Implementation of PV-QMS in Japan

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Disclaimer

- ✓ This presentation focuses on the works conducted by the groups within the Subcommittee 1, the 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.

Current Activities of the Post-marketing Division

■ Subcommittee 1 (GVP)

A: PV-QMS, B: PV Audit, C: Self-inspection

■ Subcommittee 2 (GPSP)

A: Self-inspection, B: PMDA inspection at Re-examination

■ Special Projects

G1: GVP inspection by the local government for MAH's marketing license renewal
G2: Training of self-inspection for the JSQA members
G3: Quality management in GQP/GMP
G4: Collaboration with RQA regarding Non-interventional Study

■ Post-marketing Salon:

As a place to exchange opinions candidly with a supporter who was involved in a local government (former Director of Pharmaceutical Affairs, Osaka Prefecture)

Agenda

- Background and implementation Status of PV-QMS in Japan
- PV-QMS Consisting of 12 Procedures (for example)
- Computer Systems for QMS (eQMS)
- Conclusions

Background of Implementation of PV-QMS in Japan

There are no integrated guidelines for PV-QMS in Japan, but they are scattered over several area within the Japanese GVP and GPSP Ordinance, whereas the PV-QMS concept is clearly stipulated in the EU-GVP Module I.

In Japan, because of 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 Modules as audit references and then focus on the implementation of PV-QMS within the LP’s PV system.

MAHs Types Implementing PV-QMS in Japan

- ✓ Marketing Authorization Holders (MAHs) globalized outside of Japan, especially in the EU
- ✓ MAHs of a licensed product(s) in Japan that is marketed outside of Japan, especially in the EU
- ✓ MAHs implementing PV-QMS to ensure the PV operations, being independent from the Japanese pharmaceutical regulations
- ✓ MAHs performing PV operations in compliance with the Japanese pharmaceutical regulations without PV-QMS stipulated by the EU-GVP Module I

Objectives of PV-QMS

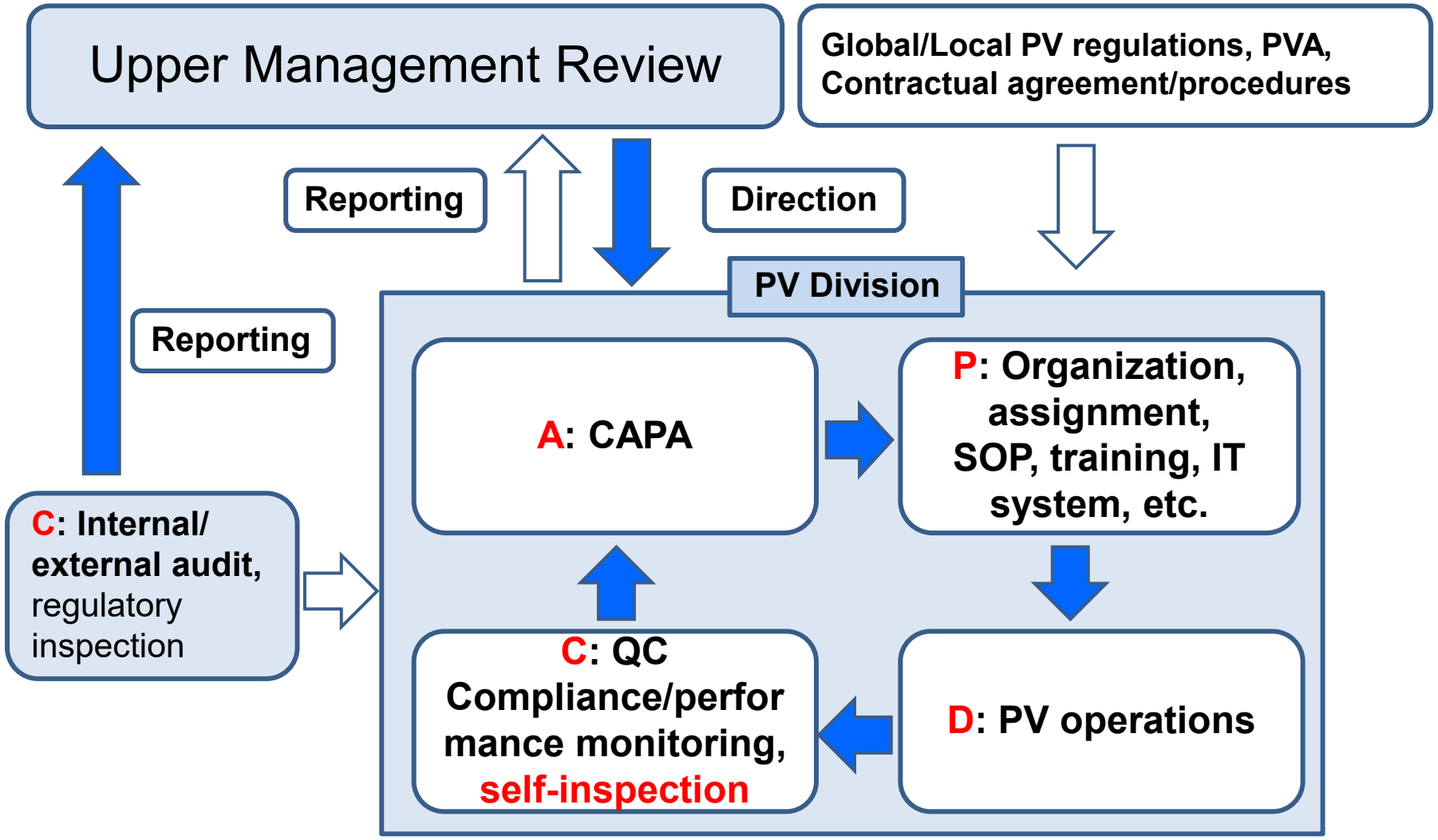
Basically, Japanese PV-QMS follows the EU-GVP Module I.

