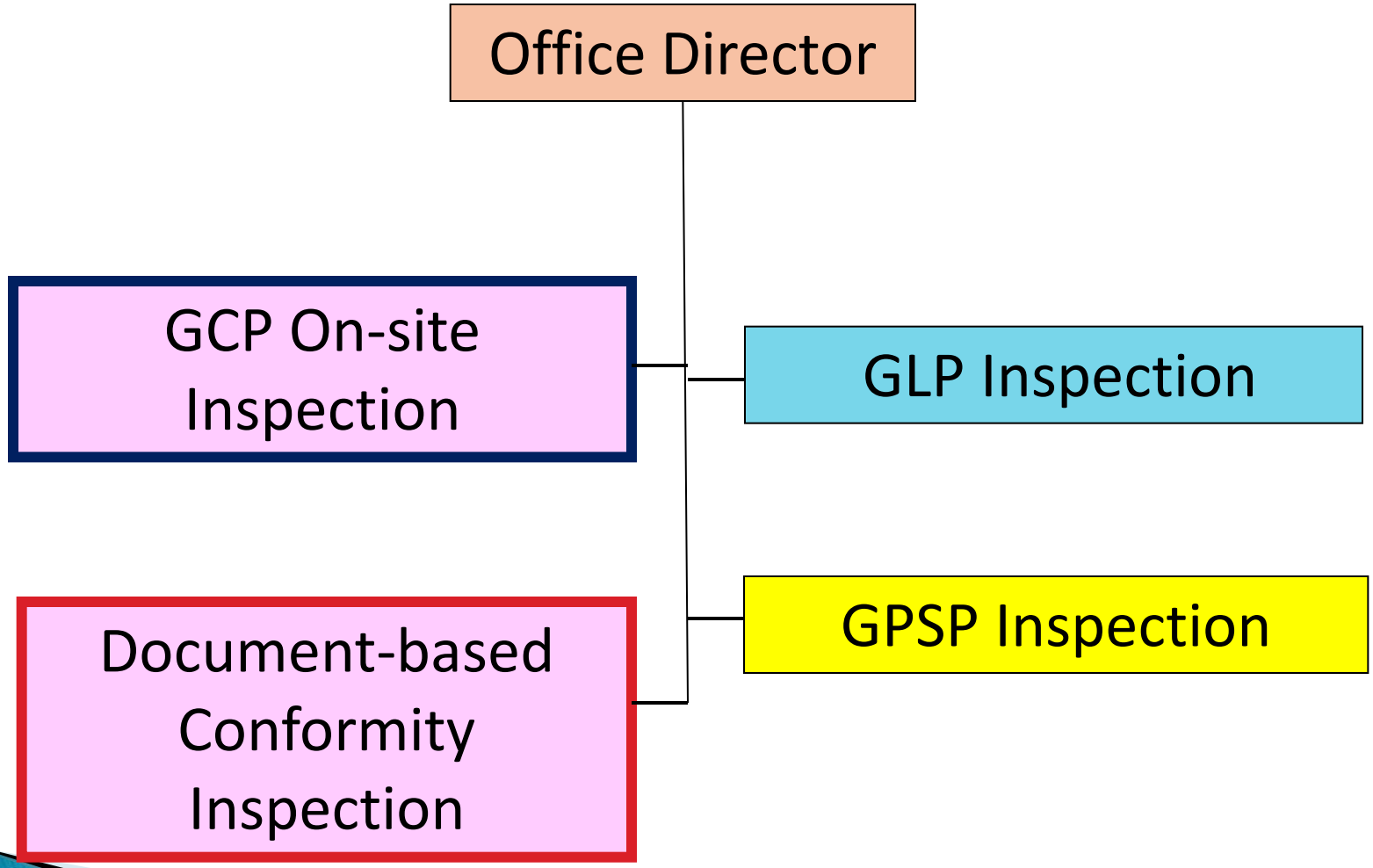
The views presented in this presentation are those of the author and should not be understood or quoted as being made on behalf of Pharmaceuticals and Medical Devices Agency (PMDA).

