EMA-FDA and PMDA GCP Pilot Collaboration Report

June 2017-December 2018

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Glossary

Acronym	Region	Term
EMA	EU	European Medicines Agency
CDER	US	Center for Drug Evaluation and Research
CHMP	EU	Committee for Medicinal Products for Human Use
CI	EU, US	Clinical Investigator
CIS	US	Clinical Inspection Summary
CorpGxP	EU	Corporate GxP database
CRO	Global	Contract Research Organisation
DARRTS	US	Document Archiving, Reporting, and Regulatory Tracking System
ECMS	US	Enterprise Content Management Server/System
EU	EU	European Union
FDA	US	(United States) Food and Drug Administration
GCP	Global	Good Clinical Practice
IIR	EU	Integrated Inspection Report
INN	Global	International Non-proprietary Name
IREQ	EU	Request for an Inspection
IWG	EU	Inspector Working Group
NDA	Global	New Drug Application
OND	US	Office of New Drug
OSI	US	Office of Scientific Investigation
PMDA	Japan	Pharmaceuticals and Medical Devices Agency
sNDA	Global	supplemental New Drug Application
US	US	United States

1. Executive Summary

This report outlines the results of the 18-month feasibility pilot initiative to include the Pharmaceuticals and Medical Devices Agency (PMDA) Japan into the existing European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) Good Clinical Practice (GCP) collaboration. This feasibility pilot was launched in June 2017 under the framework of the confidentiality arrangements established between the European Commission, the EMA, the U.S. FDA and PMDA. The main objectives of the initiative were to evaluate the timing of GCP inspections and exchange of information related to GCP issues for common marketing submissions among the three agencies as well as identify best practices in GCP process and procedure.

Eleven teleconferences and two face-to face meetings took place during the pilot phase. These meetings contributed greatly to each agency's understanding of the others' regulatory procedures, especially in the area of GCP inspections.

The agencies regularly exchanged a considerable amount of information related to the common applications, which contributed to improvements in the agencies' inspection coverage and decision making process.

Of 59 marketing application discussed:

- 24 marketing applications were received by FDA, EMA and PMDA within the same time period.
- 20 of those marketing applications were analysed, covering 209 GCP inspections including 155 CI and 54 sponsor/CRO

The GCP inspection milestones, such as the average number of days from start to end of inspections, did not show significant differences among the three agencies. Based on these findings, the three agencies agreed to continue collaboration and exchange of information related to GCP inspections, and discuss relevant GCP issues in support of regulatory decision making for common marketing applications.

2. Background

The clinical development of pharmaceutical products is a global undertaking. In most cases sponsors submit data from the same clinical trials in support of marketing approval of new medical products to EMA, FDA and PMDA.

Regulators in the United States, Japan and European Union conduct GCP inspections to verify the integrity of data generated in clinical trials and to assure the protection of human research subjects, in addition to ensuring clinical trials are conducted according to the investigational plan. The globalisation of large scale and complex clinical trials, coupled with limited inspection resources, limits the number of trials and clinical investigators (in Japan, medical institutions) which can be inspected for GCP compliance. If regulators can work in a collaborative and synergistic manner in carrying out GCP inspections and can implement information exchanges, then inspectional resources will be used more efficiently, improving inspection coverage.

Although PMDA, FDA and EMA each have systems and programs in place to verify compliance with applicable regulatory requirements, and have implemented GCP provisions, these programs have not historically included multilateral, systematic coordination and conduct of GCP inspections for marketing

applications of common interest nor have they developed a systematic and timely mechanism for sharing relevant GCP-related information or involved other regulators in their inspectors' trainings. In September 2009, EMA and FDA started an initiative to share information from GCP inspections and conduct collaborative inspections, which began with an 18-month pilot phase to assess its viability and performance. At the end of the pilot, after exchanging more than 250 documents relating to 54 different products, FDA and EMA agreed to continue the collaboration, incorporating lessons learned during the pilot initiative. Further expansion of this type of collaboration, communication and cooperation between EMA, PMDA and FDA on GCP convergence and inspection had long been a strategic objective, accompanied by formal information-sharing confidentiality arrangements.

As a result, PMDA requested on September 29, 2016 to join the ongoing collaboration with FDA and EMA. PMDA was welcomed to observe the collaboration as of April 2017. As part of a feasibility pilot, it was agreed to collect data including the number and timing of common marketing applications for 18 months starting in June 2017. There were eight regular teleconferences planned during this pilot phase. This report presents the findings of the pilot phase.

3. Scope and Method

All three agencies aimed to increase their understanding of each other's regulatory procedures especially in the area of GCP inspections.

The following actions undertaken during the pilot phase were developed and a responsible person from each agency appointed:

- Ensure the implementation of the initiative
- Streamline the sharing of information and timely communication of inspection outcomes
- Facilitate communication between the EU, PMDA and U.S. FDA inspectors and assessors regarding the exchanges of information and the collaborative inspections
- Record data about the documents exchanged, inspection knowledge and application data
- Evaluate the progress of the initiative and implement changes as needed
- Report on the initiative at the end of the pilot

The three agencies recorded data on the applications received during the pilot phase.

