Case Analysis of PMDA GCP Inspections and US FDA Warning Letters by JSQA

2025 SQA Annual Meeting

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Japan Society of Quality Assurance, GCP Division

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- Hiromichi Ishikawa (Mitch) is an Associate Director of Quality Assurance at Ono Pharmaceutical Co., Ltd.
- He has over 12+ years experience of Clinical Development, Clinical Quality Management & Audits, and GxP Quality Assurance activities.
- Since he joined Ono, he has been working in multiple regions including US, UK, EU, Asia, and Pacific. In addition, 2021-2022 he was relocated to the UK and worked for a two-year stint as an expatriate there.
- Currently he spearheads JSQA GCP Division Subcommittee #4, Group A and Group B. These groups study regulations, regulatory inspections, audits, and others QA activities that took place in Asia, Europe, and the US.
- He received his bachelor of pharmacy (a registered pharmacist) from Tokyo University of Science, and his MBA from The university of Manchester.

Introduction
Japan Society of Quality Assurance (JSQA)

Japan Society of Quality Assurance

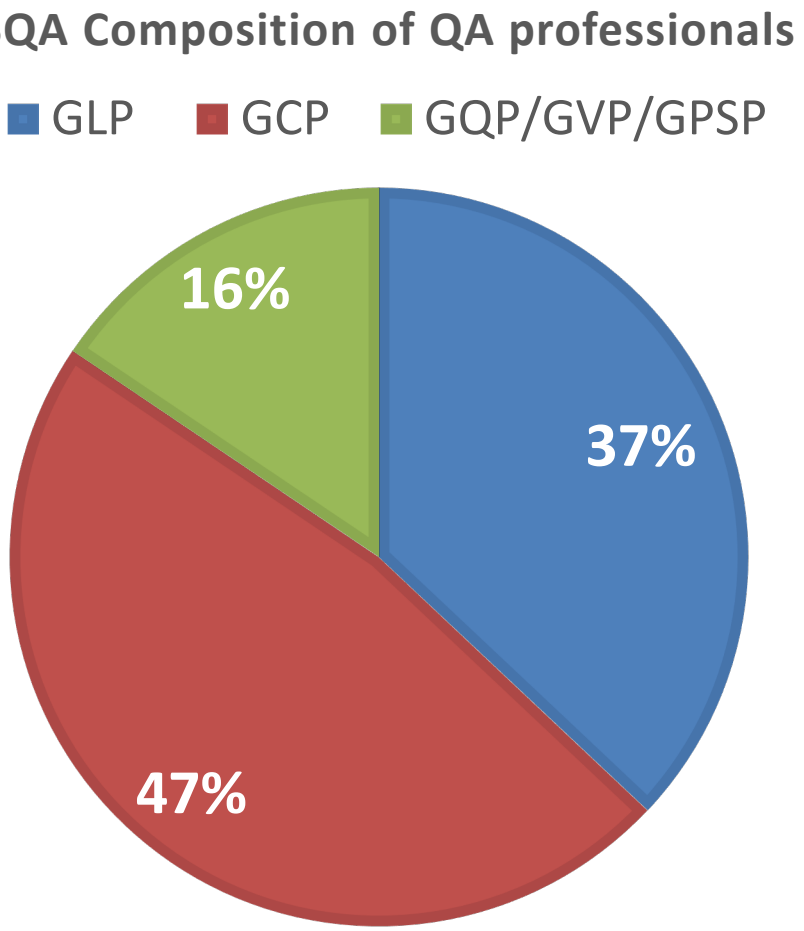
Vision

The Japan Society of Quality Assurance (JSQA) contributes to the improvement of the health and welfare of people by:

