Japanese Pharmacovigilance Audit Activity - The New Tide of Quality Assurance -

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Disclaimer

- ✓This presentation focuses on the work conducted by Groups A, B and C within Subcommittee 1, Post-marketing Division of JSQA.
- ✓ The groups have been actively involved in their respective activities since 2020.

- ✓However, the views and opinions expressed in part of this presentation are those of the author.

Missions of Subcommittee 1, Post-marketing Division (2022-2024)

- A Group（PV-QMS）:

  This group will examine the optimal state of PV-QMS in Japan and suggest a mechanism for real-time, continuous improvement of the quality and compliance of PV operations.

- B Group（PV Audit）:

  As EU-GVP has been in place for 10 years, Japanese companies have accumulated experiences in global PV audits and inspections, and trends of observed issues are also being identified. By analyzing these current situations, this group will suggest points to prepare for and pay attention to global PV audits and inspections.

- C Group（Self-inspection）:

  In recent years, there has been an increase in corporate partnerships for PV operations and outsourcing to service vendors, resulting in the need for efficient and advanced PV quality assurance to address the complex and diverse nature of the tasks. To ensure the reliability of the PV operations within this environment, this group will explore and propose effective and efficient techniques for self-inspections.

Activity of Groups within Subcommittee 1

- Setting of a mission in each group (A, B, C) every two years
- Current group members (A:14, B:17, C:13)
- On-site or remote meeting once every month from 1:30pm to 5:00pm for 3.5 hours
- Consultation for problems/challenges and discussion about making deliverables in the meeting
- A survey by using questionnaires may be performed to monitor the situation of the JSQA member companies.
- Completed deliverables will be disclosed on the JSQA website to the JSQA members.

Agenda

- Quality Management System (QMS)
- Pharmacovigilance Auditing
- Self-Inspection of Japanese GVP Regulations

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- **Quality Management System (QMS)**
- Pharmacovigilance Auditing
- Self-Inspection of Japanese GVP Regulations