The data referred to:

- Application data
  - International Non-proprietary Name (INN)
  - Trade names in each country/region
  - Type of application: accelerated or regular evaluation timeframe
  - Name of the applicant organization
  - Date of submission to each regulator
  - Outcome of the application review
- Inspection data
  - Dates of inspection request

- Type of inspection (routine or triggered)
- Site location
- Types of site: Sponsor, CRO, clinical investigator
- Dates of inspection (start and end date)
- Date of issuing the inspection report

4. Results of the GCP Feasibility Pilot

The agencies communicated regularly during the pilot phase to ensure inspection information was timely communicated, regulatory information was discussed, training opportunities were identified and progress of the initiative was monitored and recorded accurately.

The pilot included:

- Eight regular teleconferences to discuss inspection outcomes and assessment of the applications
- Four product- or inspection-specific teleconferences
- Teleconferences to review the evolution of the pilot phase and data for analysis
- Exchange of inspection documentation (including inspection reports), draft regulatory documentation, assessment information and other written information
- In-person meetings on June 6, 2018 in London and on October 11, 2019 in Bonn, Germany during the EU GCP IWG.

FDA shared 103 documents including 73 inspection summaries and 12 inspection reports; EMA shared 128 documents including five inspection reports and 33 IIRs; PMDA shared 74 documents including 37 summaries of inspections.

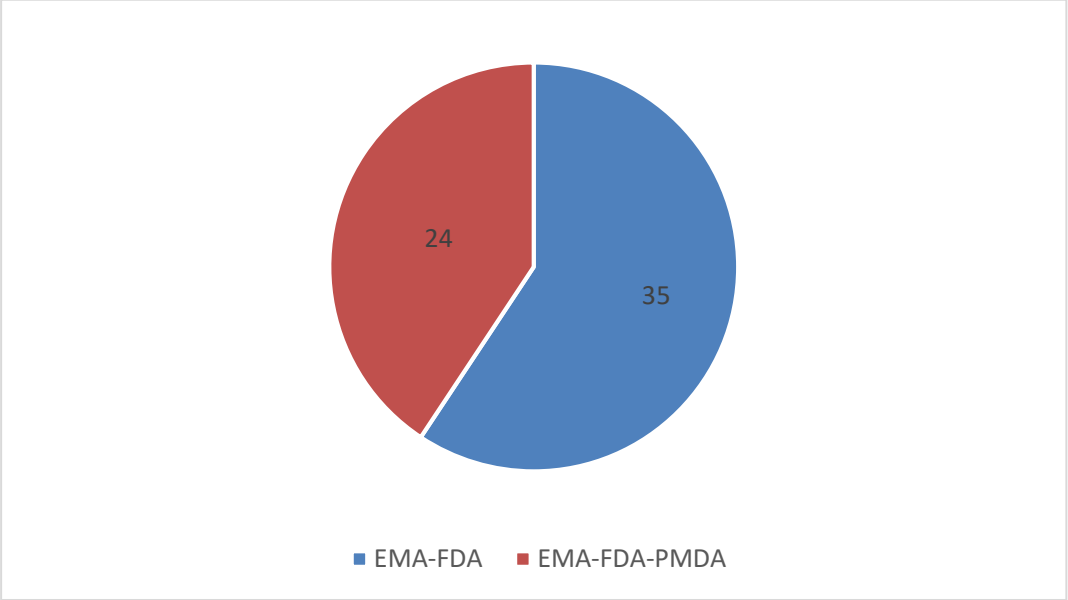
There were 37 collaborative inspections including 11 joint sponsor/CRO inspections between EMA and FDA, and 27 observed inspections.

4.1. Application Level Metrics

Applications received by EMA and FDA were added for discussion among the agencies. Agencies shared the list of applications received. Agencies discussed and tracked inspection and assessment outcomes.

During the pilot phase, 59 applications were received by both FDA and EMA and discussed during the regular teleconferences. Among them, 24 applications were received by FDA, EMA and PMDA. This information is presented in the chart below.

Figure 1. Applications received during the pilot phase



The agencies analysed the timing of applications in each region for the common applications.

Applications received within 60 days of each other were considered to be received in parallel. The agencies determined this would be the timeframe that allows mutual discussions to coordinate routine programmes.