The objectives of PV-QMS are;

- ✓ Complying with the legal requirements for pharmacovigilance tasks and responsibilities
- ✓ Preventing harm from adverse reactions in humans
- ✓ Promoting the safe and effective use of medicinal products
- ✓ Contributing to the protection of patients' and public health

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

Schema of PV-QMS

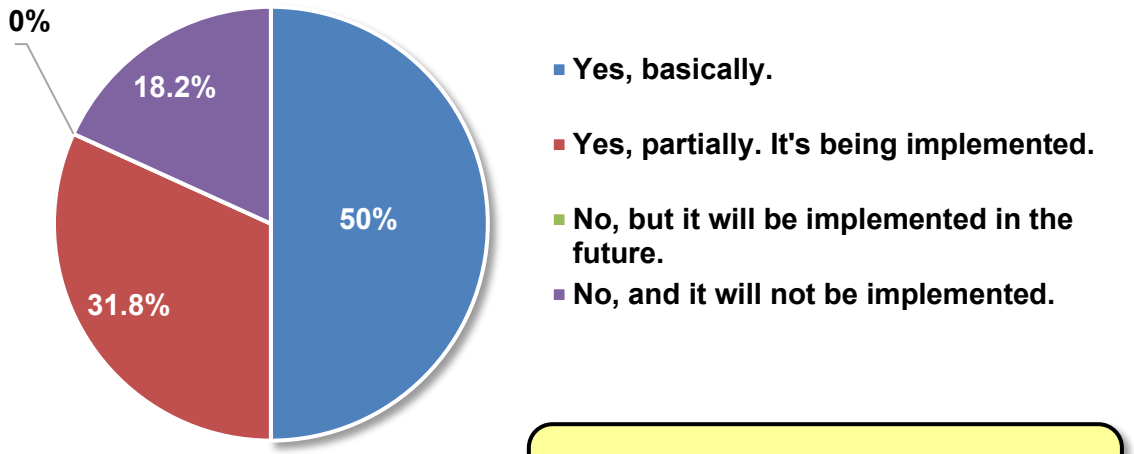


"Proposal of PV-QMS in Japan", 6th GQAC 2020 Sendai Japan

Implementation Status of PV-QMS in Japan

Reason of Implementing PV-QMS	No. of Companies (%)
Marketing products in the EU countries	10 (46)
Partnering with EU pharmaceuticals	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)
Planning launch of products in the EU	1 (5)
Marketing products only in Japan	2 (9)