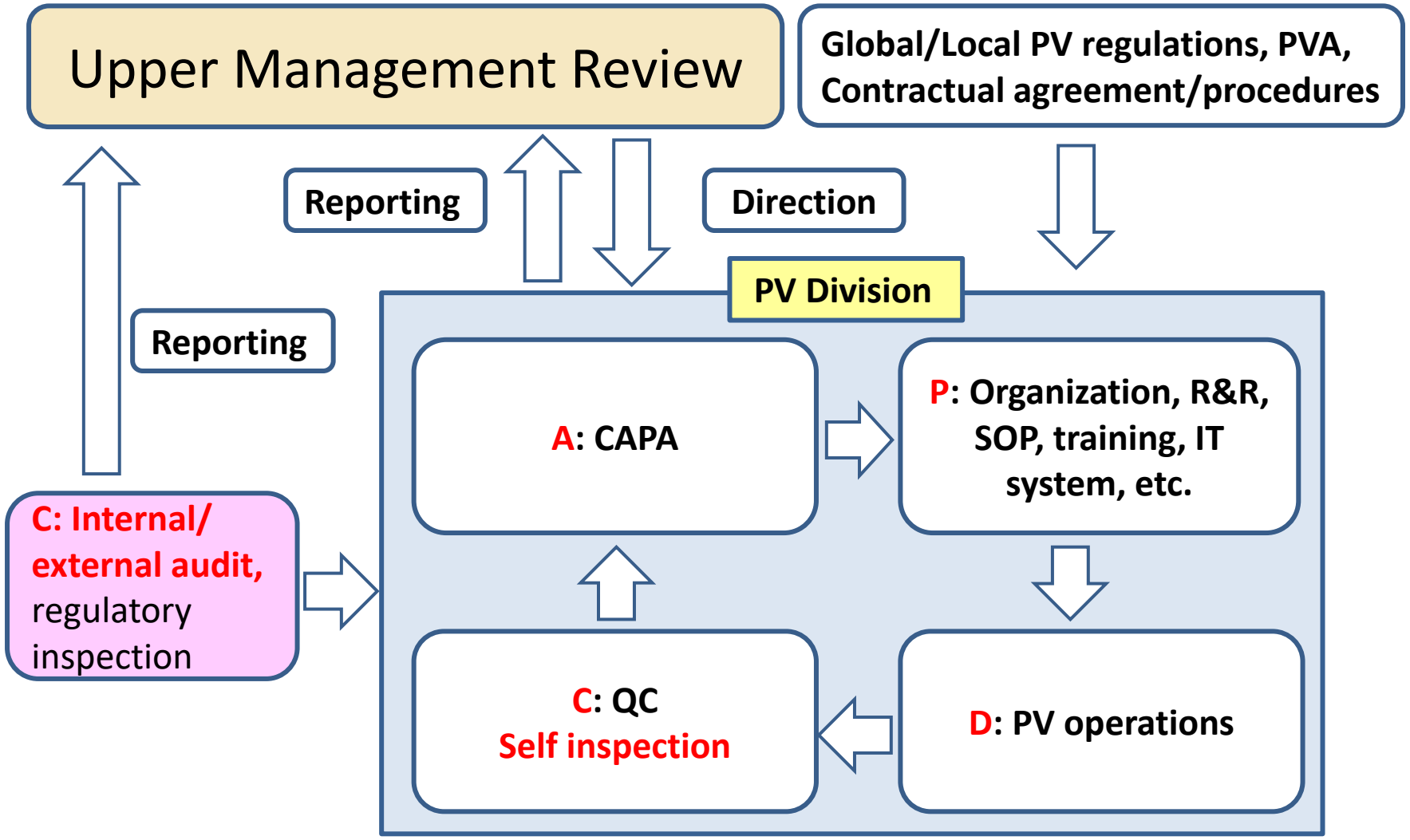
Objectives of PV-QMS

The objectives of a pharmacovigilance quality system are:

- complying with the legal requirements for pharmacovigilance tasks and responsibilities;
- preventing harm from adverse reactions in humans arising from the use of authorized medicinal products within or outside the terms of marketing authorization or from occupational exposure;
- promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public; and
- contributing to the protection of patients' and public health.

(Ref. EU GVP Module I.B.4)

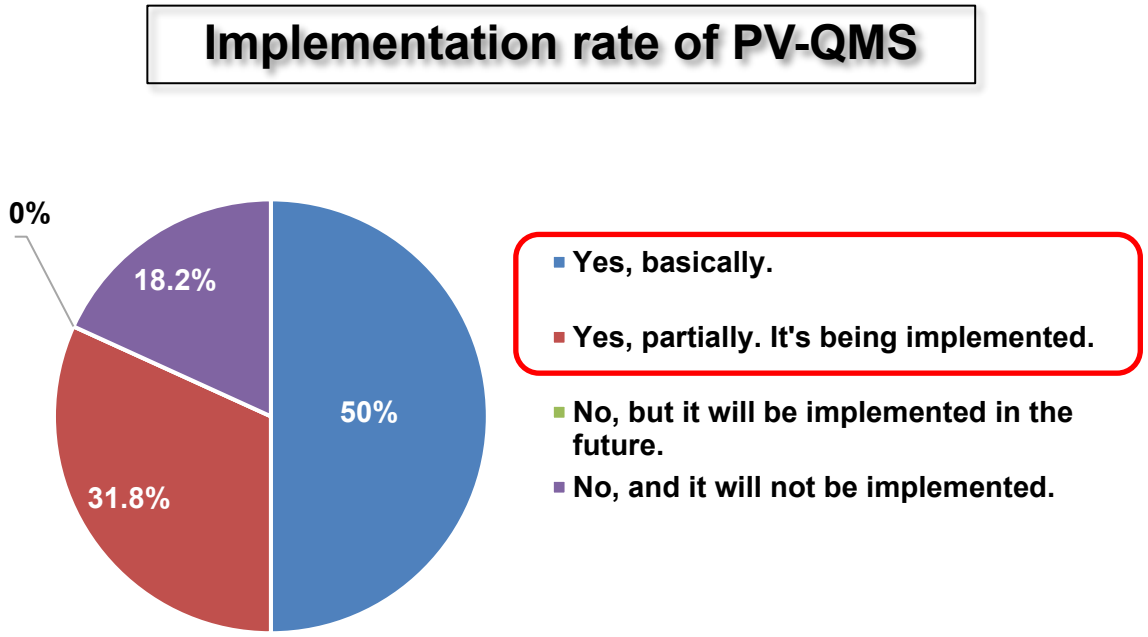
Schema of PV-QMS



"Proposal of PV-QMS in Japan", 6th GQAC 2020 Sendai Japan

Survey in the JSQA Member Companies
- Implementation Status of PV-QMS in Japanese Pharma -