Table.1 Number of parallel and non-parallel applications

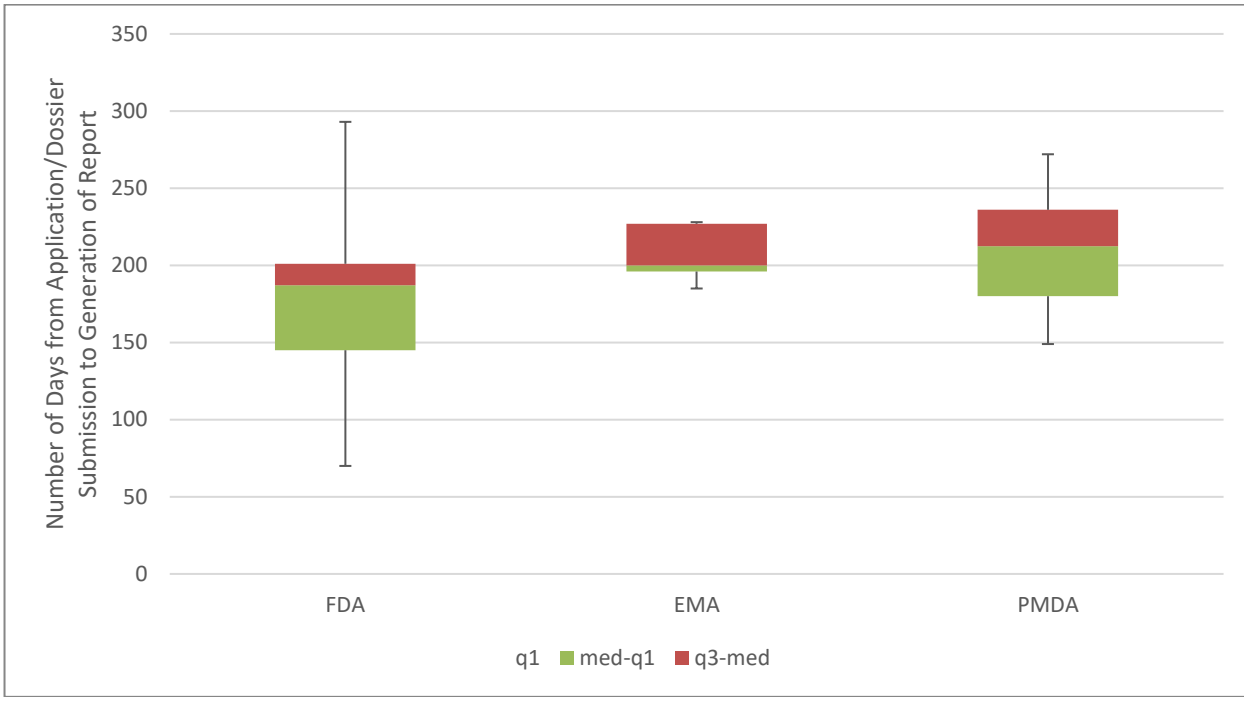
Applications received by FDA, EMA and PMDA		Applications received by EMA and FDA	
Parallel	Non-parallel	Parallel	Non-parallel
5	19	22	13

For the following analysis, data of applications received by June 2018, for which follow-up information was obtained by the end of December 2018, are included (20 applications). This is because the analysis requires sufficient follow-up information after the application is submitted.

4.2. Timeline Level Metrics

The chart below shows the number of days from submission of marketing application/authorization to generation of inspection report for the 20 applications which were received by all three agencies, EMA, FDA and PMDA and included in the analyses.

Figure 2. Number of Days from Submission of Marketing Application/Authorization to Generation of Inspection Report

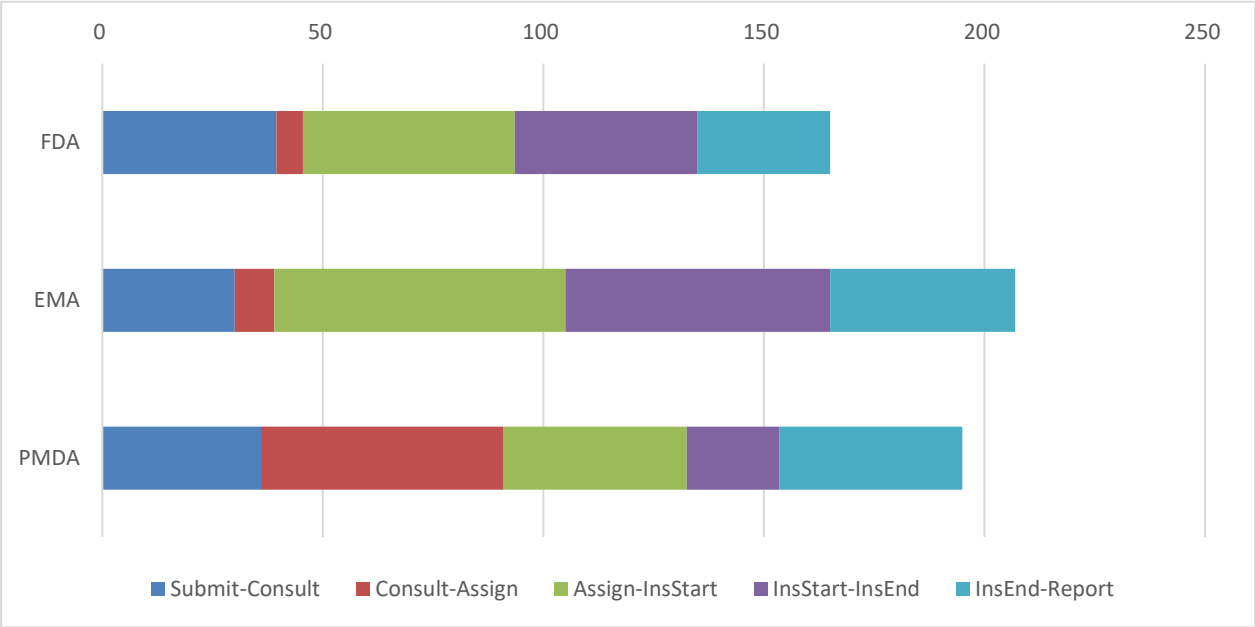


The composite bar chart in Figure 3 describes the time (number of days, median) of each inspection process, between submission of marketing application/authorization to generation of inspection report. The definitions of the terms used in the analysis are provided in Table 2. Each process is discussed in the following sections.

