Planning and Execution

A number of key factors must be considered when developing a pharmacovigilance presence in Japan

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Japan presents some unique challenges and complexities when it comes to the management of both clinical trial and marketed product pharmacovigilance (PV). The Japan Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA) have safety reporting requirements that differ significantly from EU and US standards. This article will discuss the key considerations for developing a PV group in Japan that includes the right procedures, timelines, and systems, but, most of all, the right team.

Seriousness	RSI	Domestic	Overseas
Fatal or life-threatening	Unexpected	7 days	7 days
	Expected	15 days	15 days
Other serious ADRs	Unexpected	15 days	15 days
	Expected	-	-

Table 1: Reports of ADRs in clinical trials for drugs (Article 273, Paragraph 1)

Seriousness	Expectedness per RSI	ADR report		Infection report	
		Domestic	Overseas	Domestic	Overseas
Fatal	Unexpected	15 days + fax*1	15 days	15 days + fax	15 days + fax
	Expected	15 days	-	15 days + fax	15 days + fax
Other serious cases	Unexpected	15 days	15 days	15 days + fax	15 days + fax
	Expected	15 days*2 / 30 days	-	15 days + fax	15 days + fax
Serious	Onset pattern (number of episodes, incidence, onset situation, etc) unexpected per RSI	15 days	15 days	15 days + fax	15 days + fax
	Changes in the onset pattern, which present threats of the onset or spread of harm to the public health or hygiene	15 days	15 days	15 days + fax	15 days + fax

*1 The initial report must be sent to the safety division of the PMDA as soon as possible by fax or another appropriate method

*2 During the early phase post-marketing vigilance (EPPV) or two years after approval of medicines containing new molecular entities

Table 2: Reports of ADRs in post-marketing (Article 228/20, Paragraph 1)

Individual Case Safety Report (ICSR) Processing

The enforcement regulations of the Pharmaceutical and Medical Device Act stipulates the provisions of reporting ICSRs, as indicated in Tables 1-4. A key difference from EU and US standards is the PMDA requirement to report measures taken overseas for medicinal products containing the same API and research reports. Measures taken overseas require review of regulatory authority websites to identify any ICSRs that meet the criteria (see Table 3). Typically, the process of searching these websites is subcontracted to a local vendor, which provides a daily email of potential measures taken overseas with the PV team reviewing these outputs to confirm whether the criteria has been met. Research reports involve searching both local and global scientific literature databases based on pre-agreed search strings and then reviewing the outputs to identify any ICSRs that meet the criteria (see Table 4, page 29).

Additionally, reporting certain adverse drug reactions (ADRs) assessed as expected against the current reference safety information (RSI) is needed; this is also a departure from EU and US standards.

Once ICSRs have been assessed as meeting PMDA safety reporting criteria, the next step is to submit the information to the regulatory authority in the correct format. The mechanism of transmission presents the next challenge. Much like the EU and US, the PMDA requires that ICSRs be submitted using the defined ICH E2B data elements. However, Japan-specific data elements, or J-items, must also be completed. A key part of this is ensuring event terms and medical history are coded to the Japanese version of the Medical Dictionary for Regulatory Activities (MedDRA), and suspect products, concomitant medications, etc, are coded to the Japanese drug dictionary rather than the WHO drug dictionary. Depending on the country of origin and case type of certain elements, such as the case narrative, some cases will need to be translated from English to Japanese. English language safety databases alone do not have the functionality to capture this information. Instead, they require an extension/add-on module or a single integrated global drug safety system that is specifically designed with Japanese capabilities to support the capture of these Japan-specific data elements and safety reporting requirements defined by the MHLW.

Once all the ICH E2B data elements have been completed correctly, Japan-compliant ICSRs should be transmitted electronically to the PMDA via an electronic safety module gateway or interchange. Safety reporting via paper or fax typically is not permitted unless the ICSR fits the specific criteria highlighted in Table 2. Compact disc submissions are permitted, but the information should be formatted in a specific manner, which can be time-consuming and inefficient when compared to electronic transmissions.

