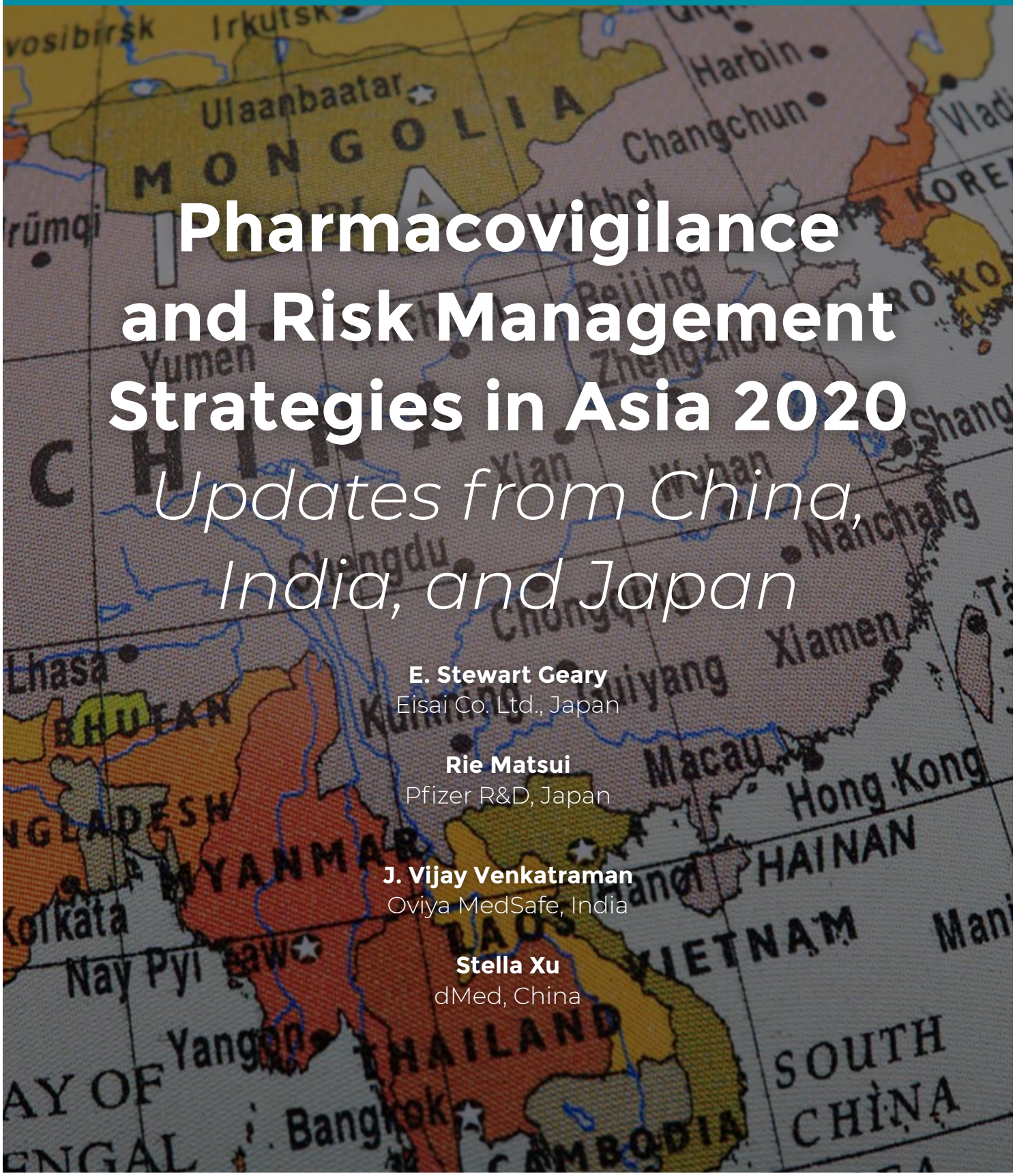


# Pharmacovigilance and Risk Management Strategies in Asia 2020

## *Updates from China, India, and Japan*

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**DIA's recent *Pharmacovigilance & Risk Management Strategies Conference 2020* opened with experts providing *Asia Region Updates* from India, Japan, and China, in a session chaired by DIA Fellow E. Stewart Geary and summarized in this report.**

## Current Scenario: Post-Approval Pharmacovigilance Obligations for Industry in India

As a major manufacturing hub as well as a huge market for both the indigenous and the international pharmaceutical industry, any drug regulation in India is of significant relevance to the global pharmaceutical community. From a pharmacovigilance perspective, the Central Drugs Standard Control Organisation (CDSCO, the National Regulatory Authority of India), the Indian Pharmacopoeia Commission which functions as the National Coordination Centre of the Pharmacovigilance Programme of India (NCC-PvPI, IPC), and the several State Drug Control Authorities (for 28 states and eight union territories in India) are the key governmental bodies. While the CDSCO's most important responsibility is to approve new drugs and the conduct of clinical trials in India, the state drug controllers are primarily responsible for licensing the manufacturing and sale/distribution of drugs. PvPI focuses on monitoring Adverse Drug Reactions (ADRs) in the Indian population and receives suspected ADR reports not only from industry but from healthcare professionals through their more than 250 ADR Monitoring Centres established throughout the country.