Table 2: Definitions of the terms

	EMA	FDA	PMDA
Submit	The date of the NDA/sNDA submission		
Consult	The date of the first adoption of IREQ by CHMP/CorpGxP	The date of the OND consult signed in DARRTS	The date when OND agreed the sites and the trials to be inspected
Assign	The date when the announcement letter is issued to inspectors/CorpGxP	The date of assignment in Complis/ECMS	The date when the responsible inspectors are assigned to each inspection
InsStart	The first date of the inspection for the application		
InsEnd	The last date of the inspection for the application		
Report	IIR issuance date	CIS issuance date	Inspection report notification issuance date

Figure 3. Average number of Days of GCP Inspection Processes in each Agency.

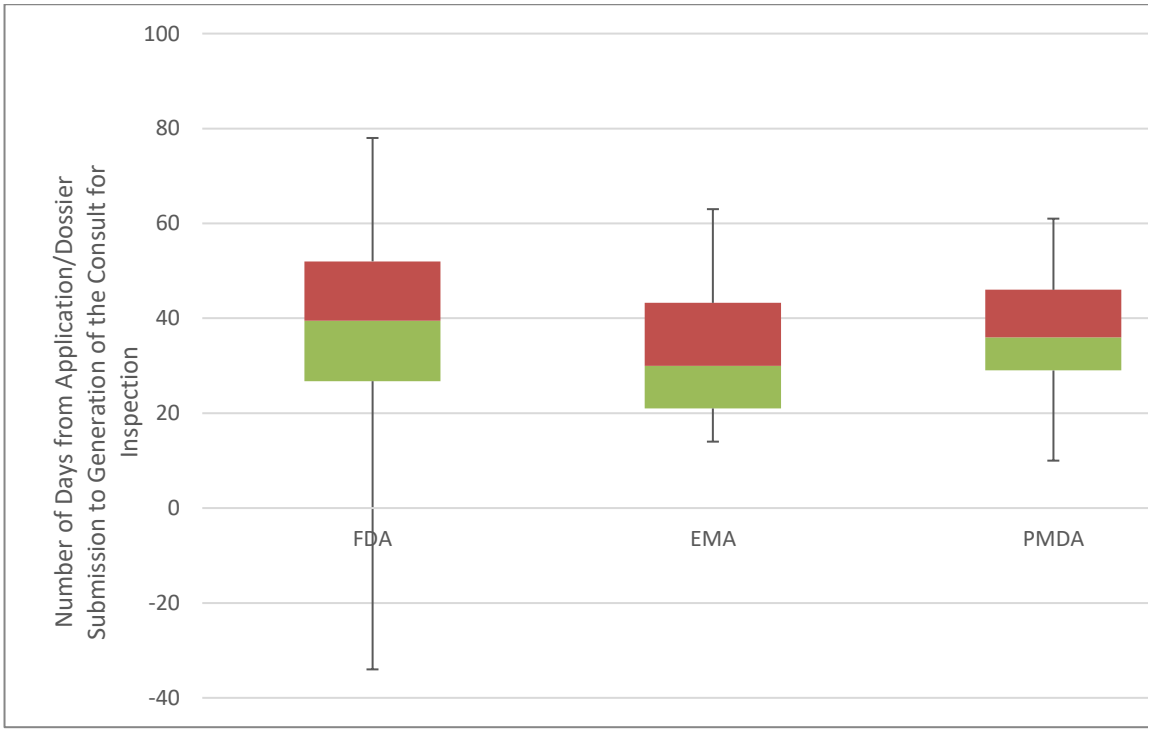


4.3. Inspection Process Level Metrics

A descriptive analysis of site inspections (CI, CRO, sponsors) for the common applications is summarized below.

First, the time between the receipt of the application and the formal request to inspect was analysed.

Figure 4. Number of days from submission to inspection consult issuance by application



FDA requests companies to send inspection-related materials as pre-submission on a case-by-case basis. Rolling submissions explain the negative numbers of days from submission of marketing application to inspection consult issuance. These negative numbers indicate that consults for inspection are generated prior to the application submission date.

The number of the days from the consult issuance to the generation of inspection assignment (Figure 5), from the generation of inspection assignment to the start date of the first inspection (Figure 6), from the start to the end of all issued inspections (Figure 7) and from the end of the last inspection to issuance of the inspection report (Figure 8) are also analysed.

Figure 5. Number of Days from Consult Issuance to Generation of Inspection Assignment by application