Introduction of PMDA

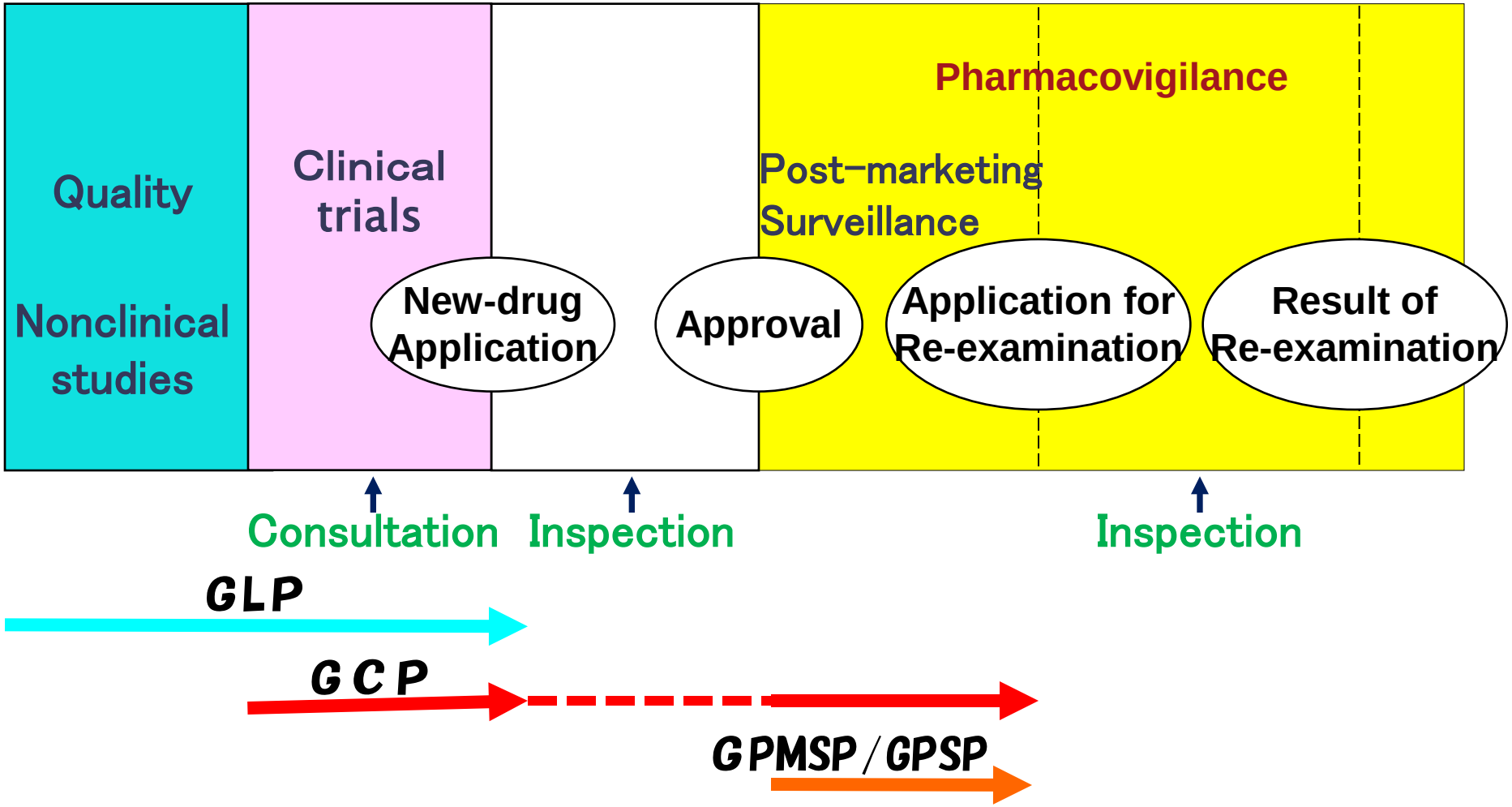
Pharmaceuticals and Medical Devices Agency

- Our mission : To continue to improve the public health and safety of our nation by reviewing application for marketing approval of pharmaceuticals and medical devices, conducting safety measures, and providing relief to people who have suffered from adverse drug reactions.
- Established in April 2004
- Number of permanent staff
  256 (Apr.'04)
  → 341 (Apr.'07)
  → 604 (Mar.'11)
  → 751 (by the end of FY 2013)
- PMDA submits performance report to MHLW annually.