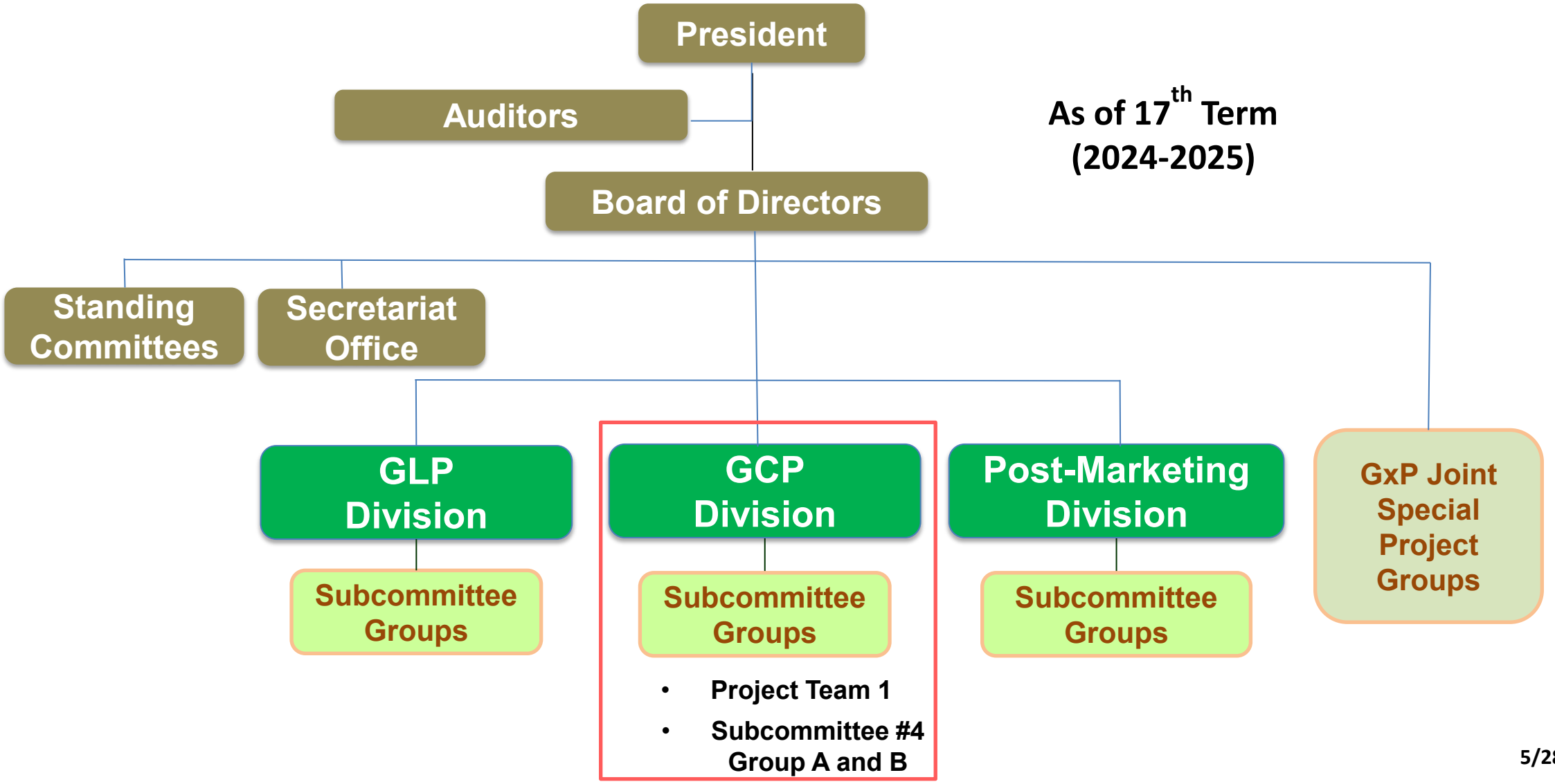
- disseminating relevant information,
- developing human resources, and
- presenting appropriate suggestions on specialized information concerning the quality assurance of drugs…etc.

Division	Number of member companies	Number of members
GLP	147 companies	390 ppl
GCP	182 companies	423 ppl
GQP/GVP/GPSP	62 companies	125 ppl

(As of 06Jan2025)