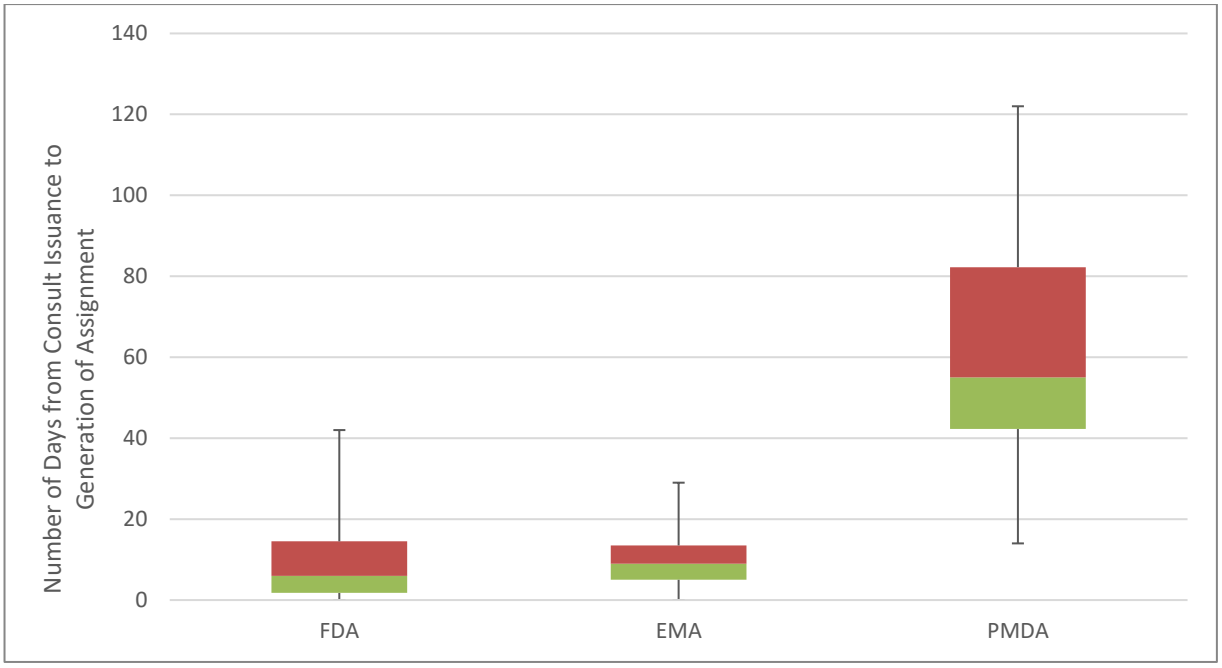


Figure 6. Number of days from generation of inspection assignment to the start date of first inspection by applications

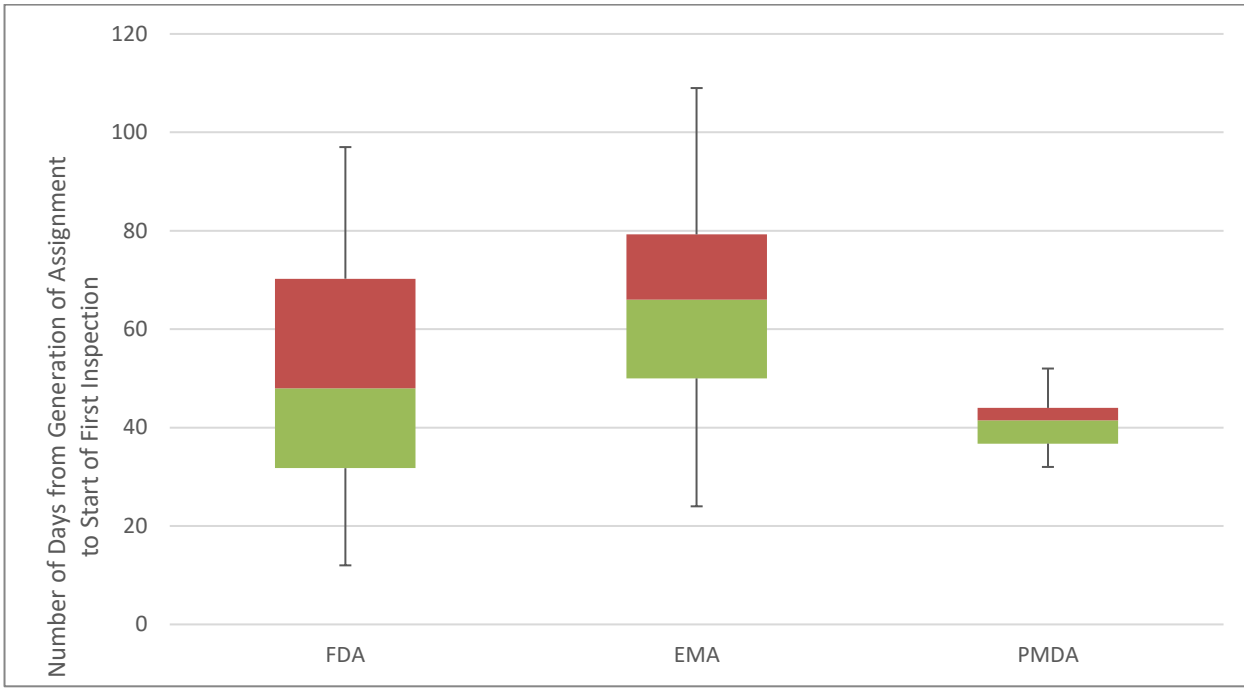


Figure 7. Number of days from start to end of all issued inspections by applications