Office of Conformity Audit



Product Lifecycle



GLP : Good Laboratory Practice, GCP : Good Clinical Practice, GPMSP : Good Post-marketing Surveillance Practice, GPSP : Good Post-marketing Study Practice

Major factors influencing the Quality of Clinical Trials

- ✓ Protocol
- ✓ Implementation system

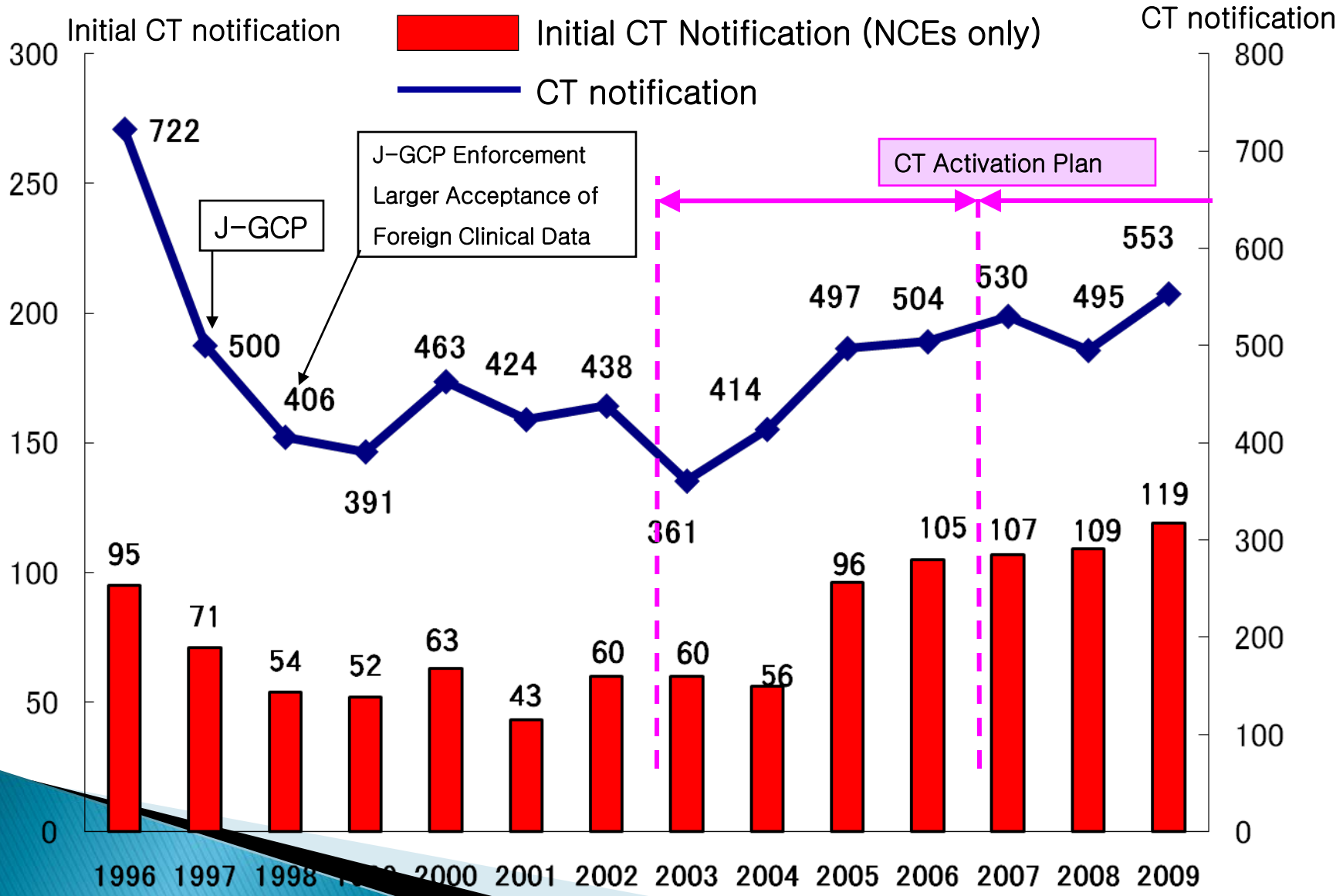
Key to Ensure the Quality

- ✓ Capture the problems on conducting clinical trials (e.g., interpretation of inclusion criteria, exclusion criteria, etc.) as early as possible.
- ✓ Feed back the solutions to all related sites.