Medicinal products containing the same API	Overseas	
	Clinical trial	Post-marketing
Measures taken to prevent onset or spread of problems related to public health	15 days	15 days + fax

Table 3: Measures taken overseas for medicinal products containing the same API (Article 273, Paragraph 1)

Aggregate Safety Reporting

As with ICSR reporting, the partnership discovered several nuances to consider when preparing aggregate reports for submission to the PMDA. Three aggregate reports require submission in Japan:

- Japan development safety update report (J-DSUR)
- Japanese periodic safety report (J-PSUR)
- Periodic report for unexpected, non-serious ADRs

The J-DSUR is a clinical trial aggregate report and comprises of the ICH DSUR, prepared following ICH E2F guidance, along with Japan-specific elements, which include an executive summary and domestic, serious ADR listing in Japanese. The J-PSUR is a post-marketed aggregate report that follows a similar approach, comprising the PSUR in periodic benefit-risk evaluation report format per ICH E2C, along with Japan-specific elements and line listings in a specific format. The periodic report for unexpected, non-serious ADRs is a post-marketed aggregate report unique to Japan, comprised entirely of Japan-specific elements and line listings.

Other requirements of the Japan PV system include, but are not limited to:

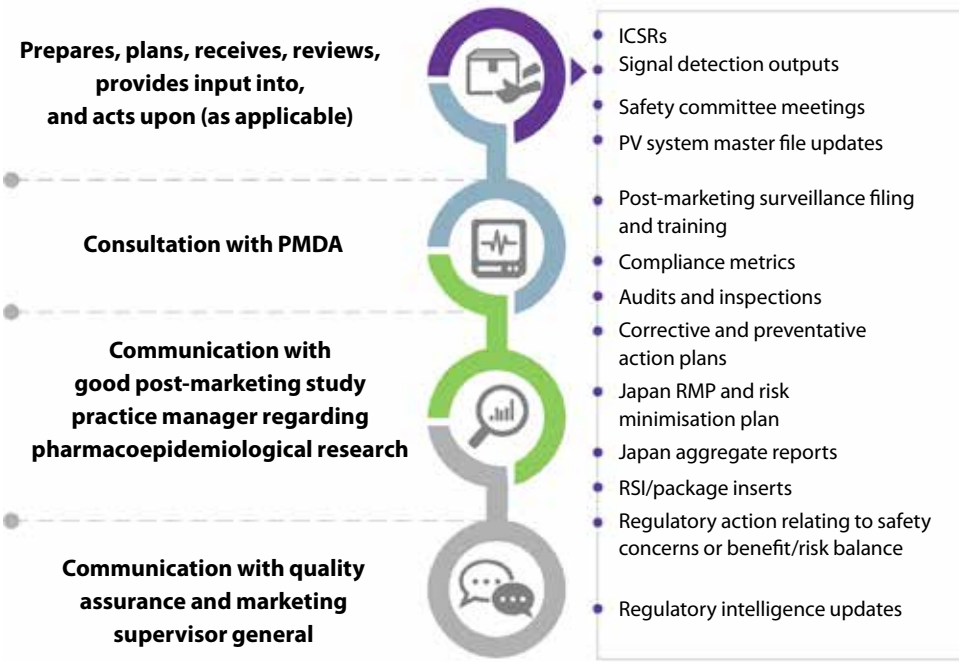

Figure 1: Japan PV system requirements

Good Vigilance Practice (GVP) Activities

Marketing authorisation holders in Japan need to meet three minimum requirements to assure the safety of the product(s):

- Develop and implement standard operating procedures (SOPs) detailing the post-marketed safety management role
- Establish an independent function responsible for safety management, overseen by a GVP manager (Japan-equivalent of a local qualified person for PV). This unit cannot be part of the marketing or sales departments
- Prepare risk management plan (RMP) documents for each product, including information regarding EPPV

Development of Procedures, Timelines, and Systems

As a result of the complexities described in the previous section, the partnership carefully considered the development of procedures, timelines, and systems required to support PV in Japan, all of which needed to provide seamless integration with existing global PV infrastructure designed to support the needs of the EU, US, and other regions.

Procedures

The partnership identified that the development of robust processes to support Japan's unique requirements is an extremely important piece in the global PV system. Where possible, these processes should be integrated into global procedures, SOPs, etc, with the Japan PV team adhering to the standards and quality requirements. Due to the uniqueness of some of the regulations, the partnership recommended that separate procedures be created in support of these requirements; in particular, Japan-specific case processing (including research report and measures taken overseas reviews), safety report distribution in Japan, and the preparation of Japanese aggregate safety reports. The creation of such procedures will not only provide consistency to the Japan PV group and wider PV team, but also give clients and the PMDA the assurance that the team has an appropriate understanding of the requirements to successfully execute PV operations in Japan.

