The role of conformity audits for the Japanese Authority and the quality of clinical trials in Japan.

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<The views expressed in this presentation are those of the presenter and do not necessary reflect the official views of Pharmaceuticals and Medical Devices Agency>

Background

In Japan, the services of the PMDA include the reviews of and related services for new drug applications. “Document Based Inspections/data integrity assessment (DBI)” of the “Office of the Conformity Audit(OCA)” verifies the accuracy and reliability of the clinical trial data (every application) submitted to PMDA in accordance with the regulations set forth in the Pharmaceutical Affairs Law (Article 15).

DBI is a system unique to Japan. The purpose of the system is to assess compliance with GCP, GLP and other standards in relation to applications for “new drug applications” (NDA).
DBI verifies whether the submitted data comply with the reliability standards for regulatory submission documentation by checking the raw data or source data archived by pharmaceutical sponsors.

The inspected objects of DBI include not only Clinical Trial data but also Chemistry, Manufacturing and Control (CMC) and Non-Clinical Study data.

Background (cont.)

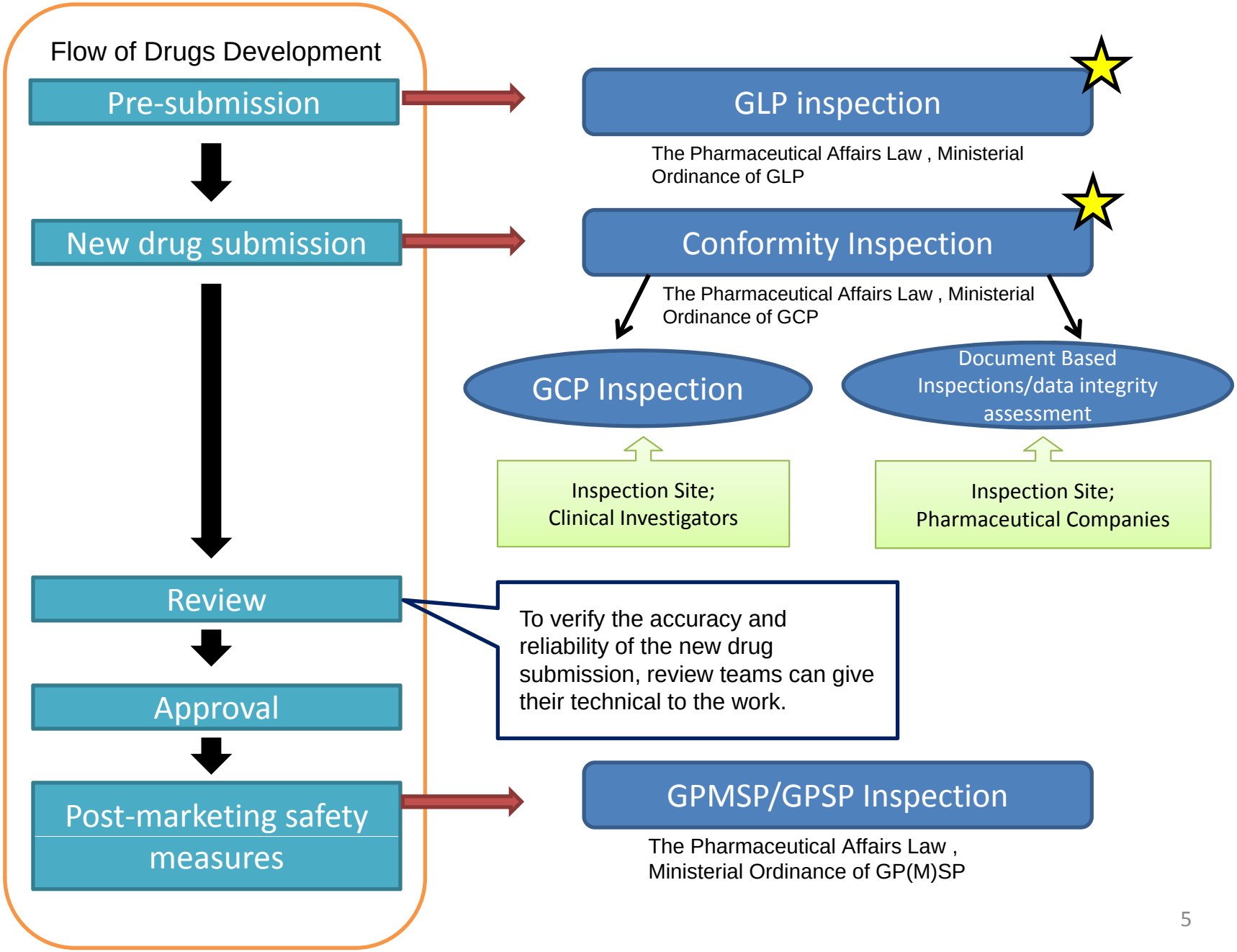
In Japan, Japanese-GCP (J-GCP) came into effect in 1997.
In 2004, J-GCP was greatly revised in order to ensure further quality of clinical studies.
After revision of J-GCP, the environmental of clinical studies should also be improved.