Reason of Implementing PV-QMS	No. of Companies (%)
Marketing products in EU countries	10 (46)
Partnering with EU pharma	7 (32)
Being implementing PV-QMS relating to partnering with EU pharma, but not completed	5 (23)
Marketing products only in Japan, but it's useful to implement PV-QMS	4 (18)
Marketing products only in Japan	2 (9)
Planning launching of products in EU	1 (5)



Survey in the JSQA Member Companies
- Findings Pointed out by LP's Audit -

Process	No.	Process	No.
QMS SOP management	8	ISCR processing/evaluation	7
Training	13	AEs from clinical study/PMS	1
JD/CV	4	Medical info./call center	1
Audit/self-inspection	5	PQCs associated with AEs	1
Deviation/CAPA management	4	Literature search/review	3
Record management	9	Signal detection	1
Service vendor management	6	RMP	1
PVA/SDEA	5	CCDS/Labeling mgt	4
BCP	8	PSUR/DSUR	2
PV computerised system	4	Personal info. Protection	4
ICSR collection	3	Others	7

Total: 32 audits

Challenges of Japanese PV-QMS

- ✓ There is less concept of QMS in Japanese GVP regulations.
- ✓ Organizations and SOPs that are optimized to comply with Japanese GVP regulations are instead delaying adaptation to global standards.
- ✓ Optimization of global/local organizations and related global/local SOP structure
- ✓ CAPA management
- ✓ IT system management
- ✓ Service vendor management
- ✓ Record management with ALCOA+
- ✓ Business continuity plan (BCP)

Agenda

- Quality Management System (QMS)
- **Pharmacovigilance Auditing**
- Self-Inspection of Japanese GVP Regulations

Background of Japanese PV Auditing

Until now, as a method of monitoring the quality of PV operations in Japan, "**self-inspections**" have been carried out by the PV divisions themselves, as required by the Japanese GVP/GPSP regulations.

However, with the globalization of PV business in recent years, there are increasing opportunities to be audited and audit based on Pharmacovigilance Agreement (PVA) exchanged with License Partners (LPs). At this time, most LPs conduct "**PV audits**" using the EU-GVP guidelines as audit references.

The EU-GVP guidelines require the implementation of a QMS. PV auditing is one of the monitoring functions to drive the Plan/Do/Check/Act (PDCA) cycle required by the QMS and to improve the quality of the PV operations at the global level.

Rationale of Japanese PV Auditing

- ✓ Marketing Authorization Holders (MAH) outside of Japan, especially in EU
- ✓ MAH of a licensed product(s) in Japan that is marketed outside of Japan, especially in EU
- ✓ MAH implementing PV auditing to ensure the PV operations, being independent from the Japanese regulations/requirements
- ✓ MAH performing self-inspection in compliance with the Japanese GVP/GPSP regulations without PV auditing

Audit Universe

1. Pre and post-marketing safety management activities:
- Company's internal QMS and PV operations (global/local)
- PV service vendors (case processing, literature search, medical information/call center, IT system mgt, etc.)
- License partners (licensor/licensee) if the Japanese company is a Market Authorization Holder (MAH) outside of Japan, especially in EU

2. Post-marketing studies:
- Drug-use Result Survey under the GPSP (J-PMS)
- Pharmacoepidemiology Study (with RWD)

PV Audit Procedure following EU-GVP Module IV

Audit planning with 3 levels is as follows.

1. Strategic level: The audit strategy is a high-level statement of how the audit activities will be delivered over a period of time, longer than the annual program, usually for a period of 2-5 years.

2. Tactical level: An audit program is a set of one or more audits planned for a specific timeframe, normally for a year.

3. Operational level: Planning and conduct of individual audits

-> Master, annual and individual plans should be generated in compliance with EU GVP Module IV.