⇒Monitoring ・・・Initiation, Intervals, etc.

⇒Audit

Trend in Notified CT in Japan



New 5-Year Clinical Trial Activation Plan

MEXT / MHLW March 2007

1. Build clinical study infrastructure
2. Human resource development for clinical research
3. Publically promote clinical trials and encourage participation
4. Improve clinical research management efficiency and ease for sponsors
5. Other

- Review GCP regulations and Clinical Research Guidelines for international harmonization and patient protection

Our major activities for the purpose

- ✓ Consultation
  - Before application
- ✓ Inspection
  - After application
- ✓ Workshop
  - Conduct every year
  - Intended participants
    (Sponsors, Medical institutions, CRO, SMO, etc.)
  - Provide information on inspection
    (Purpose, Points to consider, Findings in recent inspections, etc.)

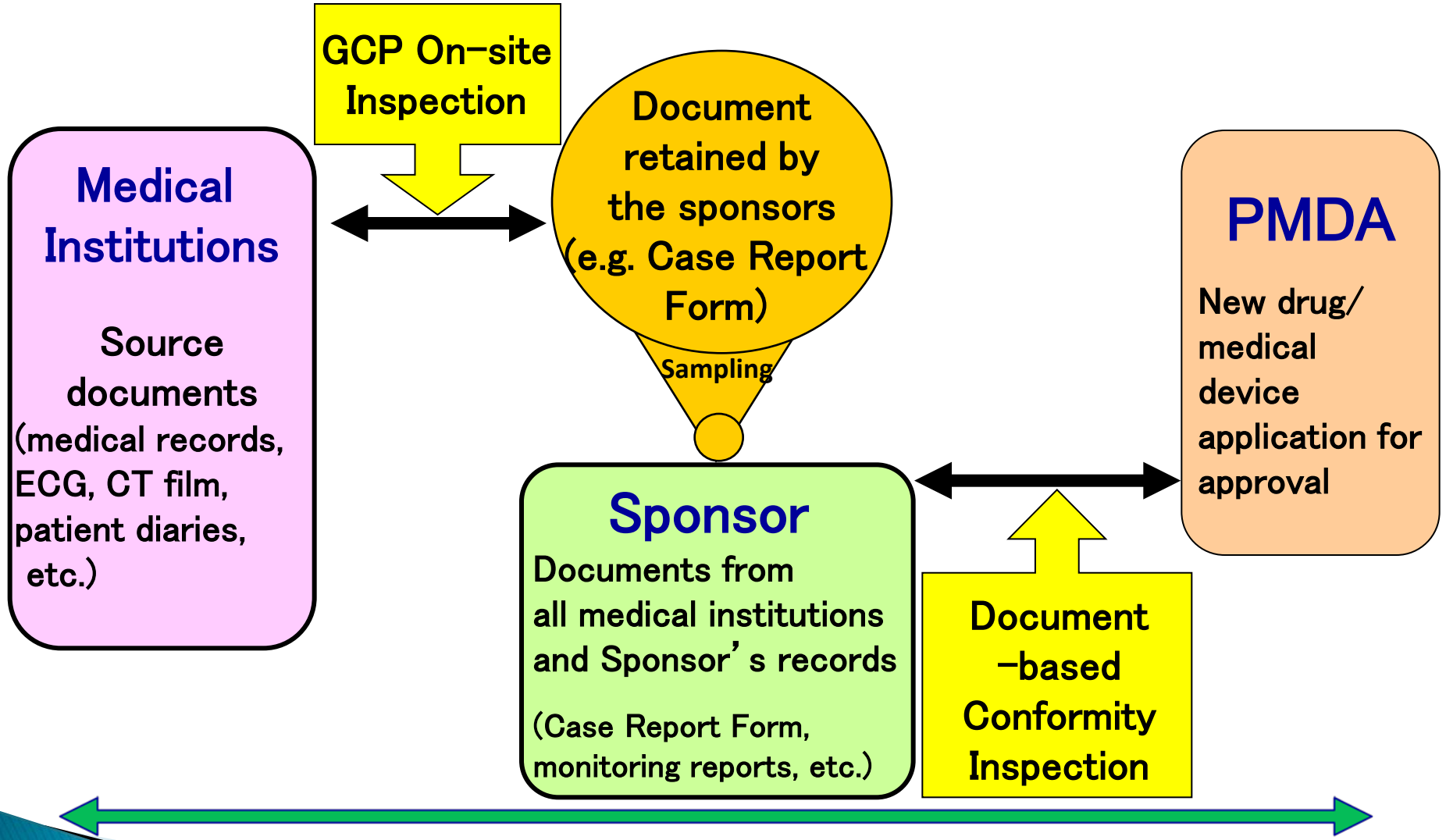
About our Inspection

- ✓ Application-based
- ✓ Conducted after the clinical trials (or surveys) have finished

⇒ By verifying the implementation status of the finished clinical trials (or surveys), we aim to secure the quality of ongoing clinical trials (or surveys), and/or trials (or surveys), scheduled in the future.

- ✓ Timing
  - New-drug Application <Pre-approval>
  - Re-examination Application <Post-marketing>

We conduct Application-based Inspection.



Our office Ensure conformity of the data of clinical trial

Conclusion of Inspection

Compliance :

accepted as application dossier
(Voluntary, improvements are indicated)

Compliance with condition :

the violation of GCP was confirmed for a part of the subjects

→ accepted as application dossier after deleting the data from NDA package.

Non-compliance :

the violation of GCP was found generally and systematically

→ no reliability

→ whole clinical trial data should be deleted

Trend of GCP on-site Inspections

	FY '05	FY '06	FY '07	FY '08	FY '09	FY '10
Number of drugs(NMEs)	50 (1)	51 (0)	82 (0)	95 (3)	74 (7)	82 (7)