In addition, to resolve the “drug lag”, PMDA has reinforced the review system by shortening the period from the start of clinical trials to approval of the NDA and so on.
Therefore, the OCA division tries to increase efficiency.

Purpose

- The overview of the OCA in PMDA
- The role of DBI in the NDA reviews process
- The results of NDA submission in Japan, and the number of inspection days for NDA (FY 2004 – 2009)
- The changes in the inspection findings about GCP non-compliance or compliance with conditions
- Discussion of the scientific quality of Japanese clinical trials and the study results.

The role of Conformity Audit Division in Drug Approval



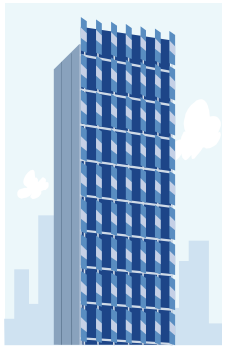
Summary of the GLP Inspection

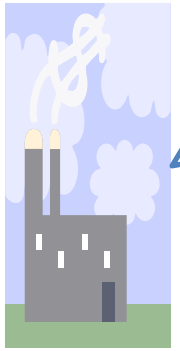
Contract

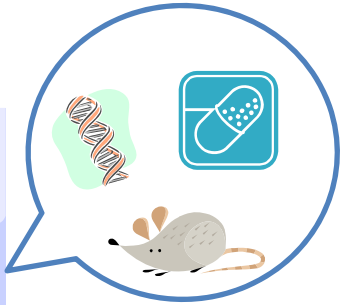
Pharmaceutical company

Inspection

Inspection
-Test facility inspection
-Study audit







Test facility

Application of GLP inspection

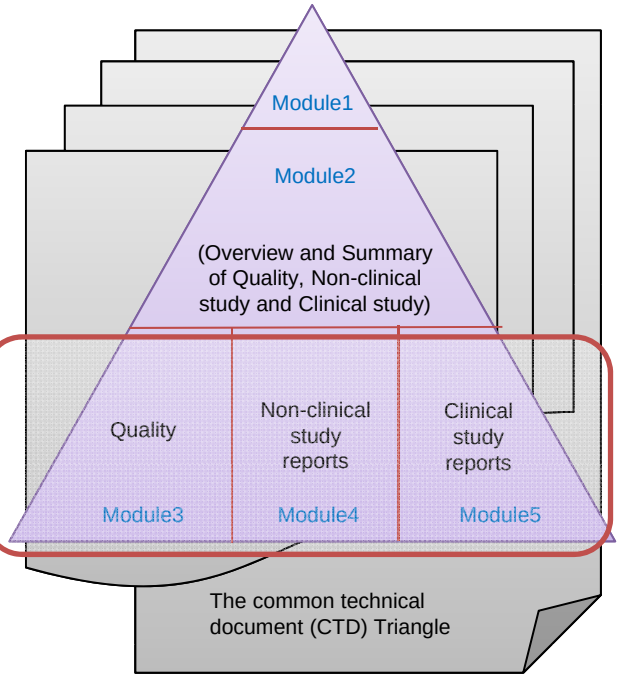
Conformity Audit in PMDA

Notification

The result of Inspection

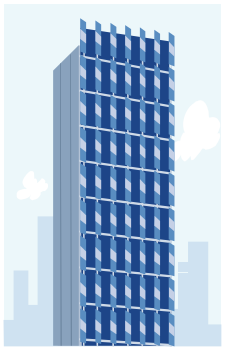
GLP compliance certification (A, B or C)

Summary of the conformity inspections



Ensure the veracity of raw data, records and reports.