Implementation Rate of PV-QMS



Ca. 80% in 2023

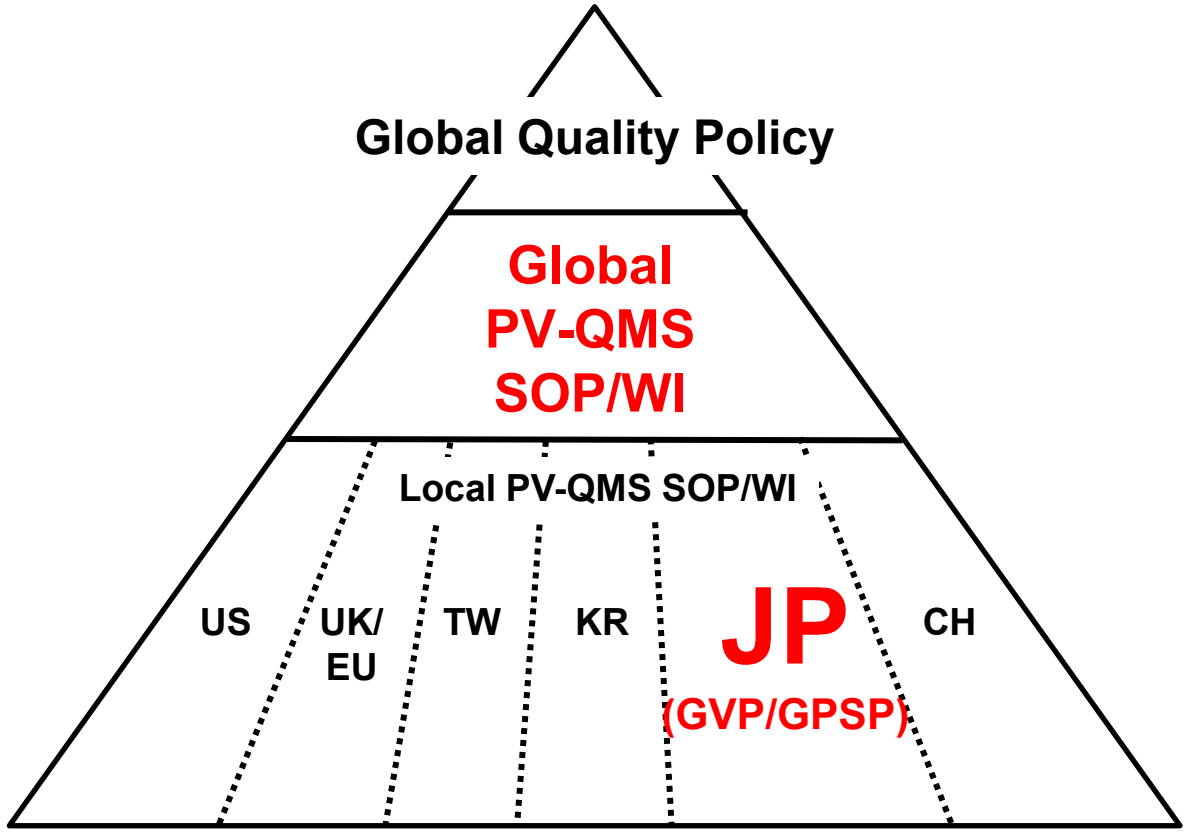
Challenges of Japanese PV-QMS

- ✓ There is less concept of QMS in the Japanese pharmaceutical regulations.
- ✓ Organizations and SOPs that are optimized in accordance with the Japanese regulations are instead disturbing adaptation to global standards.
- ✓ Consistency of global/local PV operations and related global/local SOP descriptions and their management
- ✓ Deviation/CAPA management, audits (with readiness), record management with ALCOA, regulatory intelligence, business continuity plan (BCP) , computer system management, management review
- ✓ Integration of GxP-QMS (GCP, GVP, GMP/GQP)