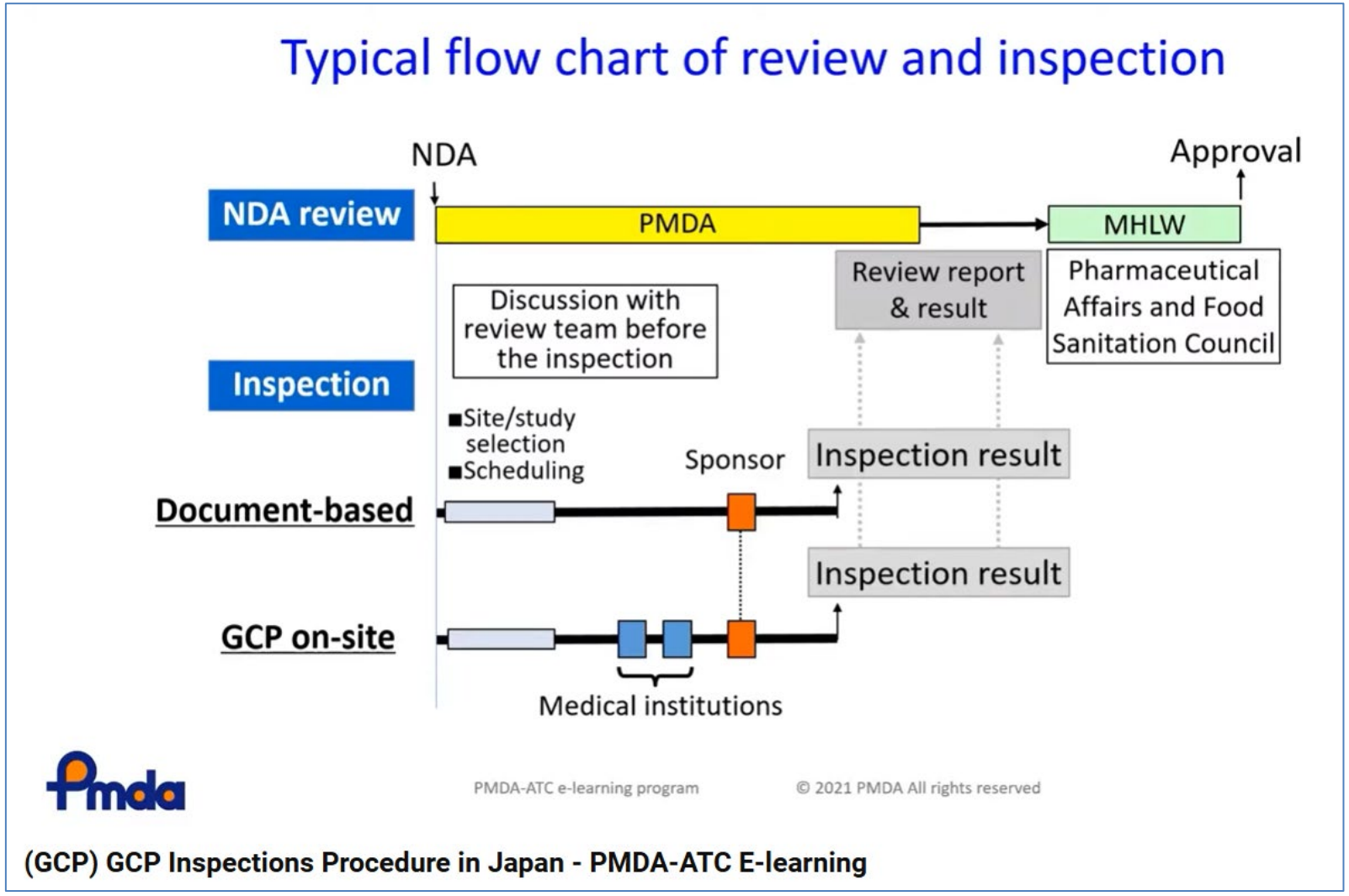


Japan Society of Quality Assurance (JSQA) Organization Chart



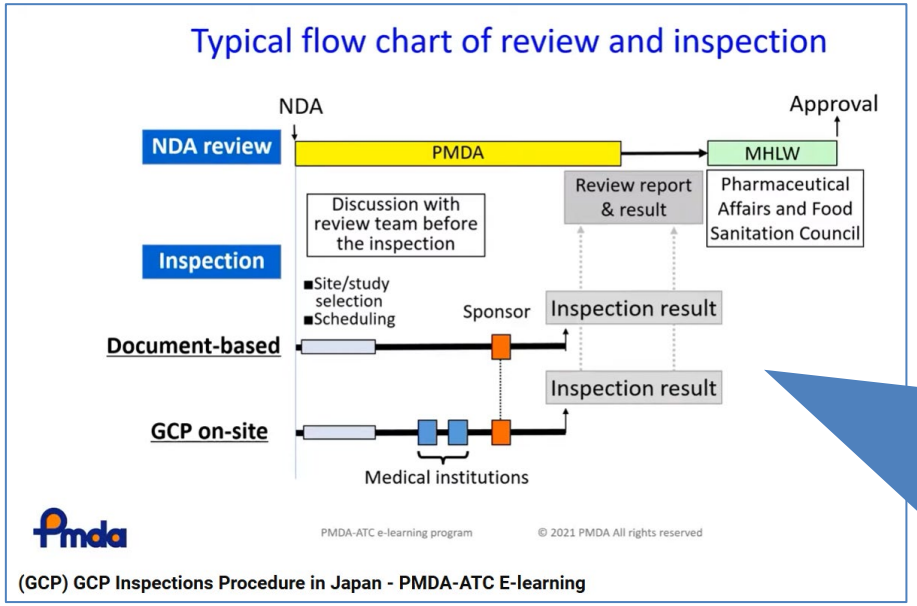
Introduction
Outline of Japan PMDA GCP Inspections

PMDA Inspection Overview



Source: '(GCP) GCP Inspections Procedure in Japan - PMDA-ATC E-learning'