Fix the CTD



Pharmaceutical company

Application documents
(The common technical documents)

Inspection

Notification

Conformity Audit in PMDA

Document Based Inspections/data integrity assessment

GCP Inspection

Clinical trial site

Submit to the CRF

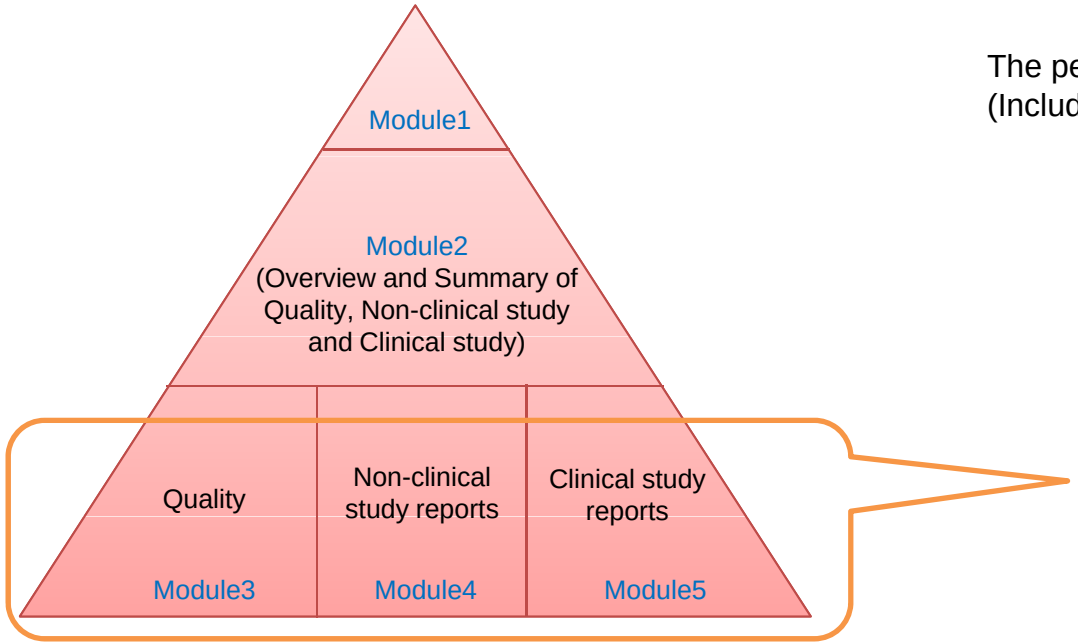
The result of Inspection (for Pharmaceutical company & Clinical trial site

GCP compliance certification (for Clinical site)

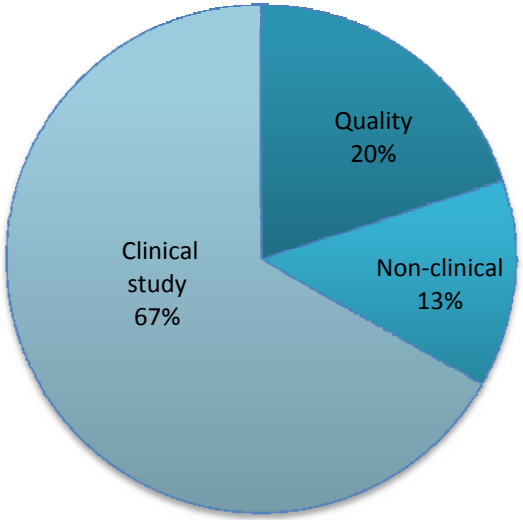
New prescription drug classification system for NDAs in Japan

Included in clinical trial data in NDA	Prescription drugs with new active ingredients	<Conformity Inspection Type> DBI and GCP inspection
	New combination prescription drugs	
	Prescription drugs with new administration routes	
	Prescription drugs with new indications	
	Prescription drugs with new dosage forms	
	Prescription drugs with new doses	
	Similar biological drugs	
	Combination prescription drugs with similar formulations	
Not included in clinical trial data in NDA	Prescription drugs with additional dosages forms	<Conformity Inspection Type> DBI only
	Other prescription drugs	