Audit Areas in the QMS and PV Operations

- Quality Management System (QMS):

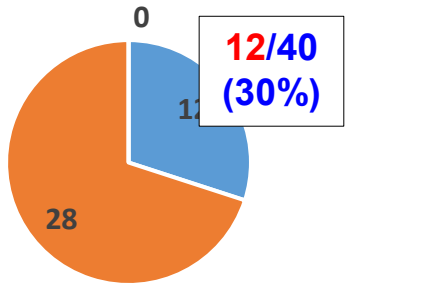
  Organization, SOP mgt, compliance/performance monitoring, deviation/CAPA mgt, audit/self-inspection, training/qualification, record mgt, vendor mgt, IT system mgt, facility, BCP/DRP

- PV Operations:

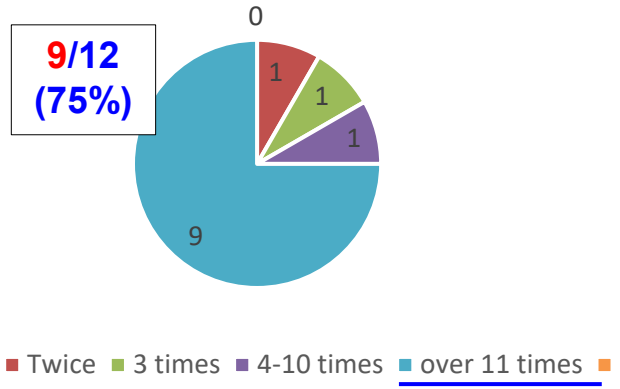
  ICSR processing/evaluation (pre/post-marketing), literature search/review, aggregate report (DSUR/PBRER), signal detection/mgt, CCDS/CCSI, RMP, labeling, IB/RSI, regulatory intelligence, product complaints/recall, social media, medical representative (MR), medical affair (MA), market research, contact records with CA, post-marketing observation (pharmacoepidemiology) studies

Survey in the JSQA Member Companies
- Audit Experiences -

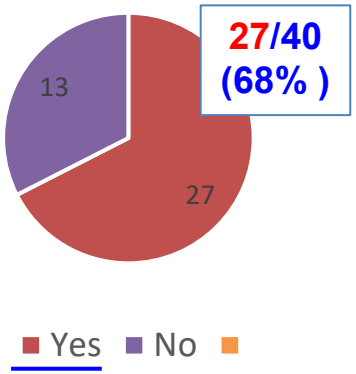
1. Have you performed PV audits?



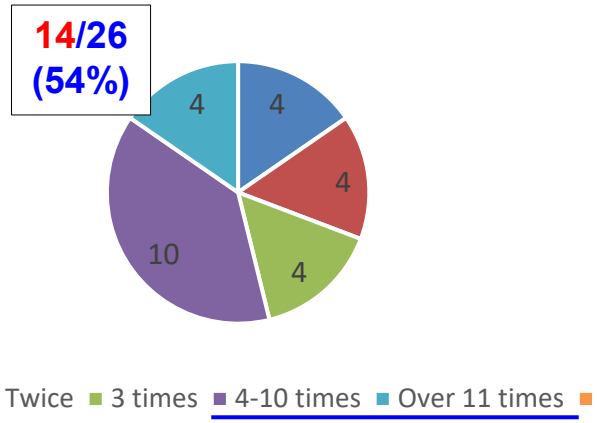
2. Number of Performed PV Audits



A. Have you received LP's PV audits?



B. Number of Received PV Audits



Challenges of Japanese PV Auditing

- ✓ Differentiation between PV audits and self-inspections
- ✓ Training and qualification of global PV auditors
- ✓ Risk assessment of the PV operations to have data-driven auditing
- ✓ Seamless auditing in the pre and post-marketing PV operations and relevant service vendors
- ✓ Collaboration/communication with other GxP QAs
- ✓ QA for the computer system management and the data integrity of the GSDB
- ✓ Contribution of the (PV) QA to the CAPA management
- ✓ Dealing with the pharmacoepidemiology study (with RWD)

Agenda

- Quality Management System (QMS)
- Pharmacovigilance Auditing
- **Self-Inspection of Japanese GVP Regulations**