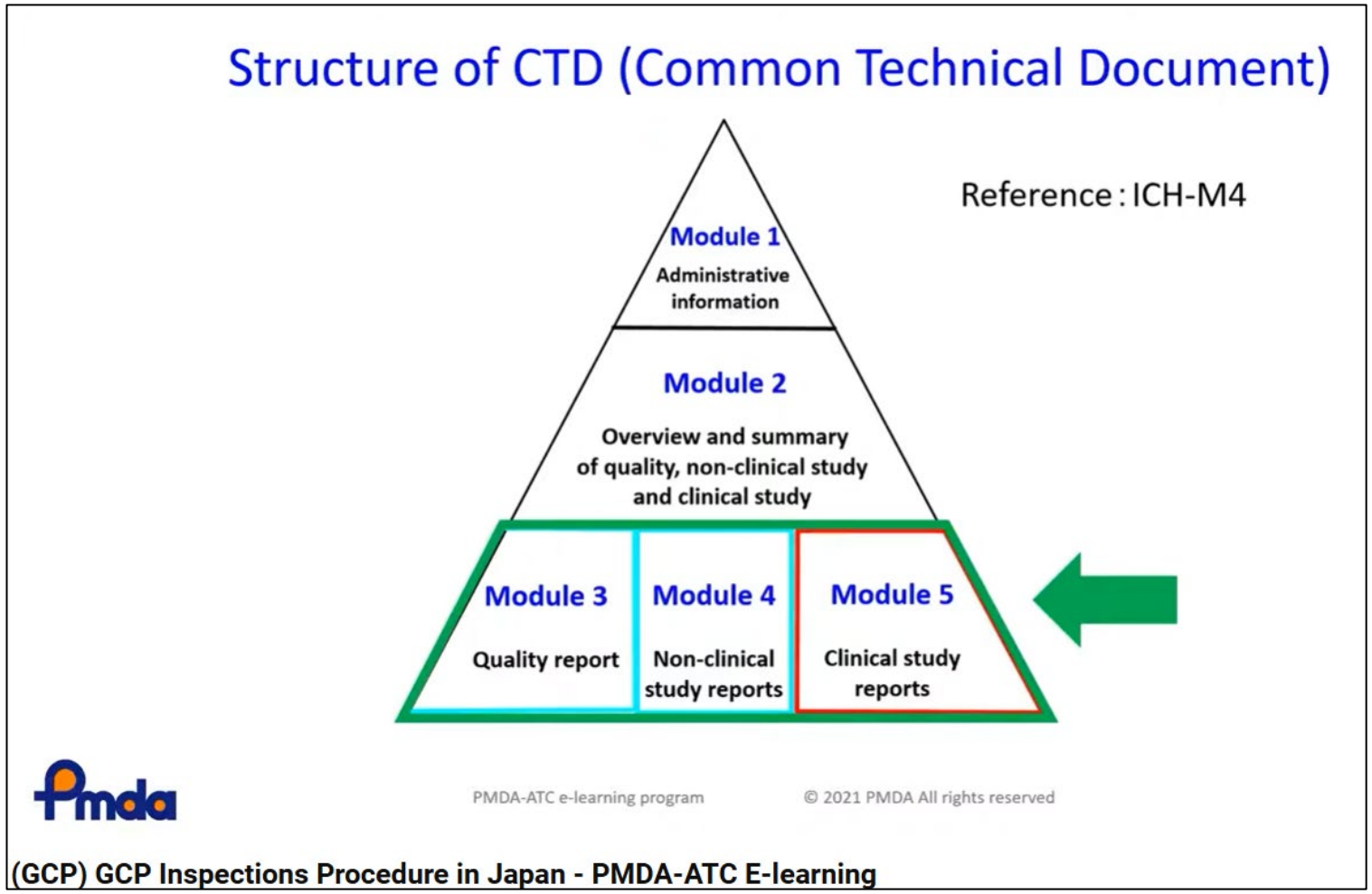
Key takeaways



Source: '(GCP) GCP Inspections Procedure in Japan - PMDA-ATC E-learning'

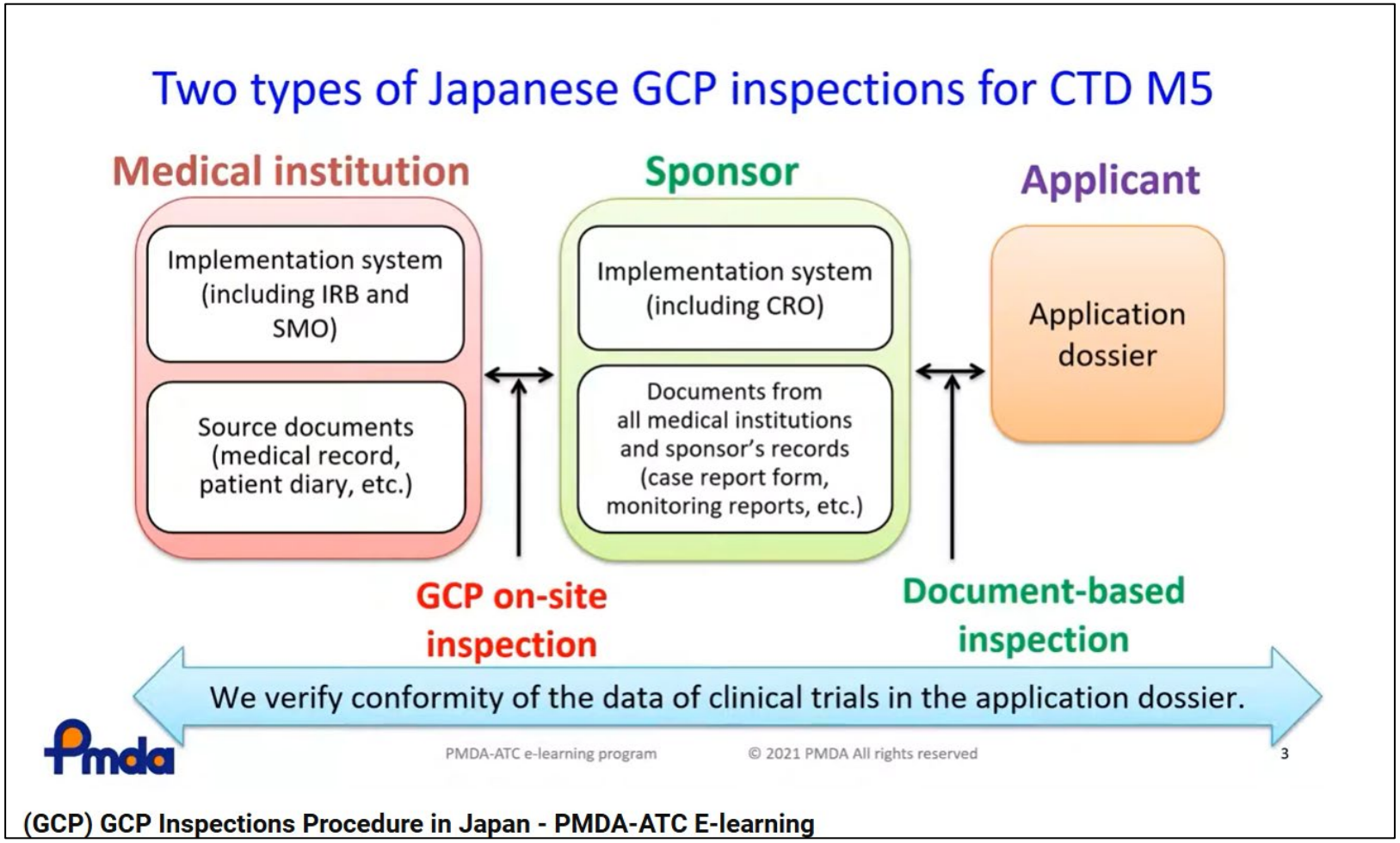
- **PMDA conducts two types of GCP inspections.**
- **The trigger of GCP inspections is NDA submission.**
- **Negative inspection results could possibly affect NDA review.**