The outline of target for DBI



The percentages of conducted DBI in FY2009
(Include clinical trial data in NDA)



The details of DBI conducted in FY2009 (Including clinical trial data in NDA)

(products)

Quality		Non-clinical		Clinical study	Total documents
3.2.P(S).5	3.2.P(S).8	non-GLP	*GLP		
39	38	42	9	257	385

Number of NDA in Japan (FY2005 to FY2009)

(products)

		FY2005	FY2006	FY2007	FY2008	FY2009
Products submitted	Approval	95	120	142	170	149
	Partial change	133	247	245	271	349
	Total	228	367	387	441	498
Products approved	Approval	85	102	141	143	137
	Partial change	195	136	229	209	329
	Total	280	238	370	352	466

Number of DBI for NDA (FY2005 to FY2009)

(conducts)

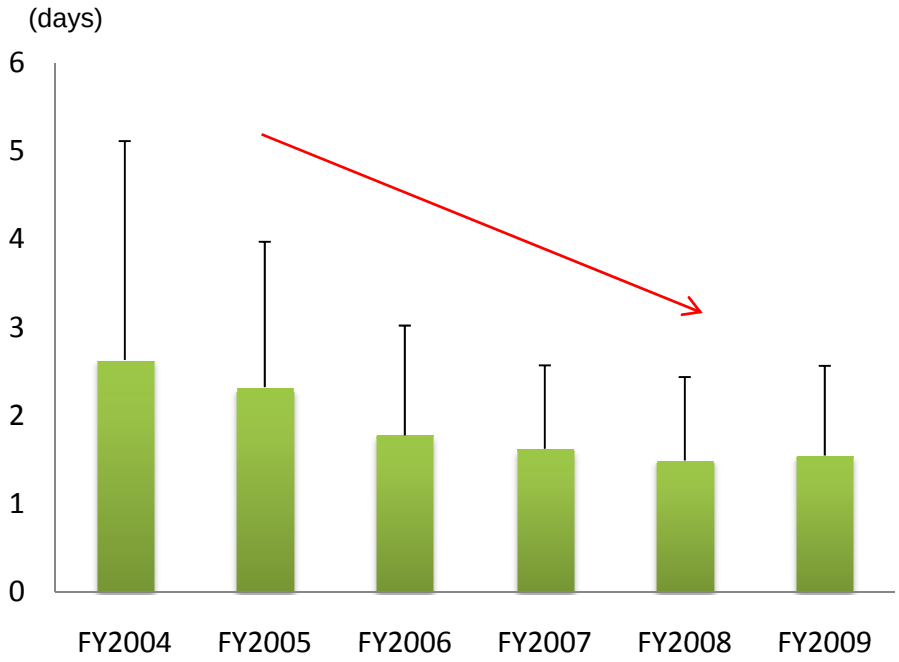
	FY2005	FY2006	FY2007	FY2008	FY2009
New Drugs	135	251	234	293	246

In Japan, the number of approved new drug products is increasing year by year.
The ratios of the “partial change application” are higher than the “approval application”.
The peak of on-site and document based inspections conducted was in FY2008.