Japanese Pharmaceutical Regulations

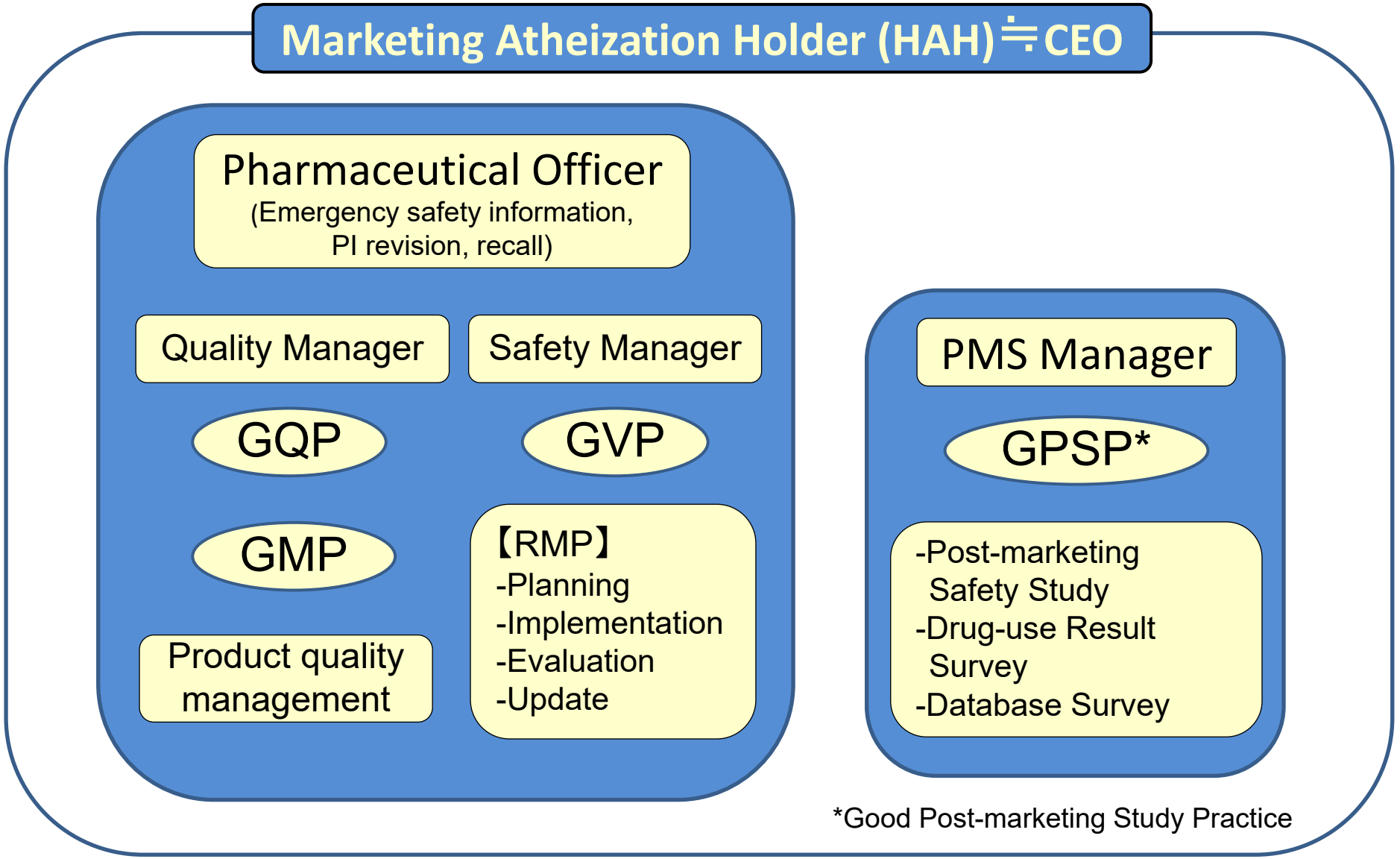
- *Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960)* (https://www.japaneselawtranslation.go.jp/ja/laws/view/3213/je) (English)

- *Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Order of the Ministry of Health, Labour and Welfare No. 1 of 1961)*
  (https://www.japaneselawtranslation.go.jp/ja/laws/view/3215) (English)
- *Good Vigilance Practice* (GVP) Ordinance
  (https://elaws.e-gov.go.jp/document?lawid=416M60000100135) (Japanese)