Differences between the EU-GVP and the Japanese GVP/GPSP

QMS Processes	EU-GVP Module I	GVP / GPSP Ordinance
1. Organisation	Qualified Person for Pharmacovigilance (QPPV)	Pharmaceutical Officer (GVP/GQP), Safety management supervisor (GVP)
2. SOP management	Yes	Yes
3. Training & Assignment	Yes	Yes
4. Deviation & CAPA	Yes	No
5. Audit	Yes	No (Self-inspection?)
6. Compliance/performance monitoring	Yes	No (Self-inspection?)
7. Record management	Yes	Yes (Archiving)
8. Service provider management	Yes	Yes
9. Business continuity plan	Yes	No
10. Regulatory intelligence	Yes	No
11. Computer system management	Yes	No
12. Management review	Yes	No

PV-QMS SOP Management



- ✓ Global SOP/WI management
- ✓ Generation & periodical review
- ✓ Planned deviation
- ✓ Change control/management

QMS Processes	Global/Local
1. SOP on SOP	G
2. Organisation	G
3. Training/Assignment	G/L
4. Deviation/CAPA	G/L(?)
5. Audit	G
6. Compliance/performance monitoring	G/L(?)
7. Record management	G
8. Service provider management	G/L(?)
9. Business continuity plan	G/L
10. Regulatory intelligence	G/L
11. Computer system management	G/L(?)
12. Management review	G

Training & Assignment

- ✓ Refresh training
- ✓ Onboard training
- ✓ All employee AE training #
- ✓ SOP training with a training matrix
- ✓ Management of Curriculum Vitae (CV) and job description (JD) #
- ✓ Assignment of functional managers/leads

#: not required by J-GVP

Points to consider:

- Training materials written in local languages with consistency of the contents
- Learning management system (eLMS)
- HR management system for CV/JD and all employee AE training

Deviation & CAPA

- ✓ Identification and capture of quality issues in PV activities
- ✓ Assessment of the quality issues and their grading (critical/major/minor)
- ✓ Assignment of CAPA owner
- ✓ Making of a CAPA plan (generally for critical and major)
- ✓ Tracking of CAPA
- ✓ CAPA evidence check and its closure
- ✓ Effectiveness check (if applicable)

Points to consider:

- Misunderstanding of definitions for correction and corrective action
- Shallow route case analysis (5 ways, fish bone, BS, etc.) and insufficient CAPA plan
- Involvement of QA or QM
- Involvement of the Pharmaceutical Officer, Safety/PMS Management Supervisor (J-GVP/GPSP)
- CAPA management system (eQMS)

Pharmacovigilance Audits

Basically, Japanese PV Audit Procedure follows EU-GVP Module IV.

- ✓ The audit universe is internal system/processes, service providers and license partners.
- ✓ Three levels of audit planning as follows; strategic level (usually for a period of 5 years, tactical level (normally for 1 year), and operational level (individual audits)
- ✓ Initial, routine, for-cause audit
- ✓ On-site, remote audit (no questionnaire audit)
- ✓ Audit findings are graded with critical, major and minor.
- ✓ CAPA is generally required for critical and major findings.

Points to consider:

- The master plan is generated based on a risk assessment for the PV system.
- The risk assessment should be linked to compliance/performance monitoring for the internal system/processes, service providers and license partners.

Compliance/Performance Monitoring

- ✓ Compliance monitoring plan (CMP)
- ✓ Periodical review and revision of the CMP
- ✓ Monitoring items and KPIs (for example):
  - ICSR reporting to CA (98%<, 100% for PMDA)
  - ICSR reporting to LP (95%<)
  - Periodical aggregate report reporting (100%)
  - Safety variations reporting to CA (100%)
  - RMP commitment compliance (100%), etc.