Number of sponsors	59 (1)	66 (0)	90 (0)	97 (4)	76 (7)	85 (8)
Number of medical institutions	120 (2)	100 (0)	177 (0)	214 (6)	180 (14)	200 (14)

( ): The number of inspections in foreign countries

Inspection for New-drug Application

Applicable Regulatory Requirements

- ✓ Good Laboratory Practice（GLP）
- ✓ Good Clinical Practice（GCP）
- ✓ Data Reliability Standards for Applications

-Article43 of Ordinance for Enforcement of the Pharmaceutical Affairs Act-

Our point of view

<GCP>

- ✓ Protection of trial subjects
- ✓ Appropriate implementation of clinical trials in accordance with the protocols and related standard operation procedures
- ✓ Implementation of clinical trials under appropriate system

…

< Data Reliability Standards for Applications>

-Article43 of Ordinance for Enforcement of the Pharmaceutical Affairs Act-

- ✓ Accuracy
- ✓ Completeness
- ✓ Retention

How can we get involved?

- ✓**Protocol**

=at the consultation=

Reviewers (not inspectors) help design the protocols to fit the purpose within the consulting service.

At notification, safety assurance is priority, but reviewers also check the reflection of the consultation conclusions.

- ✓Implementation System

How can we get involved?

- ✓ **Protocol**

  ＝at the inspection＝

  - Deviation from the protocol

    ⇒Often quality of the protocol has a large impact on quality of clinical trials.

- ✓ Implementation System

Findings and our point of view

- Deviation from the Protocol

  ・The eligibility of subject was not examined appropriately.

  ⇒Was the criteria well-defined?

  ⇒Was the criteria reasonable from ethical and/or scientific point of view?

Findings and our point of view

- Deviation from the Protocol

  ・Noncompliance with the rules on evaluating product efficacy and/or safety

  ⇒Was the method and/or index for evaluation well-defined, and reasonable from the scientific point of view?

  ⇒Did PI(or responsible person) ask about or confirm the interpretation to the sponsor when he/she was not sure about it?