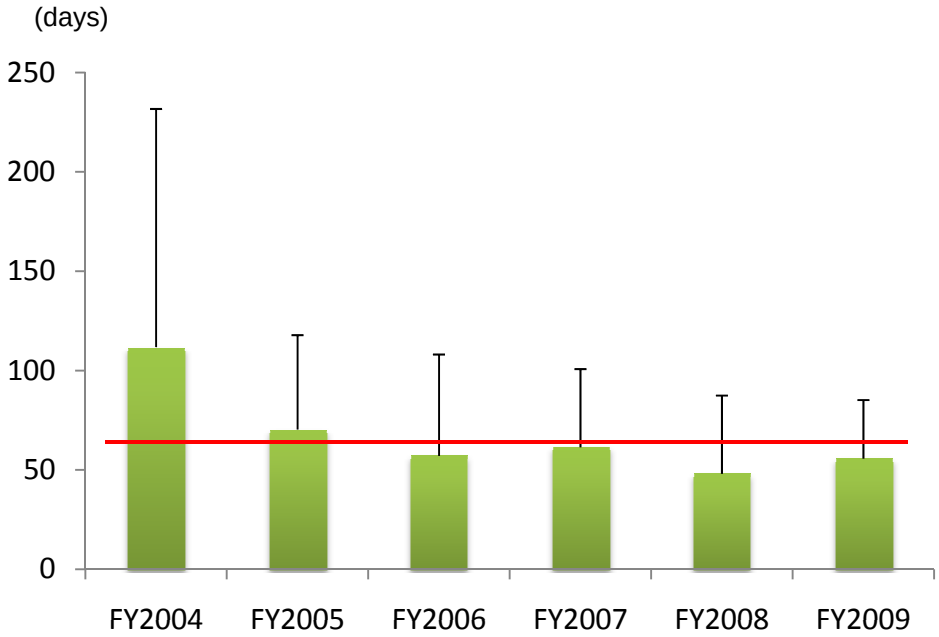
Ref; PMDA Annual Report (FY2009)

Changes of DBI (FY2004 to FY2009)

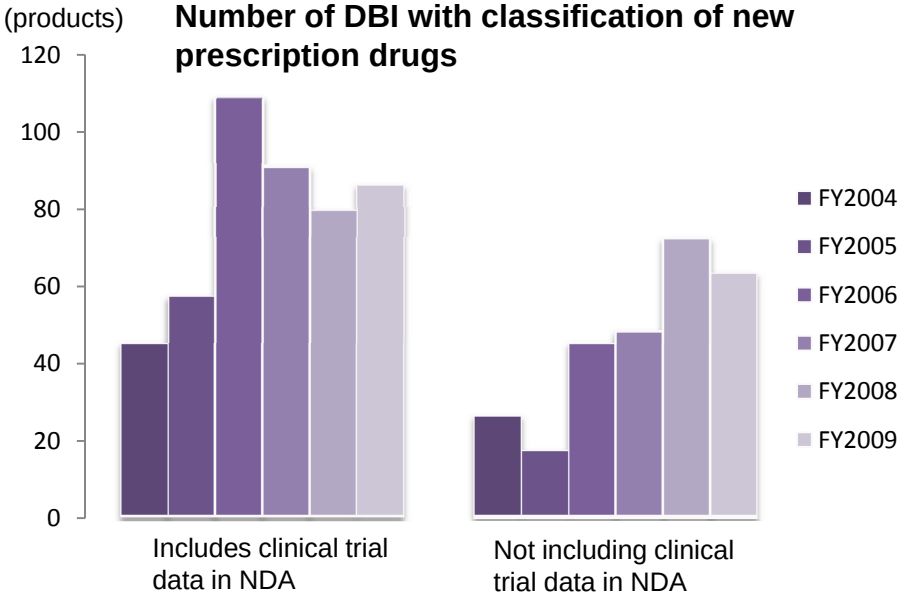
The average inspection time of DBI



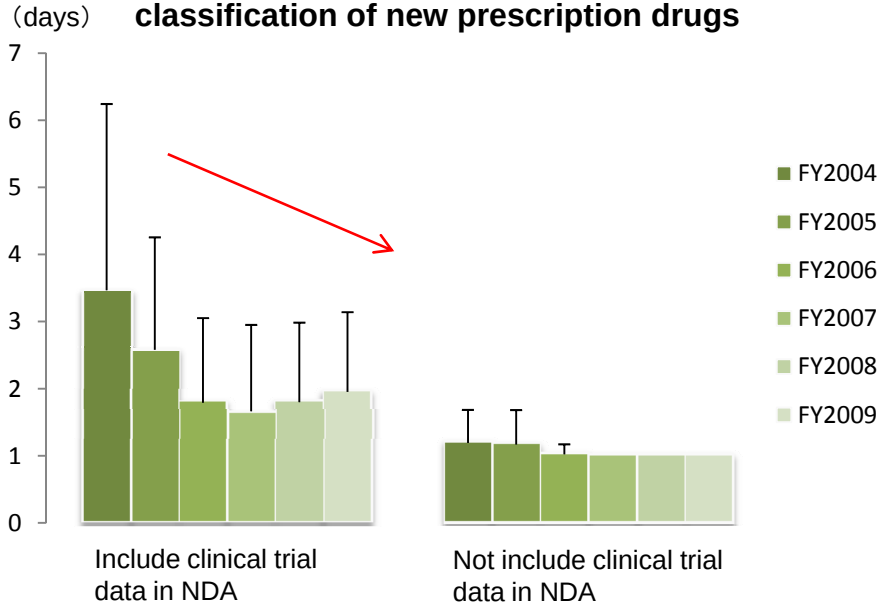
The average time between the notification on DBI and the report of DBI results.