PMDA Inspection Scope



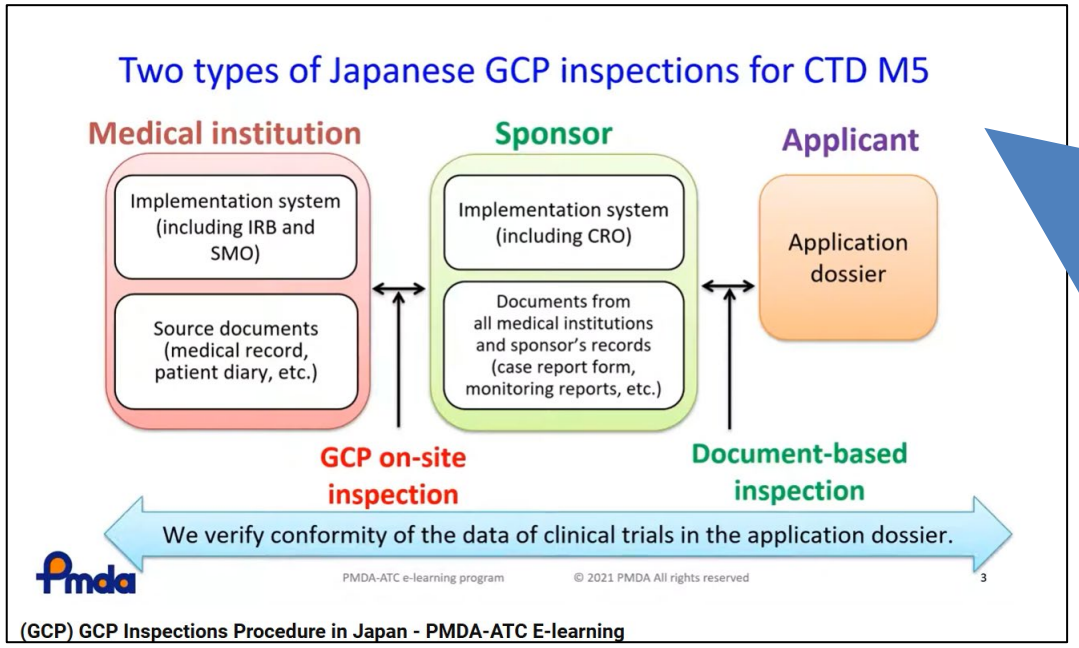
Source: '(GCP) GCP Inspections Procedure in Japan - PMDA-ATC E-learning'

PMDA Inspection Types



Source: '(GCP) GCP Inspections Procedure in Japan - PMDA-ATC E-learning'

Key takeaways



Source: '(GCP) GCP Inspections Procedure in Japan - PMDA-ATC E-learn

The difference between 'GCP on-site inspection' and 'Document-based inspection' is scope:

- **The scope of 'GCP on-site inspection' includes medical institutions (clinical investigators) and sponsor. The inspectors focus on certain clinical trial(s).**
- **The scope of 'Document-based inspection' is the NDA applicant. The inspectors focus on (all) clinical studies and non-clinical studies included in CTD M5.**

Note: PMDA recently have been conducting remote 'Document-based inspections', depending on risks associated with NDA submission.

Sources to learn about PMDA GCP inspections

Sources:

- PMDA uploads a video on YouTube to describe GCP inspection procedures.

‘(GCP) GCP Inspections Procedure in Japan - PMDA-ATC E-learning’,
Available at: https://www.youtube.com/watch?v=UMLTSkeiUBw (Accessed: 17 March 2025)

- ‘PMDA GCP Compliance Inspection Procedure’

Available at: https://www.pmda.go.jp/files/000251862.pdf (Accessed: 17 March 2025)

- ‘Procedure for Remote Inspection as a Part of Compliance Inspection on Drugs and Regenerative Medical Products

Available at: https://www.pmda.go.jp/files/000264393.pdf (Accessed: 17 March 2025)

- 'Checklist for GCP On-site Inspection/Document-based Compliance Assessment for New Drug (for Sponsor)' and;
- 'Checklist for GCP On-site Inspection for New Drug (for Medical Institution)'

Available at: https://www.pmda.go.jp/english/review-services/glp-gcp-gpsp/0003.html (Accessed: 17 March 2025)

Recent remarkable PMDA GCP inspection findings, and comparison with FDA GCP inspection findings

Creation Flow of Today's Deliverables

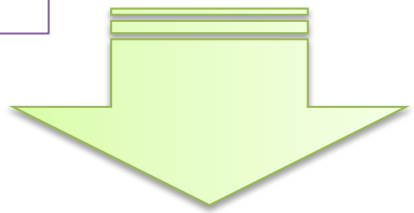
GCP Division

PJ Team 1

- Reviews PMDA GCP inspection findings every year.
- Runs Root-Cause Analyses (RCA) and draw potential CAPAs for findings.