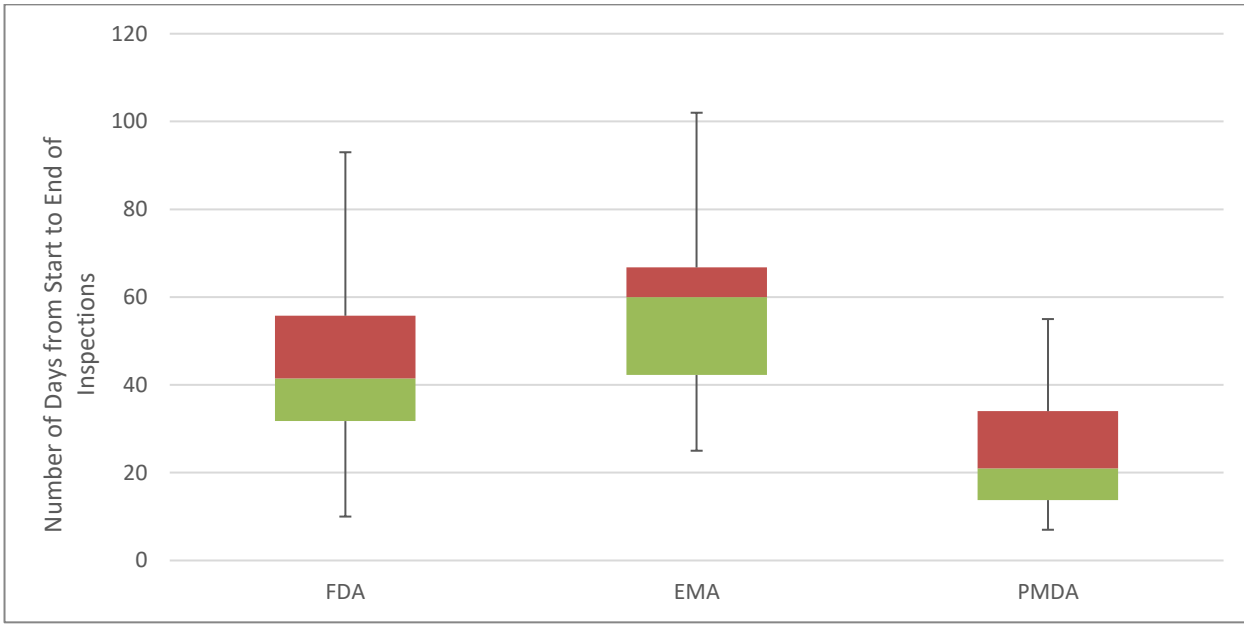
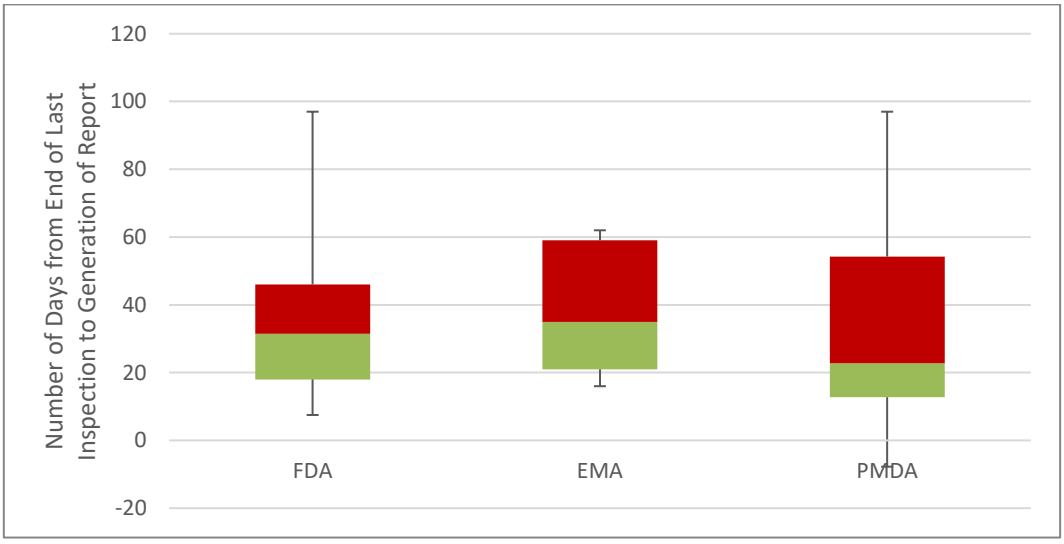


Figure 8. Number of days from end of last inspection to generation of inspection report



4.4. Inspection Level Metrics

An analysis by site type was also conducted. A total of 209 sites where inspected, corresponding to 155 clinical investigators, 44 sponsors and 10 CROs. The number of inspections by each agency is shown in Table 3.

Table 3: Number of inspections by site type

	FDA	EMA	PMDA	Total
Sponsor	12	9	23	44
CRO etc	4	6	0	10
Clinical Investigator	78	18	59	155
Total	94	33	82	209

Timeline by site type is presented below (Figure 9-11).