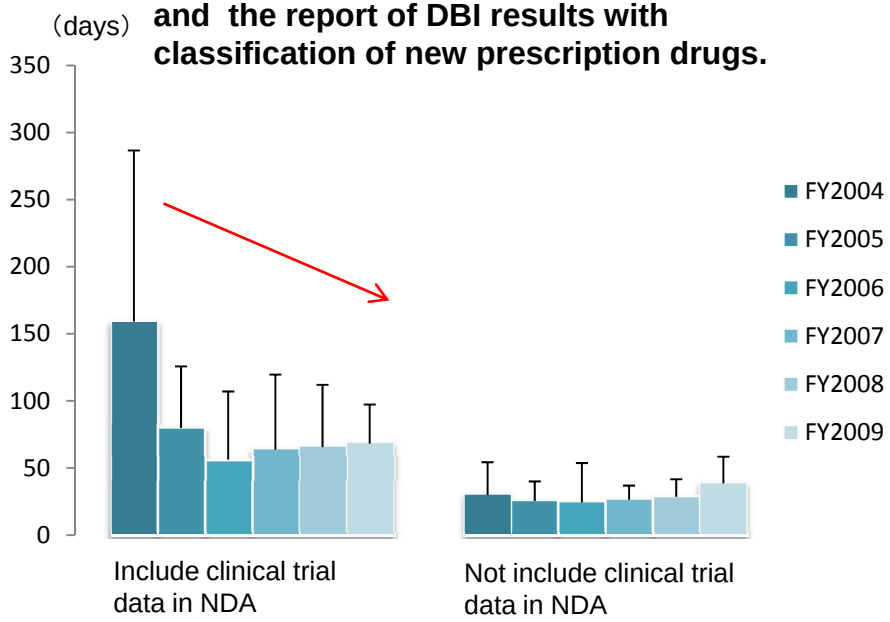
Number of DBI with classification of new prescription drugs