  ⇒Did sponsor provide the answer for the question to all related sites as necessary?

  ⇒Did sponsor revise the protocol as necessary?

  …

How can we get involved?

- ✓ Protocol
- ✓ Implementation system

=at the consultation=

- ・Composition of DMC and/or IRB
- ・Change of IRB in the course of trial
- ・Handling of Adverse Event
- ・Requirement for application using EDC

・・・

Inspection relevant to EDC

<Structure of our EDC checklist>

-For Sponsor-

1. Summary of the system
2. Sponsor's organization, outsourcing status, etc. relevant to EDC system operation
3. Validation
4. User management
5. Data storage
6. Creation, amendment and signature of eCRF

-For medical institution-

1. User management
2. Data storage

Although we conduct the inspection using the checklists noted above, we are prepared to modify our approach according to feedback from inspectee.

How can we get involved?

- ✓ Protocol
- ✓ Implementation system

=at the inspection=

- ・Appropriateness of the procedure to obtain informed consent
- ・Pertinency of the IRB review
- ・・・

Findings and our point of view

- **Inappropriately obtained informed consent**

  ・Although the written information document was revised, nor were the subjects informed in a timely manner or was the communication of this information documented.

  ⇒Check if the subject decided to continue participation with his/her own will.

Findings and our point of view

- Inappropriately obtained informed consent

  ・Informed consent was obtained by using the not fully explained information document.

  ⇒Check if the IRB reviewed the document appropriately.

Findings and our point of view

- The IRB/EC might not meet the qualifications required.

  ・A member appointed as independent of the medical institution might have a stake in the institution.

  ⇒Check the background of appointment and his or her statement in the committee based on related documents

Re-examination system

- In Japan, severe damages caused by adverse reaction to drugs like thalidomide, clioquinol, etc. were experienced.
- In accordance with the lessons learned, drug re-examination system was introduced to prevent additional tragedy, within the partial amendment of the Pharmaceutical Affairs Law in 1979, coupled with the enactment of the Law for the Adverse Drug Reaction Relief Service Fund.
- As data obtained by approval is very limited, Safety, Efficacy and Quality of the product are to be assessed based on data collected during a certain period after approval.

Inspection for Re-examination Application

Applicable Regulatory Requirements

- ✓ Good Post-marketing Surveillance Practice (1997.3)(GPMSP)
- ✓ Good Post-marketing Study Practice(2004.12) (GPSP)
- ✓ GCP
- ✓ Data Reliability Standards for Re-examination Application

-Article61 of Ordinance for Enforcement of the Pharmaceutical Affairs Act-

What is required within GPSP? (1 /2)

- Preparation of operating procedures for Post-marketing surveillance(study)
- Appointment of supervisor of Post-marketing surveys
- Implementation of survey, Self-inspections, Training, Retention of Records in accordance with the operating procedures

…

What is required within GPSP? (2/2)

- Responsibilities of the marketing authorization holder etc.
  - Pharmaceutical development
  - Knowledge Transfer between Development branch and Post-marketing branch
  - Post-marketing
  - Product-discontinuation

- ICH Q10:Quality System

Our point of view

<GPSP>

- Was the operating procedures for Post-marketing surveillance(study) prepared appropriately?
- Was the supervisor of Post-marketing surveys appointed properly?
- Were the Survey, Self -inspections, Training, Retention of Records, etc. conducted in accordance with the operating procedures?
- Was(Were) the marketing authorization holder etc. informed in a timely manner by document?

...