Schedules Y, D and M of the Drugs & Cosmetics Act, 1940 & Rules, 1945 form the basis of India's pharmacovigilance regulations. The Rules have been amended from time to time by release of gazette notifications, the most remarkable being **GSR 287(E) dated March 2016** which mandated pharmacovigilance as a legal obligation for the pharmaceutical industry. The Pharmacovigilance Guidance Document for Marketing Authorization Holders (MAHs) of Pharmaceutical Products, effective since January 2018, describes the pharmacovigilance system necessitated by GSR 287(E) and details the routine pharmacovigilance activities to be performed by the MAH (the holder of a valid manufacturing or import license). An **overview of the Guidance Document** was summarized by this author for the January 2018 *Global Forum*. In short, the Guidance Document may be best seen as a "companion book" to the Drugs & Cosmetics Act, 1940 & Rules, 1945, including the recent amendments.

Operationally speaking, NCC-PvPI, IPC acts as the central processing unit of India's suspected ADR data. Typically, the PvPI Signal Review Panel shares its recommendations with CDSCO so that the latter may be better positioned to make regulatory decisions. CDSCO issues guidelines to state authorities to ensure that their licensees update their labels. Moreover, PvPI has been issuing drug safety alerts on a monthly basis since March 2016, which indicates a good amount of coordination between the three governmental authorities whose efforts in pharmacovigilance complement each other.

Even so, some challenges remain. Expecting Periodic Safety Update Reports (PSURs) to be submitted within 30 calendar days from the end of the reporting period poses immense difficulty for organizations having voluminous data. In addition, the International Birth Date (IBD) is not followed in India for purposes of setting the frequency of PSUR submissions. Similarly, Risk Management Plan (RMP) requirements are somewhat ambiguous and must be streamlined. There is no dedicated Signal Detection guidance material available. And last but not least, debate on whether the Guidance Document's obligations will be applicable for companies that only function as marketing partners to the manufacturing/import license-holders is yet to be settled.

## New Japanese Package Insert Format and Overview of Labeling in Asia

Although Asia's economy has grown rapidly, the regulatory environment for labeling in most Asian markets is still evolving toward convergence of labeling requirements. Each country in the Asia region has its own regulations and harmonization of labeling has never been effectively attempted. Not many countries require patient labeling for most products. Some countries in Asia are interested in eLabeling, making it a new regional "hot topic."

Labeling regulations for Japan had not changed since 1997 until the revised regulations/guidance were issued in June 2017. These have been effective since April 2019, beginning a five-year transition period to full implementation by March 2024. However, PMDA has issued the schedule for reviewing the revised labeling based on the new regulations and directed MAHs to follow this schedule.

There are three main changes according to the new format: The "Relative Contraindications" and "Careful Administration" sections have been deleted and a new section, "Precautions for Specific Populations" (such as elderly, pediatric, and renal-impaired patients), has been established. In addition, redundant content should be eliminated, and section numbering has been introduced.

Approved labels are published on PMDA's website in Japan, which are available in SGML, HTML, and PDF format. These labels are searchable across products. Converting SGML to XML format began in April 2019. Furthermore, in November 2019, the Japanese government decided in principle that labeling information should be provided electronically. Instead of attaching paper labeling to products, paper labeling should be provided to pharmacies and hospitals when needed.

## Implementing E2B (R3) for Pharmacovigilance Reporting in China

With China joining ICH as its eighth regulatory member in June 2017, the National Medicinal Product Administration (NMPA) has accelerated the pace of regulatory reform by implementing ICH guidelines, including ICH M4, E2A, E2B (R3), M1 and E2D, and several tier 3 guidelines. This is a major step for the China Health Authority to be more harmonized with international standards.

NMPA has set aggressive timelines for ICH E2B R3 safety reporting compliance. The Center for Drug Evaluation (CDE), affiliated to the NMPA, is responsible for technical review of drug registration applications and the Center for Drug Re-evaluation (CDR) is responsible for drug adverse reaction and medical device adverse event monitoring.

For IND safety reporting, it has been mandatory to submit domestic and foreign SUSARs in ICH E2B R3 format to CDE since May 2019. During the transition period (May 2018 through the end of April 2019), the clinical trial sponsor could submit SUSARs in the ICH E2B R2 format. To fulfill the ICH E2A expedited reporting requirement, the English version may be submitted within seven to fifteen days, and the Chinese version should be submitted in an additional 15 days.

For ADRs of marketed products, CDR has started to accept cases in E2B R3 format since the beginning of January 2020. It will be mandatory for all MAHs to submit all post-marketing ADRs in E2B R3 format at the beginning of July 2022.

The E2B (R3) China specification was finalized and published in November 2019 and is applicable for both IND safety reports and post-marketing safety reports. China health authorities held several rounds of industry feedback meetings to review the detailed data field requirements and incorporated 19 new elements required by regional requirements in the final specification.

E2B (R3) implementation brings challenges as well as opportunities to the whole industry. To stay compliant with the regulatory requirements, all sponsors and MAHs must start to establish or upgrade safety databases capable of generating safety reports per NMPA requirements. We have also seen many local CROs and system solution companies developing rapidly to establish a pharmacovigilance system with traceability and signal detection features compliant with ICH E2B guidelines.