- *Good Post-marketing Study Practice (GPSP) Ordinance*
  (https://elaws.e-gov.go.jp/document?lawid=416M60000100171_20220520_504M60000100084)(Japanese)

Japanese Law Translation
https://www.japaneselawtranslation.go.jp/ja

Japanese Pharmaceutical Safety Management



Contents of GVP Ordinance

- Responsibilities of Pharmaceutical Officer (delegate of MAH)
- Organization and staff
- Standard operating procedure (SOP)
- Responsibilities of Safety Manager (≒QPPV)
- Collection of safety information
- Review of safety information and development of safety measures
- Implementation of safety measures
- Risk management plan (RMP)
- Early post-marketing phase vigilance (EPPV)
- Self-inspection
- Training of PV staff
- Record retention

Self-Inspection Stipulated by the GVP Ordinance

Article 11: The MAH should conduct regular self-inspections of post-marketing safety management activities by designated individuals, based on procedures and documents related to post-marketing safety management.

2. If the designated individual is the Safety Manager, the MAH should ensure that the Safety Manager creates and retains records of the self-inspections mentioned in the preceding paragraph.

3. If the designated individual mentioned in paragraph 1 is someone other than the Safety Manager, the MAH should ensure that this individual creates records of the self-inspections mentioned in paragraph 1, reports them to the Safety Manager in writing, and ensures that the Safety Manager retains them.

4. The MAH should require the Safety Manager to report the results of the self-inspections to the MAH and the Pharmaceutical Officer in writing and should retain copies of such reports.

5. The MAH should enable the Pharmaceutical Officer to examine the necessity for improvement in post-marketing safety management based on the results of the self-inspections mentioned in paragraph 1. If there is a need for improvement, the MAH should ensure that appropriate measures are taken and records are created.

6. The MAH require the Safety Manager to retain records of the preceding paragraph.

General Procedure of Self-inspection

- Annual Plan (master plan)
- Annual plan for every PV function that is relevant to the articles of the GVP Ordinance
- Notification to Functional Lead/Manager
- Confirmation of quality of deliverables generated during targeted period (generally 1 year) by using check lists to show whether they comply with GVP SOPs
- Individual report on each PV function
- Annual summary report attached the individual reports
- Reporting to Safety Manager, Pharmaceutical Officer and MAH

Sample of Check List

SOP No./Name: GVP-08/Risk Management Plan (RMP) #1
Stuff name: Yoshiya Aze
Targeted period: 2022-MM-DD to 2023-MM-DD #2, #3
Performed date: 2023-MM-DD to 2023-MM-DD

Items	SOP No	Session	Deliverables	Result	Notes
SOP narrative A	GVP-08	1.1	a	(Y) / N / NA	
SOP narrative B	GVP-08	1.2	b	(Y) / N / NA	
SOP narrative c	GVP-08	1.3	c	(Y) / N / NA	
-	-	-	-	-	
-	-	-	-	-	
-	-	-	-	-	

Note: #1: For this kind of area, 100% of deliverables can be checked.
#2: No blank period between the previous and present targeted period
#3: Targeted period is generally 1 year.

Sampling of Deliverables and Data

- For the area such as collection of safety information (ICSRs) where huge deliverables and data are generated, sampling methods may be applied as follows.

- √n , √n+1, ISO2859-1 (JIS29015-1) or Max 30-50 cases

QC or QA

- Recently, some companies have changed the technic of self-inspection partially from quality check/control (QC) to quality assurance (QA) focusing on PV system, relating to the expansion of the PV business.

- Relating to the above situation, differentiation or integration of self-inspection and PV auditing has been discussed in JSQA member companies in recent few years.

- However, most Japanese pharmaceuticals conduct both self-inspections and PV audits respectively complying with Japanese GVP regulations and EU-GVP Module IV.

Self-inspection for Service Vendors

- Use the report of self-inspection performed by the service vendors themselves
- On-site visit or remote meeting performed by PV staff and/or PV QA
- Use the results of PV auditing for service vendors as self-inspection
- CAPA for quality issues observed in the self-inspection by the service vendors are recorded in their report
- The annual report containing the results from vendor's self-inspection should be circulated to Safety Manager, Pharmaceutical Officer and MAH.