Timelines

As part of developing succinct and robust procedures, ensuring timelines are established for each step in the process is critical to ultimately guarantee safety information is delivered to the PMDA within 7-15 calendar days. This is especially important for

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domestic (originating from Japan) and global ICSR processing where it is crucial to ensure domestic ICSRs (typically processed by the Japan PV group) are available in sufficient time for global processing teams to submit to US and EU regulatory authorities. Likewise, making sure global ICSRs (typically processed by global PV groups) are available in sufficient time is necessary to allow for the Japan processing team to complete Japan-specific processing and submit to the PMDA. As with ICSR processing, the process of preparing the Japan-specific sections of aggregate reports must allow sufficient time to write the report, generate the necessary listings, and convert to the correct format. In this instance, the key is to ensure global teams are given a strict timeframe for delivery of the reports in EU format to the Japan PV team.

Systems

When implementing a global drug safety system that includes Japan, the partnership found that the key to success is having harmonisation of global and Japanese business processes and data entry conventions. Ensuring that all teams truly understand both global and Japanese resource requirements and aligning the workflows to guarantee cases are not delayed or have unnecessary handling steps is essential. The ability to pool drug safety data into one integrated system that handles both global and Japanese needs will produce a more efficient process in the management of worldwide safety information with the added benefit of lower cost of compliance, resulting in lower risk. Ultimately, it eliminates double data entry, reduces translation efforts, accelerates the process of managing/reporting safety cases, and allows for signal analysis across all cases with a single solution.

> **"The development of robust processes to support Japan's unique requirements is an extremely important piece in the global PV system"**

Research reports	Domestic	Overseas
	Clinical trial	Post-marketing
Possibility to cause cancer or serious diseases/disorders or fatal due to ADR is shown	15 days	30 days
Marked change in the onset pattern is shown	15 days	30 days
Medicinal product not effective in the indication having been approved is shown	15 days	30 days

Table 4: Research reports (Article 273, Paragraph 1)

Building the Right Team

Identifying employees with appropriate experience and language skills is critical to success in Japan. When building a PV team, balancing prior language skills with PV experience and/or a healthcare professional (HCP), such as a person with a nursing or pharmacy background, is important. Due to PMDA requirements to provide specific ICH E2B data elements items in Japanese, code event terms to the Japanese version of MedDRA, translate narratives, etc, it is vital that a percentage of employees are fluent in both Japanese and English. Based on experience, entry-level PV candidates should have an English language qualification and/or may have spent time training or working in English-speaking territories outside of Japan. In addition to the PV work itself, another key benefit of fluency in both languages is the ability to engage in direct communication with global internal and external clients, along with the Japan affiliates of global clients. The joint venture fulfils these criteria and brings to the partnership a wealth of local Japanese regulatory experience and insight, with a specific emphasis on Japanese regulatory requirements.

Creating an experienced PV team when a new hub is developed is challenging, as people traditionally do not want to move; therefore, careful consideration was given when approaching experienced PV candidates with a new opportunity. The joint venture understood the advantage to the organisation in establishing an experienced PV leader with local knowledge who can provide strategic direction to the team and that it is critical to have individuals with a solid knowledge of local PV regulations. This, combined with a team of HCPs that have the ability to critically analyse safety data, ensured a strong foundation for the delivery of a high-quality end product.

Local appropriately qualified physicians should be carefully considered as part of developing a PV group in Japan. When processing domestic ICSRs, it maximises efficiency to have these cases medically reviewed by bilingual (English and Japanese) physicians. Additionally, these positions become critical when interacting directly with investigators and key opinion leaders where language fluency, expertise, background, and tenure are paramount in navigating discussions. A strategic recruitment plan is vital in securing the best candidate, as these positions are highly desirable.

Japanese PV Management

This article has discussed the unique challenges and complexities in the management of PV in Japan. Establishing the right team to develop effective procedures, timelines, and systems can be achieved, and success involves a significant investment of time, resource, and expense, but the ultimate return is a seat at the table of the largest pharma market outside the US.

About the authors

Gary Barker joined PPD's PV department in 2005 and has spent time in Singapore and Australia developing the company's capabilities in Asia-Pacific. He is accountable for clinical trial and marketed product PV across Asia-Pacific Eastern Europe and projects in North America.

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Tsutomu Yonehana joined the PPD-SNBL PV department in 2018. He has worked in PV roles of responsibility for 20 years. Most recently, he served as Senior Safety Manager at Celgene Japan where he was responsible for the oversight of all PV activities for sponsored clinical trial and marketed product programmes.

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