Points to consider:

- Thresholds of KPIs to trigger CAPA

Record Management

Points to consider:

- Globally centralized archiving
- Security control but easy retrieval
- Transition from paper to electronic
- General Data Protection Law (GDPR)
- Computerized systems in accordance with regulatory requirements such as CFR 21 Part 11, EudraLex Volume 4 Annex 11 and ER/ES Guidance

  - Archiving/sharing (BOX, SharePoint, etc.)
  - Electronic signature (DocuSign, Acrobat Sign, etc.)
  - Document manage system (Veeva, CARA, etc.)

Service Provider Management

- ✓ Service provider (SP) candidate selection
- ✓ SP qualification
- ✓ Master and service level agreement
- ✓ Safety Management Plan (SMP)
- ✓ Quality Management Plan (including KPIs for compliance monitoring) and Communication Plan
- ✓ Monthly reporting or meeting for oversight
- ✓ Routine/for-cause audit
- ✓ Self-inspection for Japan specific PV operations

Points to consider:

- Globally centralized SP management for PV operations
- Inventory of the SPs
- Dealing with local SPs

Business Continuity Plan (BCP)

- ✓ Creating BCP stipulating targeted functions and recovery time frame depending on disaster levels
- ✓ Preparation of scenarios for recovering
- ✓ Annual BCP drill and making of a report

Points to consider:

- Disasters: natural disaster, terrorism, pandemic, cyber-attack, etc.
- Functions: ICSR processing and reporting, aggregate report preparation and reporting, other PV functions
- Disaster Recovery Plan (DRP) for Safety Database and its drill

Regulatory Intelligence

- ✓ Periodical search and capture of regulatory changes in the marketing countries and area
- ✓ Evaluation of their impact on PV operations
- ✓ Revision of procedures, if needed

Points to consider:

- Responsible function, QA or QM
- R&R between global and local RI activities
- Linkage to SOP management
- External database/RI solutions (Thomson Reuters, IQVIA, ivigee etc.)

Computerized System

- ✓ Management of PV-related computerized systems from development to operational phases (management of incidents, configuration changes, individual accounts, periodical review for the management, etc.)
- ✓ Inventory presenting system name, functionality, system owner, GAMP category, CSV status, etc.

Points to consider:

- Transition from computer system validation (CSV) to computer software assurance (CSA)
- Strengthening the management in the operational phase
- Auditing for IT vendors (service level and/or CSV level)

Management Review

EU-GVP Module I requires management review process within the PV-QMS.

- ✓ Management Review Board involving upper GxP managers
- ✓ Escalation of quality issues to the MRB
- ✓ Periodical reviewing of the quality issues, every 6 months or annually
- ✓ Output from the MRB for improving the PV system