GCP Subcommittee 4 (C4)

- Reviews FDA warning letters (WL) every month.
- Summarize the FDA WL and publish the summary in JSQA.



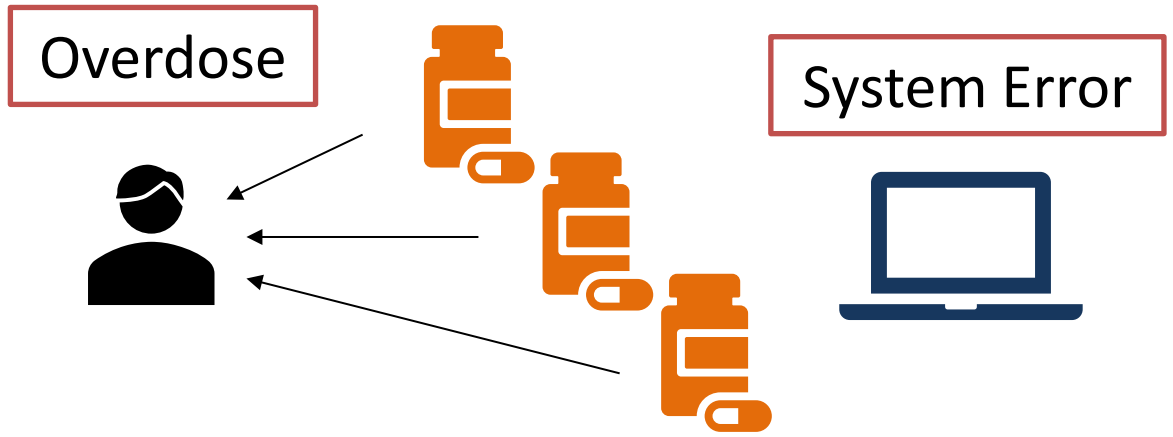
Today's Presenter from C4

- Focus on Remarkable PMDA inspection findings, RCA, CAPA (PJ 1).
- Make comparison of those findings between PMDA and FDA (C4).

PMDA finding case No. 1: Configuration errors in IRT

Finding statement:

- Due to a configuration error in the Interactive Response Technology (IRT) system managed by the sponsor, investigational products (IPs) were not correctly assigned to some participants in compliance with the trial protocol, which resulted in overdoses of the IPs.
- The sponsor should have created appropriate procedures and maintained a quality assurance and quality control system based on these procedures to ensure that the trial was conducted in compliance with GCP and the protocol.



Source: The finding information was obtained through the application based on Japan Information Disclosure Act.

PMDA finding case No. 1: Configuration errors in IRT (con't)

Finding statement (details):

- As per the protocol, in the active group participants should receive the IPs at week 12 and at week 16, while a placebo should be administered from week 13 to 15.
- In the placebo group, while the protocol specifies that the IPs should be administered weekly from week 12 to week 16 after the efficacy evaluation period.
- Due to a configuration error in the IRT system, 36 subjects across multiple medical institutions were mistakenly assigned the IPs instead of the placebo from week 13 to week 15, resulting in overdoses exceeding the protocol-specified dosage.
- This issue was discovered when a vendor responsible for the IRT system noticed the configuration error.