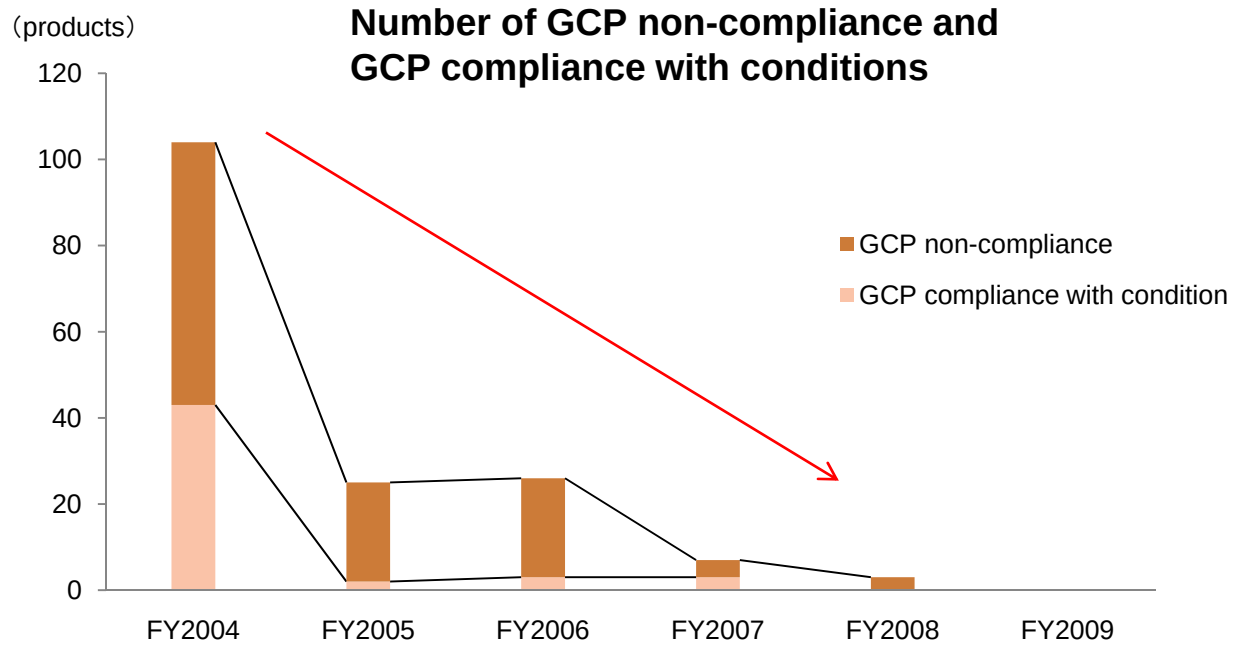


Average inspection time of DBI with classification of new prescription drugs



Average time between the notification on DBI and the report of DBI results with classification of new prescription drugs.





The details of GCP non-compliance

(study audits based)

	FY2004	FY2005	FY2006	FY2007	FY2008	FY2009
GCP Article 9	4	0	0	0	0	0
GCP Article 13-1	0	2	0	0	0	0
GCP Article 15	0	0	0	1	0	0
GCP Article 17	0	1	0	0	0	0
GCP Article 21-1	11	5	1	0	0	0
GCP Article 24-1	0	0	0	1	0	0
GCP Article 26-1	0	0	1	0	2	0
GCP Article 28-1	0	1	1	0	0	0
GCP Article 47-1	15	4	3	0	0	0
GCP Atricle 47-3	0	0	1	0	1	0
Basis of the reliability of the new drug submission data	5	0	0	0	0	0

Japanese GCP (excerpt)

Ministerial Ordinance on Good Clinical Practice for Drugs

GCP Article 9	Requests for preparation of written information.
GCP Article 13-1	Clinical trial contract; A clinical trial contract shall be concluded by means of a document specifying the following information about the person who intends to sponsor a clinical trial and the medical institutions (or the persons who intend to sponsor a clinical trial, contractor(s), and medical institution when a part of the duties pursuant to the preceding Article is outsourced).
GCP Article 15	Clinical trial In-country representative.
GCP Artiicle 17	Supplying investigational products.
GCP Article 21-1	Monitoring; The sponsor shall prepare written operating procedures for monitoring, and conduct monitoring activities in accordance with the procedures.
GCP Article 24-1	Premature termination etc. of clinical trial; If it is found that a medical institution has violated this Ministerial Ordinance, the protocol or the clinical trial contract, resulting in interference with the proper conduct of the clinical trial (excluding the cases specified in Article 46), the sponsor shall cancel the contract and prematurely terminate the clinical trial at the medical institution.
GCP Article 26-1	Recoding keeping etc.; The sponsor shall appropriately retain the following records including documents and data) related to the clinical trial until the day on which marketing apprval of the test drug is obtained (or the day 3 years after the date of notification in the case of a notification pursuant to Article 24, Paragraph 3) or the day 3 years after the date of premature termination or completion of the clinical trials, whichever comes later:
GCP Article 28-1	Composition etc. of Institutional Review Board (IRB); The IRB shall meet the following qualifications:
GCP Article 47-1	Case Report Form (CRF) etc.; The investigators etc. shall prepare CRFs accurately in compliance with the protocol and sign and seal, or sign the forms.
GCP Atricle 47-3	Case Report Form (CRF) etc.; The investigator shall inspect the CRFs prepared by the subinvestigator(s) and, upon confirmiting the content thereof, shall sign and seal, or sign the forms.

Conclusion and Discussions

1. The efficiency of DBI is increasing.

   The average inspection time is becoming shorter and shorter, while the number of NDA is increasing.

2. The GCP-quality of Japanese NDAs is improving.

   The number of GCP non-compliance or compliance with condition is decreasing year by year.

3. The DBI system ensures the scientific quality of clinical trials, the reliability of the results and the veracity of the NDA documents.