CAPA for Quality Issue from Self-inspection

- Improvement of quality issues is stipulated by the GVP Ordinance.
- Therefore, most Japanese pharmaceuticals implement CAPA procedures within their GVP SOP.
- Grading of critical, major and minor for quality issues is generally applied.
- All graded quality issues should be subjected CAPA together with approval by Safety Manager, complying with the GVP Ordinance.
- The results of CAPA should be described in the annual report of self-inspection.

Self-inspection and PV Audit

	Self Inspection (an example)	PV Audit
Definition of procedure	Stipulated by each company's SOPs	Stipulated by EU-GVP Module IV, ISO9001 and ISO19001
Operator	PV division	Independent organization from the PV division
Evaluation	• Evaluate whether the deliverables are generated in compliance with the relevant SOPs	• Evaluate the extent to which the PV system/process meets regulatory requirements and its effectiveness
Review method & period	• Random data extraction with $\sqrt{n+1}$ • Documents (basically 100%) • No blank period between annual self-inspections.	• Risk-based system/process review • The review focuses on the most recent 6 months to 1 year.
Overview	• Quality assurance of PV deliverables	• PV system/process verification

Challenges of Self-inspection

- Methodology selection of QC or QA relating to expansion of PV business due to globalization, launching of oncology products, etc
- Differentiation or integration of self-inspection and PV auditing
- Integration of self-inspection within PV-QMS as compliance/performance monitoring
- “Annual” to “real time” compliance monitoring using PV IT platform (with AI?)
- Quality monitoring/control for service vendors

Conclusions

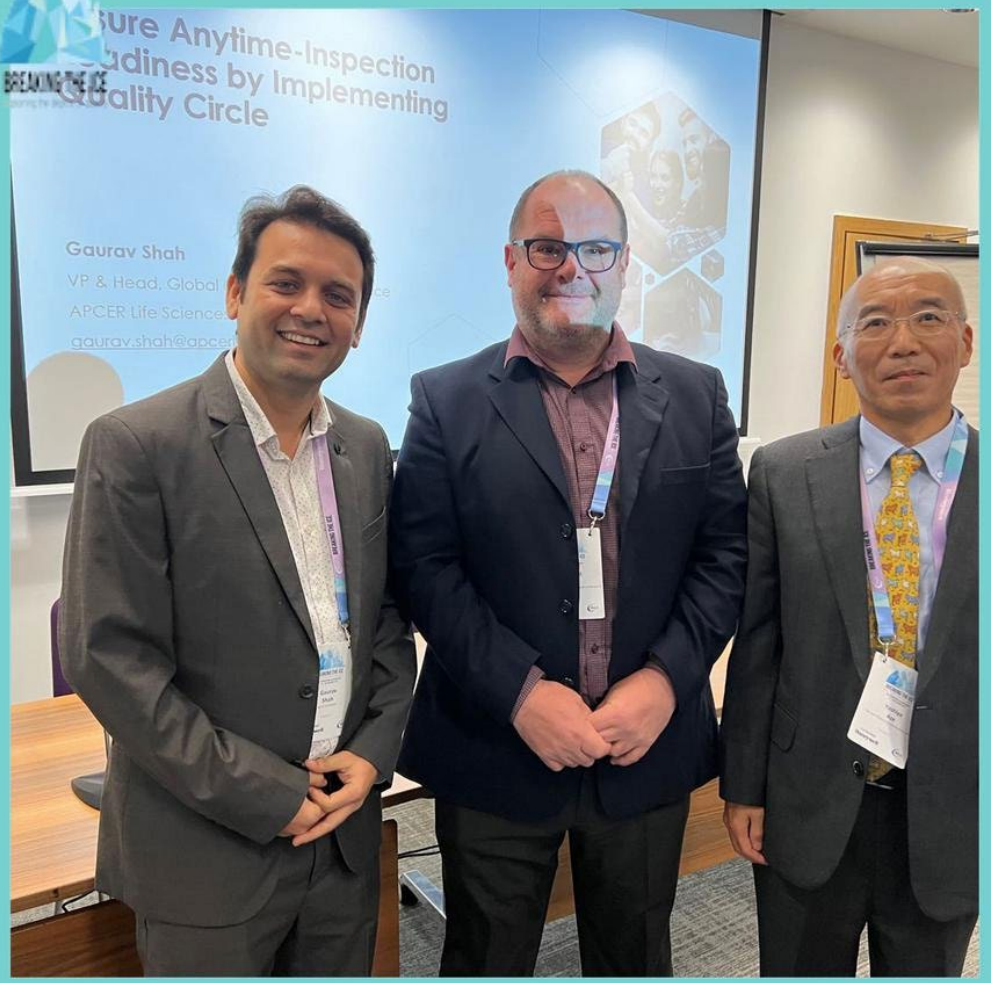
JSQA P1 Groups have been working with making recommendations for PV-QMS, PV audit and self-inspection techniques/procedures for the Japanese pharmaceutical companies.