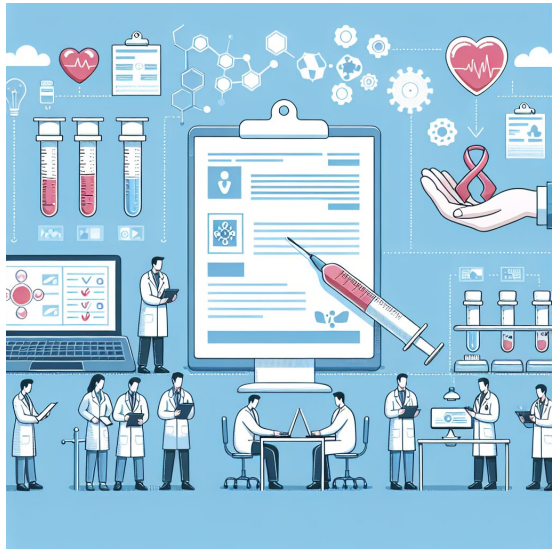
【Schedule per protocol】

【Actual administration】

IP Placebo

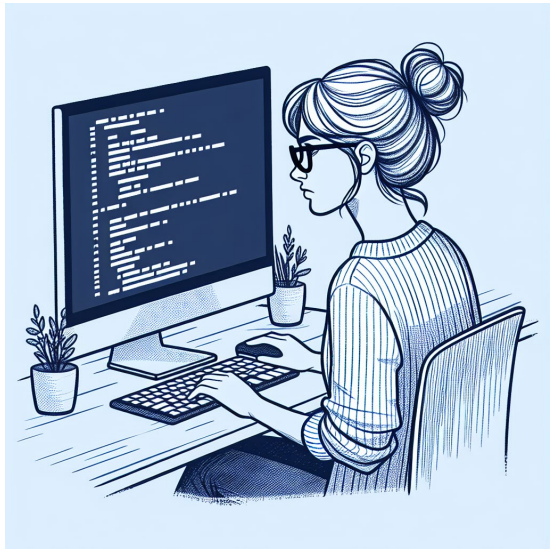
Source: The finding information was obtained through the application based on Japan Information Disclosure Act.

Analysis of the configuration errors in IRT



error

error



Protocol　　IRT Specification　　Programming

Source: These images were generated by AI.

Two root-causes behind the configuration errors:

- Cause 1: Program was configured based on **incorrect IRT specification**.
- Cause 2: Although the IRT specification was correct, **the programming was not done correctly**.

→These two kinds of (independent) errors caused multiple incorrect configuration cases.

Source: The finding information was obtained through the application based on Japan Information Disclosure Act.

Sponsor’s response to the error

<After the Issue was discovered>

Safety analysis

- The sponsor confirmed that there were no safety signals that differ from the overall safety profile of the IP so the sponsor determined that the clinical trial could continue.
- The sponsor explained the issue to the investigators and confirmed with them that no (S)AEs were observed in subjects who might have experienced overdoses.
- The sponsor compared the incidence of (S)AEs between the group affected by the incorrect dosing and the group that was not and found no new safety concerns in the affected group.

Efficacy analysis

- Since the incorrect dosing occurred after Week 12, which is the evaluation period for the primary endpoint, there was no impact on the primary evaluation.
- Sensitivity analyses were conducted for the secondary endpoints, but no clinically meaningful conclusions were drawn.

Source: The finding information was obtained through the application based on Japan Information Disclosure Act.

Discussion held by JSQA

JSQA GCP Division Project Team 1 discussed this inspection finding and analyzed the root-causes as follow:

Inadequate Vendor management and unclear R&R :

1. The study-specific aspects of the protocol were not sufficiently conveyed to the vendor during the IRT system setup.
2. The sponsor failed to fulfill its vendor-management responsibilities, leaving too much to the IRT vendor.
3. There was no process in place that both the sponsor and the vendor ensure the validity of the IRT specifications.
4. Validation, including the User Acceptance Test (UAT), was not properly carried out. (The sponsor did not sufficiently oversee the validation conducted by the vendor.)

Discussion held by JSQA (con't)

JSQA GCP Division Project Team 1 proposed the following CAPAs for the sponsor for the causes behind this error:

No.	Causes	Sponsor CAPAs
1	Not conveyed the study-specific aspects of the protocol	To perform risk-assessment on the protocol from IP allocation viewpoint and implement risk-mitigation measures preemptively.
2	Failure to fulfill its vendor-management responsibilities	To generate a vendor management plan and make agreement with the vendor on the plan.
3	No process that both the sponsor and the vendor to assure IRT specifications	To create UAT test scripts based on the procedures outlined in the protocol. (Not based on the IRT specifications.)
4	Insufficient validation/UAT	To engage in the validation process (e.g., review on the deliverables) or hire another vendor to ensure validation/UAT has been done properly.

Comparable FDA findings? (from WL database)

- JSQA GCP Division C4 has been monitoring FDA Warning Letters since 2013.
- The team has been periodically running search within FDA WLs database.
- However, there were no comparable findings reported in FDA WLs to date

Discussion (inference):

As Japan PMDA routinely inspects sponsors whenever NDA applications are submitted, the sponsor's quality of work might be reviewed more frequently by PMDA than by US FDA.

Thus, it's more likely that this type of error could have been spotted in PMDA inspection.

PMDA finding case No. 2(A): Enrollment of the trial participant who used prohibited concomitant drug

Finding statement:

- A trial participant who used the prohibited concomitant drug A was enrolled in the trial and administered the IP. In addition, CRA did not identify this issue in a timely manner and failed to take necessary

1. The participant had been taking the prohibited concomitant drug A since April 2017.
2. The investigator was unaware that the participant had met the exclusion criterion, so the investigator considered the participant as eligible in February 2019.
3. Five days later, the CRA confirmed that the participant had been using drug A for more than 30 days prior to enrollment but did not realize that it was prohibited.
4. The subject was hospitalized at another institution due to a SAE in March 2019.
5. Upon receiving the SAE report, the CRA reviewed the source documents on the next day and realized that drug A was prohibited.
6. The CRA then requested the investigator and the study collaborators to discontinue the use of drug A.

Source: The finding information was obtained through the application based on Japan Information Disclosure Act.

PMDA finding case No. 2 (A): Enrollment of the trial participant who used prohibited concomitant medications (con't)

April 2017
Concomitant medication started

February 2019
Participant Enrollment

February 2019
CRA Direct Access (5 days after enrollment)

March 2019
SAE occurred to the participant

March 2019
CRA Direct Access (the next day)

overlook → overlook → Detection

Source: The finding information was obtained through the application based on Japan Information Disclosure Act.