Figure 9. Number of days of GCP inspection process by (sponsor) site per regulator

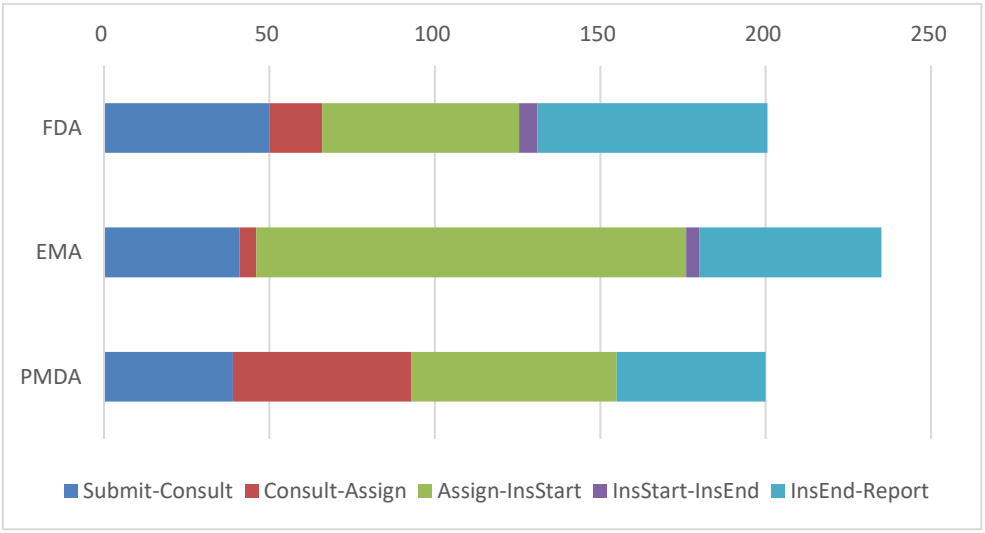


Figure 10. Number of days of GCP inspection process by (CRO) site per regulator

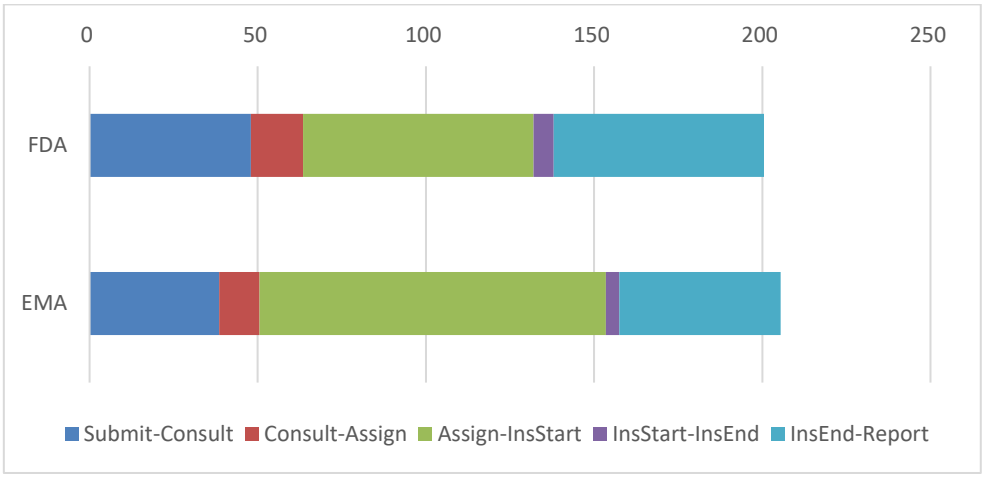
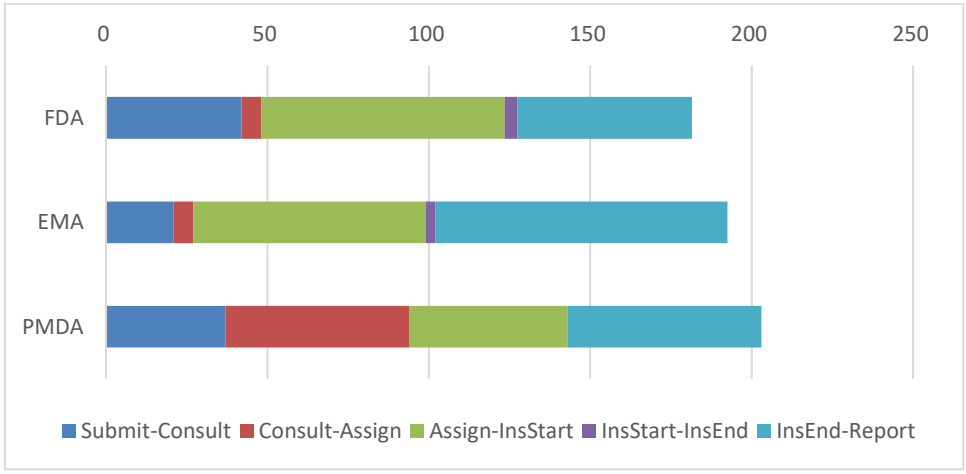