- ✓ The implementation of the PV-QMS and PV auditing is still in a development status in Japan.
- ✓ Japanese PV auditing follows EU-GVP Module IV and is generally conducted in the same way.
- ✓ There are several challenges of Japanese PV-QMS, PV auditing and self-inspection, relating to the expansion of PV business with its globalization.

In Europe and the United States, the idea of PV-QMS has already become common for the purpose of improving the quality of the PV operations.

It is expected that our activities will help Japanese pharmaceutical companies to implement and improve the PV-QMS including PV audit and self-inspection.

Japan Society of Quality Assurance



2023 RQA International QA Conference

Michael Bean (center) was the chair of our session. He was an MHRH inspector and is now charged in Johnson & Johnson.

My presentation was from 11:45-12:30 on 2nd November, 2023 at ICC Belfast.

A total of 10 questions came up from the audiences as below.

Q1. Does MHLW or PMDA publish or present inspection findings for GVP or GPSP?
Andrew Cooper (GSK)

A1. PMDA discloses summary of findings observed on re-examination (GPSP) at their website and YouTube (GPSP gate). GVP is local government matter (Tokyo, Osaka, etc), but undisclosed.

Q2. Can you expand on some of the challenges of self-inspection in relation to oncology products being launched as mentioned on presentation?
Allison Jack (BMS)

A2. Oncology products generate huge AE information rather than primary products. As I introduced, we confirm every deliverable by self-inspection during a target period. It's huge burdensome.

Q3. Are there any plans for revision of GVP or GPSP ordinance?
Andrew Cooper (GSK)

A3. No information (GVP/GPSP) regarding pre-revision announcement by PMDA, so far.

Q4. Do the PMDA publish inspection findings metrics reports?
Andria Wilk (argenx BV Gent)

A4. No metrics reports of PMDA's inspections are disclosed.

Q5.Is there a concept of "signal management" in the PV regulation? is it similar to the EU-GVP?

Emeline Pierre (Colibir Braine l'Alleud)

A5. There are no detailed stipulations such as EU-GVP Module IX. In addition, PMDA focuses on only local case. Therefore, there are no sufficient case number that can be applied statistical methods.

Q6.Have you been involved in auditing overseas companies and what was the biggest challenges?

Michael Bean (Johnson & Johnson United, Kingdom)

A6. Yes, understanding of local regulations is biggest challenges without matured global regulatory intelligence.

Q7.How easy is it to recruit PV auditors in Japan?

Michael Bean (Johnson & Johnson United, Kingdom)

A7. It’s difficult, I think. Because most Japanese companies have initiated PV audits since around 8 years ago. So far, the literacy of PV auditor is still shallow.

Q8.Do the self-inspections include vendor PV activities or only internal PV functions?

Emeline Pierre (Colibir Braine l'Alleud)

A8. We do self-inspection for vendor activities as well as internal PV functions.

Q9.In your dream of real time compliance monitoring what would you monitor regularly?
Alison Allen (Alnylam Pharmaceuticals Maidenhead, England)

A9.Global ICSR reporting compliance.

Q10.How effective it can be to conduct audit with help of Japanese Translator. Is it possible at all?
Gaurav Shah (APCER)

A10.The quality of Japanese translators is pretty good. They can understand technical terms in the life-science area.