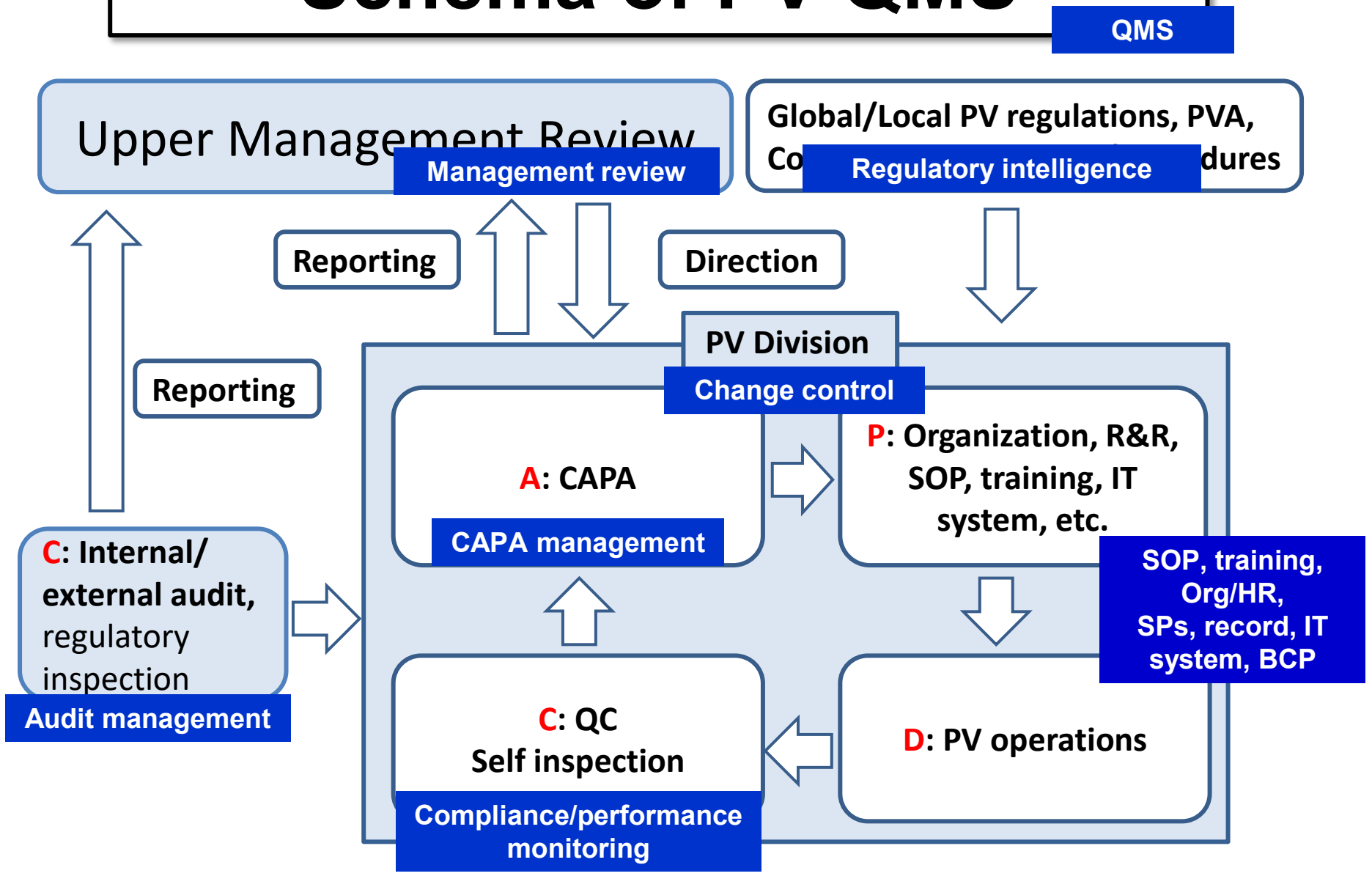
Points to consider

- The pharmaceutical supervisor, safety management supervisor (GVP) and product quality supervisor (GQP/GMP) would participate in the MRB.
- Integration of management review processes among GxP-GMP/GQP, GCP and GVP
- Periodical reporting to the GxP-responsible executives including CEO

Computerized Systems for QMS (eQMS)

Systems	QMS Modules	Other Functions
TrackWise	SOP, CAPA, Training, Audit	-
MasterControl	SOP, CAPA, Training, Audit	-
Veeva	Vault QMS (SOP, CAPA, Audit), Vault Training	clinical data/operation, regulatory, quality, safety, medical, commercial
CARA	SOP, CAPA, Training, Audit	regulatory, quality, safety, clinical, enterprise

Schema of PV-QMS



Conclusions

The Post-marketing Subcommittee 1 has been working with making recommendations for PV-QMS for the Japanese pharmaceuticals.

- ✓ We have been trying to implement PV-QMS within Japanese pharmaceuticals since 2018.
- ✓ The implementation and improvement of the Japanese PV-QMS have dramatically progressed during the past few years.
- ✓ However, there are several challenges for the Japanese PV-QMS in balancing its globalization process with the unique aspects of the Japanese pharmaceutical regulations.

In Europe, the idea of PV-QMS has already become common for the purpose of improving the quality of the PV operations in accordance to the EU-GVP Module I.

It is expected that our activities greatly assist Japanese pharmaceutical companies to implement the PV-QMS which will them ensure the higher PV business quality.