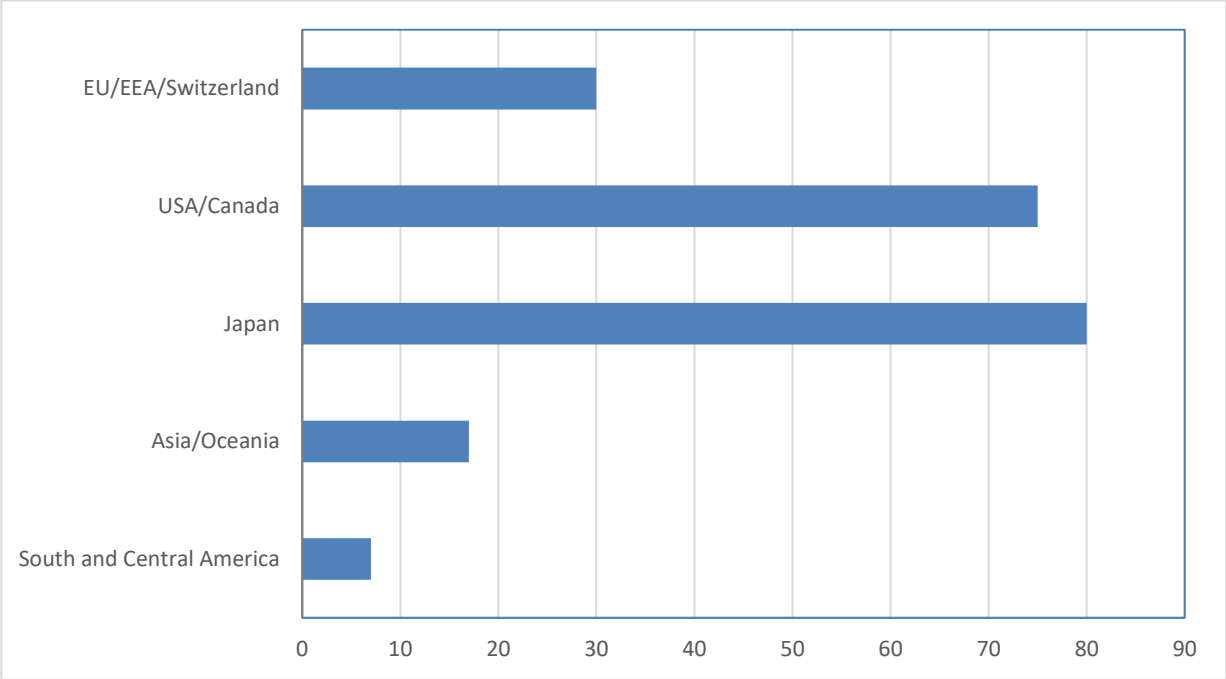
Figure 11. Number of days of GCP inspection process by (clinical investigator) site per regulator



4.5. Inspection Coverage

All 20 products included in the analysis were inspected by at least one of the agencies. Ten applications were inspected by FDA and PMDA. Among 155 inspections on clinical investigator sites, only two inspections were conducted by two agencies independently for the same application, suggesting that duplication of inspections was minimal. Inspections were conducted worldwide.

Figure 12. Inspection by location



5. Discussion and conclusion, next steps

During the 18-month pilot period, 48 common applications (FDA-EMA) and 20 common applications (EMA-FDA-PMDA) were discussed. Useful information was obtained thanks to the analysis of the process of inspections of these applications. As seen in Table 1, a considerable number of NDA/sNDA were submitted in parallel. This suggests that sharing information in timely manner, including on sites to be inspected and available inspection results, enables agencies to conduct more efficient and effective inspections. When an application is submitted to an agency and another agency has recently conducted inspection(s) relevant to that application, the second agency may consider not conducting the inspection but utilizing the existing inspection results.

There is no significant difference between three agencies in time spent from the submission to the generation of inspection reports (Figure 2). Although there are some differences in process and time spent for each inspection process, the total inspection period was similar in each agency.

Variations in durations of individual processes by agency are explained below:

- Longer period at PMDA (from the consult issuance to the generation of inspection assignment) (Figure 5)

The longer time spent for this process is because PMDA inspectors are assigned only once an approximate inspection date has been arranged with applicant and sites. Since inspections begin once inspectors are assigned, the overall duration (time from the submission to the generation of inspection reports) is not affected. When PMDA receives applications, the Office of Non-clinical and Clinical Compliance (responsible for GCP inspections) selects studies and sites to be inspected and contacts the Office of New Drugs (responsible for review) to inform them within the following month. Schedule adjustments across applicant, sites and assignment of inspectors are conducted right before the date of inspection (usually two months before the inspection). Therefore, while the number of days from

consult issuance to generation to inspection assignment is higher, the period from inspection assignment to start date of first inspection is shorter (Figure 5, 6).

- Shorter inspection period at PMDA (Figure 7)

Inspection itself is shorter at PMDA because many documents needed for inspection are submitted in advance by the site and the sponsor.

All 20 applications submitted to all three agencies were inspected by at least one agency (FDA and PMDA). The GCP collaboration broadened the coverage of GCP inspections, by having inspection information for a larger number of applications than one agency could cover, and a higher number of sites per application. This also avoided duplicate efforts. The higher coverage ensures higher confidence that the clinical trials comply with international ethical and scientific quality standards for designing, recording and reporting trials that involve the participation of human subjects. Compliance with these standards provides public assurance that the rights, safety and wellbeing of trial subjects are protected and that clinical trial data are credible.

During the pilot, draft regulatory documents, assessment information and other written information related to GCP were exchanged in addition to the inspection reports, and joint/observed inspections were conducted. Through these communications, the three agencies were able to share mutual ideas and methods for inspection. Further information was shared among the agencies by PMDA's pilot participation.

Participation of PMDA in this pilot was completed in December 2018. Based on the outcomes described above, EMA and FDA agreed to add PMDA as an official member of the GCP initiative and to continue this activity. In the future, effective GCP inspections can be promoted globally while using limited resources more efficiently by exchanging information, discussing further mutual inspection methods and GCP-related topics and continuing to share inspection information.