The other PMDA finding No.2 (B): Prohibited concomitant medications

Finding statement (the other case reported by PMDA):

- A trial participant who used the prohibited concomitant drug B was enrolled in the trial and administered the IP.
- The CRA did not identify this issue in a timely manner and failed to take necessary actions.

Circumstances:

- According to the Monitoring plan for the inspected study, CRAs shall review use of prohibited concomitant medications through 100% Source Document Review.
- In the study, there were two cases of the use of prohibited concomitant medications:
  - For the first case, the CRA found it one year after the trial ended and reported it as a protocol deviation afterwards.
  - For the second case, it was discovered during a remote PMDA inspection.

Source: The finding information was obtained through the application based on Japan Information Disclosure Act.

Discussion held by JSQA

JSQA GCP Division Project Team 1 discussed these inspection findings and analyzed the root-causes as follow:

1. Sponsor: The list of prohibited concomitant medications in the clinical trial protocol may have been inconsistent with real-world clinical practice.
2. Sponsor/Investigator: It could be hard to keep a complete and up-to-date the prohibited concomitant medications list.
3. Investigator: Prohibited concomitant medications would be prescribed in routine clinical settings, making them prone to being overlooked.
4. Sponsor: Detecting deviations in a timely manner using EDC is challenging.

Discussion held by JSQA (con't)

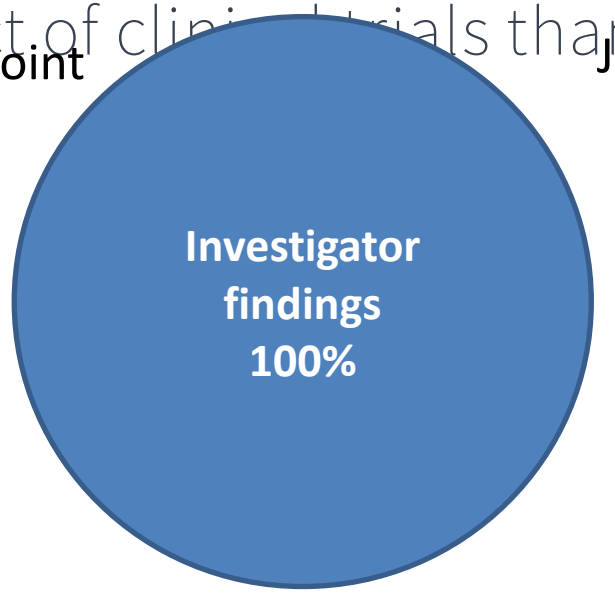
JSQA GCP Division Project Team 1 proposed the following CAPAs for the causes of the use of prohibited concomitant medications:

No.	Stakeholder	Causes	CAPAs
1	Sponsor	Discrepancy between the list and actual medical practice	To deliberately consider the necessity of setting prohibited concomitant medications in a protocol and designate the medications that are absolutely necessary to prohibit in a clinical trial.
2	Sponsor/ Investigator	Incomplete and not up-to-date prohibited drug list	To assign proper human resources to manage the complete and up-to-date list.
3	Investigator	Prohibited concomitant medications are prescribed in routine clinical settings.	To carry out measures at medical institutions to emphasize that the medications are prohibited in a clinical trial.
4	Sponsor	Difficulty in detecting deviations in a timely manner through EDC	To improve communication between investigators/study coordinators and CRAs

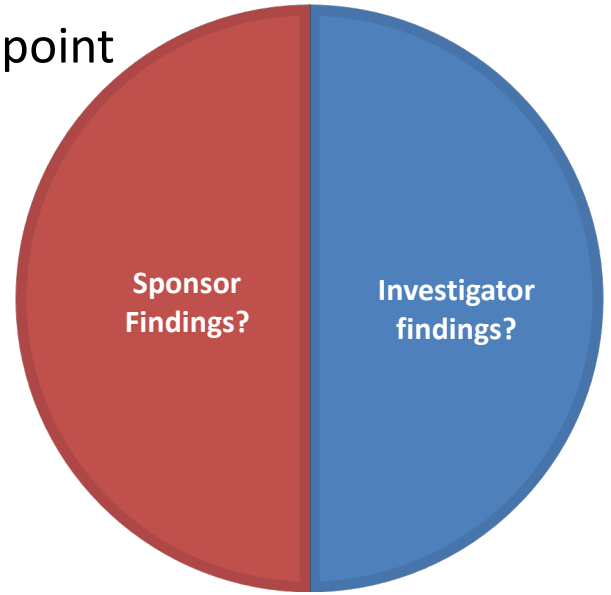
Comparable FDA findings? (from WL database)

- Since 2013 there have been seven FDA Warning Letters containing similar deviations (i.e., use of prohibited concomitant medications).
- All the seven FDA WLs were issued to clinical investigators.
- In contrast, Japan PMDA issued inspection findings both for clinical investigators and for sponsors.
- It is concluded that PMDA more often sheds light on sponsors' responsibility to perform proper and adequate monitoring of the conduct of clinical trials than FDA.

US FDA's viewpoint



Japan PMDA's viewpoint



Japan Society of Quality Assurance

Thank you for listening.
Any questions?