< Data Reliability Standards for Re-examination Applications>

-Article61 of Ordinance for Enforcement of the Pharmaceutical Affairs Act-

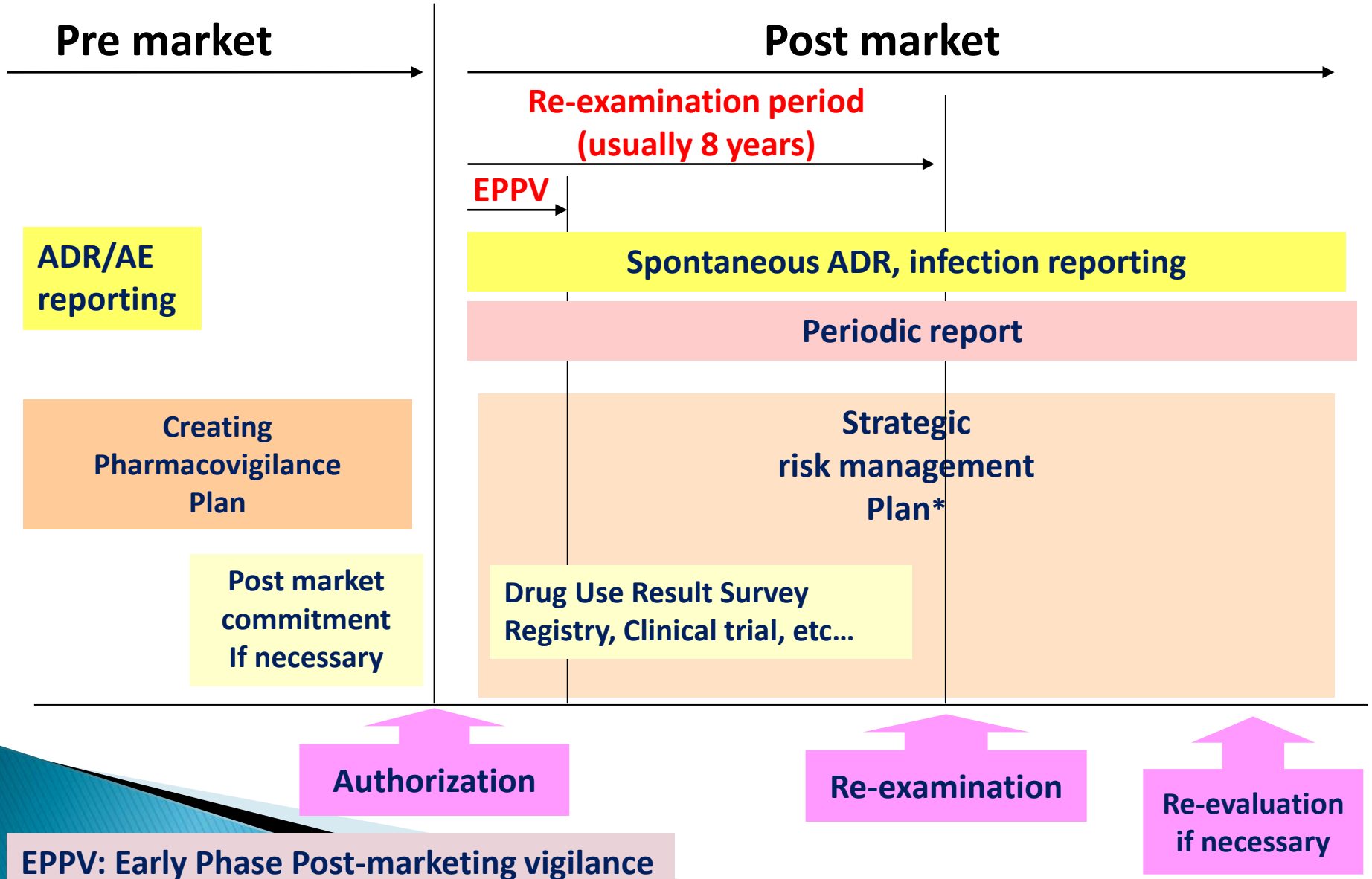
- Accuracy
- Completeness
- Retention

Post-marketing safety measures and Inspection for Re-examination Application

Check if the marketing authorization holder etc. collect(s) and provide related information appropriately.

- ✓Preparation of the standard operation procedure for collecting information
- ✓Appropriateness of the keywords, information source, interval, etc. to collect necessary information
- ✓Adequateness of the evaluation(known or unknown, severity) and clarification of the locus of responsibility
- ✓Appropriateness of information provision(report to the authority, amendment of package insert, etc.)

Pharmacovigilance activities in Japan



EPPV: Early Phase Post-marketing vigilance

We try to help improve public health by watching the pre-approval and post-marketing stages also from inspectors' point of view.

Thank you for your attention!